In Supportive Care Oncology

CANadian Vision for oncology

SPOTLIGHT ON BENDAMUSTINE
Exploring its use in hematological malignancies

INVESTIGATOR INTERVIEWS
Interviews with Dr. Martin Dreyling on results from the MCL elderly study and with Dr. Liat Vidal on a meta-analysis of bendamustine studies

Managing hematological toxicities with FCR in chronic lymphocytic leukemia

Moving Toward Improved Patient Care
EHA/ICML 2011

INSIDE THIS ISSUE

CHRONIC LYMPHOCYTIC LEUKEMIA
Improving tolerability of treatment with new agents and treatment combinations

NON-HODGKIN LYMPHOMA
New management strategies

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New Evidence in Oncology is a publication that provides oncology specialists with scientific data from research presented at international and Canadian oncology conferences. A special feature of the journal, the Canadian perspective, gives key opinion leaders a forum to discuss recent developments in oncology and to comment on how these advances may shape Canadian clinical practice. In addition, the investigator commentary sections provide information on key clinical studies from interviews with principal investigators. *New Evidence* also publishes discussion and expert opinion papers on timely topics of interest to oncologists in Canada.

Our August 2011 issue presents coverage from the 16th Annual Meeting of the European Hematology Association (EHA), held in London, England, from June 9–12, 2011 and the 11th Annual Meeting of the International Conference on Malignant Lymphomas (ICML), held in Lugano, Switzerland, from June 15–18, 2011. The issue examines key studies in chronic lymphocytic leukemia and indolent non-Hodgkin lymphoma aimed at improving patient care. We would like to thank Dr. Bernard Lemieux, Dr. Laurie Sehn, and Dr. Doug Stewart, for their Canadian perspectives, and Dr. Martin Dreyling and Dr. Liat Vidal for their investigator commentaries.

We invite you to visit our website at www.newevidence.com for the online version of *New Evidence* and more reports on current research. Slide presentations on various topics are available for download.
Contents

EHA · ICML

Chronic Lymphocytic Leukemia

9
The Search for Effective, More Tolerable Treatment Combinations in CLL

• Rituximab plus chlorambucil (R-chlorambucil) as first-line treatment for CLL: Final analysis of an open-label phase II study (Hillmen P, et al. ICML 2011: Abstract 120)

• Fludarabine plus rituximab chemoinmunotherapy followed by a consolidation and maintenance plan with rituximab improves outcome in CLL (Del Poeta G. EHA 2011: Abstract 0531)

• Phase II study of navitoclax safety and efficacy in patients with relapsed or refractory CLL: Interim results (Seymour F, et al. EHA 2011: Abstract 0534)

• Low-dose FC combined with R in the treatment of elderly/comorbid patients with CLL: Project Q-Lite of Czech CLL Study Group (preliminary results) (Smolej L, et al. EHA 2011: Abstract 0105)

Canadian perspective by Dr. Bernard Lemieux

Follicular Lymphoma

29
New Approaches to Treatment in Follicular Lymphoma

• Preliminary results of QoL analyses from the intergroup phase III randomized trial of rituximab vs. watch and wait approach in patients with FL (Ardeshna KM, et al. ICML 2011: Abstract 019)

• Bortezomib-rituximab results in improved PFS and response rates vs. Rituximab, and quality of response is associated with improved outcomes, in patients with relapsed FL (Coiffier B, et al. EHA 2011: Abstract 0361)

• Interim results from a phase Ib study of the anti-CD20 obinutuzamab (GA101) in combination with FC or CHOP in relapsed/refractory FL (Davies A, et al. EHA 2011: Abstract 0368)

Canadian perspective by Dr. Laurie Sehn

Diffuse Large B-cell Lymphoma

40
New Treatment Options for Patients with DLBCL

• Treatment of limited-stage DLBCL can be effectively tailored using a PET-based approach (Sehn LH, et al. ICML 2011: Abstract 028)

• A phase II study of CT-011 after AuSCT in recurrent/refractory DLBCL (Gordon L, et al. ICML 2011: Abstract 063)

• Randomized phase II study of R-CHOP plus enzastaurin vs. R-CHOP in the first-line treatment of patients with intermediate and high-risk DLBCL (Hainsworth JD, et al. ICML 2011: Abstract 074)

• Lower dose intensity chemoinmunotherapy in very elderly patients with DLBCL (Vassilakopoulos T, et al. EHA 2011: Abstract 1045)

Canadian perspective by Dr. Douglas Stewart

Canadianizing a New Standard of Care in CLL

21
Managing hematological toxicities with FCR

Canadian perspective by Dr. Bernard Lemieux
Other Lymphomas

54

Optimizing Therapies and Outcomes for NHL

• Rituximab maintenance significantly prolongs duration of remission in elderly patients with mantle cell lymphoma (MCL) (Kluin-Nelemans JC, et al. EHA 2011: Abstract 0504)

• Results from a phase II study of GA101 monotherapy in relapsed/refractory aggressive NHL (Cartron G, et al. ICML 2011: Abstract 144)

• Lenalidomide plus rituximab is a highly effective and well-tolerated biologic therapy in untreated indolent B-cell NHL (Fowler N, et al. ICML 2011: Abstract 137)

Canadian perspective by Dr. Douglas Stewart

Investigator Commentary

63

An Interview with Dr. Martin Dreyling on Results from the MCL Elderly Study

A Spotlight on Bendamustine

66

Bendamustine: Shaping its Use in Lymphoproliferative Disorders

• Efficacy and safety of bendamustine plus bortezomib in relapsed/refractory multiple myeloma: A phase I/II trial (Berenson JR, et al. ASCO 2011: Abstract 8070)

• Rituximab plus bendamustine in elderly previously untreated patients with indolent, non-follicular NHL: Preliminary data of a single centre study (Pennesse E and Di Renzo N. EHA 2011: Abstract 1440)

• Bendamustine for patients with indolent lymphoma – a systematic review and meta-analysis of RCTs (Vidal L, et al. EHA 2011: Abstract 0362)


Canadian perspective by Dr. Laurie Sehn

Investigator Commentary

74

An Interview with Dr. Liat Vidal on Results of her Meta-Analysis on Bendamustine in Indolent Lymphomas
Contributors

Canadian Perspectives

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Investigator Commentaries

Martin Dreyling, MD, PhD
Dr. Martin Dreyling is an attending physician and associate professor in the Medical Department of the University of Munich, Grosshadern, Germany. His primary interests include the molecular biology and clinical care of lymphoma. Dr. Dreyling’s research activities relate to the molecular basis of malignant transformation, cell cycle dysregulation in mantle cell lymphoma (MCL), secondary genetic alterations and biological prognostic factors in malignant lymphoma, and innovative therapeutic approaches in indolent lymphoma. He is actively involved in a number of national and European study groups, and is currently the Coordinator of the European MCL Network. Dr. Dreyling has co-authored over 300 scientific papers, book chapters, and published abstracts in international peer-reviewed journals.

Liat Vidal, MD
Dr. Liat Vidal is a senior physician at the Institute of Hematology in the Beilinson Hospital, Rabin Medical Center in Israel. She received her medical degree from the Hebrew University in Jerusalem in 1998 and completed her residency in internal medicine at the Bellinson Hospital, Rabin Medical Center in 2004. From 2006 to 2007 she worked as a physician in hematology/oncology at the Hasharon Hospital, Rabin Medical Center. Dr. Vidal has a Master’s degree in epidemiology and her research interests include evidence-based medicine, systematic review, and meta-analysis.
Welcome to the New Evidence coverage of the 2011 European Hematology Association (EHA) meeting held in London, England from June 9th to 12th and the 2011 International Conference on Malignant Lymphomas (ICML) meeting held in Lugano, Switzerland from June 15th to 18th.

EHA was founded in June 1992 and has over 3,000 active members from 95 countries. Each year, EHA congresses showcase the latest research in hematology. ICML is the primary international forum devoted to basic and clinical research in lymphoid neoplasms and is held every three years in Lugano. This issue of New Evidence covers key presentations from both EHA and ICML 2011.

In recent years, the development of effective treatments for patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) has improved overall survival and extended remission. However, elderly patients and those with co-morbidities are often unable to tolerate standard treatments. The development of a number of induction and maintenance regimens with good side effect profiles is therefore an exciting step towards improving patient care. In addition, treating early in asymptomatic patients with follicular lymphoma and the development of promising new agents for NHL in the relapsed setting are exciting areas of research. In this issue, we report on a number of presentations in CLL and NHL aimed at improving the outcomes of patients in these settings.

We hope you enjoy this issue of New Evidence and hope to see you at the next EHA conference in Amsterdam, Netherlands.
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FRAGMIN is indicated for the extended treatment of symptomatic VTE to prevent recurrence of VTE in patients with cancer.

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FRAGMIN Achieved A Statistically Significant 52% Relative-Risk Reduction In Recurrent VTE vs. Oral Anticoagulant Therapy* (27/336 vs. 53/336; p=0.002)

No Significant Difference In The Incidence Of Bleeding Between FRAGMIN And Oral Anticoagulant Therapy (OAC) Was Demonstrated.†

<table>
<thead>
<tr>
<th></th>
<th>FRAGMIN n=336</th>
<th>OAC n=336</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Bleeding</td>
<td>8%</td>
<td>15%</td>
<td>n/a</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>6%</td>
<td>4%</td>
<td>0.27</td>
</tr>
<tr>
<td>All Bleeding</td>
<td>14%</td>
<td>19%</td>
<td>0.09</td>
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• Evidence-based FRAGMIN dosing: 200 IU/kg sc once daily (maximum 18,000 IU daily) for the first month, followed by a maintenance dose of ~150 IU/kg sc once daily for 2–6 months sc.
• INR or APTT monitoring is not required.§
• FRAGMIN is eligible for reimbursement under many provincial formularies.

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See prescribing summary on page 77
The Search for Effective, More Tolerable Treatment Combinations in CLL

Chronic lymphocytic leukemia (CLL) is an indolent disease characterized by the accumulation of phenotypically mature malignant B-lymphocytes in the blood, bone marrow, and lymph nodes.1 Prognostic factors allow the stratification of this disease into low-risk and high-risk groups but treatment initiation is based on symptoms, tumour burden, and stage of disease, rather than on prognosis.2 Recent developments for the treatment of CLL have identified maximum disease control as an achievable goal of therapy.2

Once treatment becomes necessary, chemoimmunotherapy is the standard of care because of improved survival compared with chemotherapy alone.3,4 However, currently available treatments can be myelotoxic, immunosuppressive, and associated with infectious complications for some patients.5 It is important to recognize that CLL is a disease of the elderly who often have comorbid conditions. The toxicities of traditional chemotherapy agents both prohibit their use in these patients, and drive the identification and development of less toxic, more tolerable treatment approaches.

Data from studies evaluating effective and more tolerable treatment approaches in CLL were presented at ICML and EHA 2011:

- The final analysis of a phase II trial of rituximab plus chlorambucil presented at ICML 2011 demonstrated efficacy and safety for previously untreated CLL patients who are considered to be unfit for more aggressive therapies.
- In a single-arm study presented at EHA 2011, the addition of rituximab to fludarabine (FR) during induction therapy for CLL patients was safe and effective with improved response rates and response duration. Furthermore, patients with persistent minimal residual disease (MRD)-negativity or those who received rituximab consolidation/maintenance therapy experienced significantly prolonged response duration and overall survival (OS) compared with those who did not receive consolidation/maintenance therapy.
- The interim results of a phase II study of navitoclax presented at EHA 2011 confirmed that this agent had a good safety profile at the studied dose and that it had significant activity in heavily pretreated CLL patients, including those with high-risk characteristics and bulky disease.
- In a different approach to treat elderly and comorbid CLL patients, a low-dose strategy of fludarabine, cyclophosphamide, and rituximab (FCR) was employed. Early results were presented at EHA 2011 and indicated that low-dose FCR has acceptable and manageable toxicity with promising activity.

Rituximab plus chlorambucil (R-chlorambucil) as first-line treatment for CLL: Final analysis of an open-label phase II study

Background
Chlorambucil is a commonly used first-line therapy for less fit patients with chronic lymphocytic leukemia (CLL) but overall response rates (ORR) are modest with very few complete responses (CR). This underscores the need for more effective regimens for patients who cannot tolerate intensive therapies.

Hillmen and colleagues studied the combination of rituximab and chlorambucil (R-chlorambucil) as first-line treatment for CLL in a multicentre phase II study (NCRI CLL208). The results were presented at ICML 2011.

Study design
- Patients with previously untreated CLL (n = 100) were treated with six 28-day cycles of rituximab (375 mg/m² on day 1 of cycle 1; 500 mg/m² on day 1 of cycles 2–6) plus chlorambucil (10 mg/m²/day on days 1–7).
- Patients who did not achieve CR but were responding at the end of the first six cycles received six additional cycles of chlorambucil alone.
- The primary endpoint was safety and efficacy was the secondary endpoint.
- Response data (CR, ORR and progression-free survival [PFS]) were compared with case-matched data from 200 patients from the chlorambucil-only arm of an earlier U.K. study (LRF CLL4, 1994–2008). Patients were matched in a one-to-two ratio by Binet stage, IgVH mutation, 11q status by FISH, and age.

Key findings
- The median age of the patients in this study was 70 years (range: 43–86 years).
- The regimen was well tolerated with most adverse events (AEs) being grade 1 or 2.
- The most common grade 3–4 AEs were hematologic (occurring in 18–41% of patients). (Table 1)
- A total of 57 serious AEs (SAEs) occurred in 39 patients and included five cases of febrile neutropenia, four cases of neutropenic sepsis, and three infusion-related reactions.
- There were 13 deaths, 11 of which were due to progressive disease and two were considered to be treatment-related (neutropenic sepsis and cerebral infarction).
- The ORR in all 100 patients was 80% (95% CI: 70.8–87.3) with 12% of patients achieving a CR, compared with 66% ORR and 6% CR in the case-matched controls. (Table 2)
- Patients with favourable prognostic markers tended to have higher CR rates but the ORR was similar.
- The median PFS was 22.0 months (95% CI: 16.7–26.9) (Figure 1) compared with 18 months in the matched pairs from CLL4.

Table 1. Most common adverse events

<table>
<thead>
<tr>
<th>Grade 3–4 adverse event</th>
<th>R-chlorambucil (n = 100)</th>
<th>Chlorambucil in CLL4 (n = 380)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, n (%)</td>
<td>Patients, n (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>68 (68)</td>
<td>41 (41)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28 (28)</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (22)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22 (22)</td>
<td>18 (18)</td>
</tr>
</tbody>
</table>
Key conclusions

- R-chlorambucil is an effective and well tolerated treatment for patients with previously untreated CLL who are considered to be unfit for FCR therapy.
- R-chlorambucil appears to result in higher response rates than chlorambucil alone with acceptable toxicity, although the remission rates are lower than those reported for FCR.
- R-chlorambucil is currently being evaluated in a randomized comparison with chlorambucil alone in the CLL11 study for unfit patients.

Fludarabine plus rituximab chemoimmunotherapy followed by a consolidation and maintenance plan with rituximab improves outcome in CLL

Background
Del Poeta and colleagues studied the sequential combination of rituximab and fludarabine in induction therapy for symptomatic previously untreated chronic lymphocytic leukemia (CLL) patients in a phase II study. A subset of patients also received consolidation/maintenance therapy with rituximab. The goals of this study were to determine remission rates and response duration in all patients as well as to determine if persistent phenotypic complete remission (CR) or consolidation/maintenance therapy with rituximab can prolong response duration and overall survival (OS). Furthermore, consolidation/maintenance therapy and biologic risk classes were evaluated as independent prognostic factors for remission duration and OS. The results of this study were presented at EHA 2011.1

Study design
- Symptomatic, untreated CLL patients (n = 138) were treated with six monthly courses of intravenous (25 mg/m²) or oral (35–40 mg/m²) fludarabine and four weekly doses of rituximab (375 mg/m²).
- Patients who responded (CR [with or without minimal residual disease, MRD], partial remission [PR], or stable disease) received consolidation therapy with four monthly doses of rituximab (375 mg/m²) followed by 12 monthly doses of rituximab (150 mg/m²).
- High-risk patients were defined as those having at least two of the following markers: unmutated IgVH, CD38 >30%, ZAP-70 >20%, intermediate/unfavourable cytogenetics (trisomy 12, or 11q or 17p deletion).
- MRD was assessed by flow cytometry and the threshold was set at more than 1% CD19+CD5+CD79b-/ bone marrow (BM) CLL cells.

Key findings
- The median age of the patients enrolled in this study was 63 years (range 37–80 years).
- 14 patients had a modified low Rai stage, 121 were classified as having intermediate-stage disease and three had high-stage disease.

Induction efficacy
- CR was achieved by 77% of patients, 19% achieved PR and 4% had stable disease or progression.
- Phenotypic CR (CD19+CD5+CD79b- BM cells >1%) was achieved in 58% of patients.
- MRD-positive patients had a significantly shorter OS compared with MRD-negative patients (24% vs. 72% at 16 years, \( p = 0.00016 \)).

Safety
- During the induction and consolidation/maintenance phases, 13 patients developed grade 2–3 pneumonia and two patients developed Richter’s syndrome.
- Hematologic toxicity was mild and mainly involved neutropenia (grade 3–4 in 60 patients) and thrombocytopenia (grade 3–4 in eight patients). (Table 1)

<p>| Table 1. Adverse events |
|-------------------------|---------|---------|---------|---------|</p>
<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever/chills</td>
<td>15</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Infections</td>
<td>9</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

Richter’s syndrome (Hodgkin lymphoma): 2 patients

Consolidation/maintenance efficacy
- 57 patients (43%) in either CR with MRD (n = 15) or without MRD (but developing MRD positivity within two years after induction; n = 24) or in PR (n = 18) received consolidation/maintenance therapy.
• The median follow-up was 59 months and the progression-free survival (PFS) after the end of the induction phase was 40% at eight years. (Figure 1)
• Cytogenetic variations did not have a significant impact on response duration \((p = 0.088)\). (Figure 2)
• 44% of patients were still alive 10 years after the end of induction and 27 deaths were reported.

• Five years following induction therapy, patients who were MRD-negative for more than two years \((n = 52)\) or patients who received consolidation/maintenance therapy \((n = 57)\) had a significantly longer response duration than patients who did not receive consolidation/maintenance therapy \((n = 22)\) \((76\% \text{ vs. } 57\% \text{ vs. } 0\% \text{ had not progressed at five years, respectively; } p <0.0001)\). (Figure 3)

**Figure 1. Progression-free survival from the end of induction**

**Figure 2. Response duration by cytogenetics**
• Similarly, the OS duration was also longer for MRD-negative for more than two years in patients who received consolidation/maintenance therapy than those who did not receive consolidation/maintenance therapy (97% vs. 61% vs. 0% were still alive at 15 years, respectively; \( p = 0.03 \)). (Figure 4)

• Within the high-risk subset of patients (\( n = 59 \)) who were ZAP-70-positive or IgVH unmutated 2.5 years following induction therapy, patients who were MRD-negative for more than two years (\( n = 20 \)) or patients who received consolidation/maintenance therapy (\( n = 20 \)) had a significantly longer response duration than patients who did not receive consolidation/maintenance therapy (\( n = 13 \)) (90% vs. 61% vs. 0% had not progressed at 2.5 years, respectively; \( p = 0.0009 \)).

• Patients who were ZAP-70-positive had shorter remission durations than those who were IgVH unmutated (17% vs. 53%, respectively, at 16 years, \( p = 0.001 \); 16% vs. 53%, respectively, at 6.5 years, \( p < 0.0001 \)).

• In a multivariate analysis, consolidation/maintenance therapy and biologic risk class were confirmed as independent prognostic factors for response duration and OS.

Figure 3. Response duration by phenotypic complete response and rituximab consolidation/maintenance

![Figure 3](image_url)

Figure 4. Overall survival by phenotypic complete response and rituximab consolidation/maintenance

![Figure 4](image_url)
Key conclusions

- The addition of rituximab to fludarabine during induction therapy for CLL patients improved CR rates and response duration without an increase in toxicity.
- Persistent MRD-negativity and rituximab consolidation/maintenance therapy significantly prolonged response duration and OS in the entire study population as well as within the high-risk subset of patients.
- Within the high-risk subset, biological markers such as ZAP-70 and IgVH mutational status retain their prognostic impact on clinical outcomes.


Phase II study of navitoclax safety and efficacy in patients with relapsed or refractory CLL: Interim results

Background

Navitoclax, a novel BH3 mimetic, binds with high affinity and inhibits multiple anti-apoptotic Bcl-2 family proteins. An earlier phase I trial established that single-agent navitoclax administered at 250 mg/day achieved predicted pharmacokinetic (PK) parameters, was well tolerated, and provided a signal of activity in previously treated patients with relapsed/refractory chronic lymphocytic leukemia (CLL), justifying phase II evaluation at this dose. The results of this trial were presented by Seymour and colleagues at EHA 2011.1

Study design

- This phase II multicentre international trial assessed safety, efficacy, and PK of oral navitoclax in patients with relapsed/refractory CLL who had been heavily pretreated (five or less prior regimens).
- Following a seven-day lead-in at 100 mg/day, navitoclax was dosed at 250 mg/day on a 21-day cycle until progression or intolerable toxicity.
- Efficacy endpoints included tumour response and progression-free survival (PFS).
- Disease was assessed at the end of cycles 2 and 4 every four cycles through cycle 20, and every eight subsequent cycles.
- Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.
- Serial blood samples were collected for PK analysis.

Key findings

- 31 patients with a median age of 70 years (range: 44–82 years) were enrolled.
  - Eight patients were fludarabine-refractory.
  - The median number of prior therapies was 2.5 (range: 1–6 therapies).
- Cytogenetic data were available for 17 patients, 11 of whom were high risk (11q del was present in six patients, 17p del was present in five patients, and two patients had both).
- The median time on study was 5.1 months (95% CI: 3.8–13.1). (Figure 1)
- Of the 21 patients with baseline lymphocytosis, 19 (90%) had ≥50% reduction (median reduction 87%). (Figure 2)
- 27 patients are evaluable for response and the confirmed overall response rate was 19%.
  - Nine (33%) had a partial response (PR), which was confirmed in five patients;
  - 17 (63%) had stable disease (SD);
  - One patient (4%) had progressive disease (PD).
- 18 of the 31 patients had bulky disease with adenopathy less than five centimeters. Of the 13 who were evaluable for response, all had anti-tumour activity (five patients achieved PR and eight had SD).

- The median PFS for the whole study group was 8.7 months (95% CI: 7.8–16.4). (Figure 3)

- For the eight fludarabine-refractory patients, the median PFS was 6.0 months (95% CI: 1.4–8.6) and the median time on study was 8.5 months (95% CI: 4.3–not reached).

- 26 patients were evaluable for nodal regression and 12 (46%) had >50% nodal regression.

- Patients who had isolated 11q del (n = 6) had a favourable outcome compared with those who had 17p del (n = 5) or those who had normal cytogenetics (n = 6) (PFS not reached vs. 183 days, p = 0.0056).

- The most common navitoclax-related AEs (all grades) were diarrhea (58%) and nausea (48%), both most likely attributable to the formulation.
• Grade 3–4 AEs included thrombocytopenia (36%), neutropenia (19%), and alanine aminotransferase increases (7%). (Table 1)

• Serious AEs (SAEs) included pyrexia, fluid overload, pneumo-

nia, tumour lysis syndrome, and dizziness. (Table 1)

• Five patients had AEs leading to discontinuation, and eight leading to dose reduction.

• 22 patients discontinued: five due to PD, eight due to AEs, six withdrew consent, and three due to other reasons (lack of response, investigator decision).

• At the time of this presentation, nine patients were still receiving navitoclax.

• PK analysis of trough concentrations suggested consistent exposure across cycles.

Table 1. Navitoclax-related adverse events (n = 31)

<table>
<thead>
<tr>
<th>Any grade, &gt;20% of patients</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea*</td>
<td>18 (58)</td>
</tr>
<tr>
<td>Nausea*</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Grade 3–4, ≥2 patients</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (36)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (19)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td></td>
</tr>
<tr>
<td>Pyrexia (grade 1, grade 3)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Fluid overload (grade 3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pneumonia (grade 3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Tumour-lysis syndrome (grade 3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dizziness (grade 3)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

*likely attributable to formulation
ALT = alanine aminotransferase

Key conclusions

■ These data confirm that navitoclax has an acceptable safety profile at 250 mg/day.

■ Navitoclax has significant anti-tumour activity in patients with heavily pre-treated CLL, including those with 17p del and other high-risk cytogenetic characteristics as well as bulky disease.

Low-dose FC combined with R in the treatment of elderly/comorbid patients with CLL: Project Q-Lite of Czech CLL Study Group (preliminary results)

Background
The combination of fludarabine, cyclophosphamide, and rituximab (FCR) is currently considered the treatment of choice in physically fit patients with chronic lymphocytic leukemia (CLL). However, many patients cannot tolerate this aggressive treatment because of advanced age and/or serious comorbid conditions. For these patients, chlorambucil has remained the standard treatment and emerging treatments include combining chlorambucil with monoclonal antibodies such as rituximab, ofatumumab, and GA-101, as well as bendamustine and lenalidomide. Additionally, small retrospective studies have shown promising results with low-dose fludarabine-based regimens.

At EHA 2011, Smolej and colleagues presented the results of their study that assessed the efficacy and toxicity of low-dose FCR in elderly and/or comorbid CLL patients.1

Study design
• Elderly and/or comorbid CLL or small lymphocytic lymphoma (SLL) patients who were deemed unfit for full-dose FCR (first-line or relapsed treatment) were included in this study.
• Six 28-day cycles were administered.
• Fludarabine was administered at 50% of the full dose (12 mg/m² intravenously or 20 mg/m² orally on days 1–3).
• Cyclophosphamide was administered at 60% of the full dose (150 mg/m² intravenously or orally on days 1–3).
• Rituximab was administered at a dose of 375 mg/m² on day 1 of cycle 1 and at 500 mg/m² on day 1 of cycles 2–6.
• Antimicrobial prophylaxis with sulfamethoxazol/trimethoprim and aciclovir or equivalents was recommended and supportive therapies included antiemetics and allopurinol.

Key findings
• Between March 2009 and June 2011, 111 patients from 14 centres have been treated.
  • 105 patients had CLL and six had SLL.
  • The median age was 70 years (range: 58–87 years).
  • The median cumulative illness rating score was 4 (range: 0–14).
  • 58 patients were receiving first-line therapy and 53 were being treated for relapsed CLL.
  • Advanced Rai stages (III/IV) were present in 63% of patients; 37% had bulky disease; IgVH was unmutated in 73%; del 11q was present in 30%, and del 17p in 4%.
• Based on intention-to-treat principle, the overall response rate (ORR) and complete response rate (CR; including clinical CR [cCR] and CR with incomplete blood count recovery [CRI]) was 79% and 41% in first-line treatment, and 73% and 31% in relapsed patients, respectively. (Table 1)
• Data on progression-free survival (PFS) and overall survival (OS) are not yet available.
• Serious (grade 3–4) neutropenia occurred in 55% of first-line patients and 49% of relapsed patients, thrombocytopenia in 7% of first-line patients and 18% of relapsed patients, and anemia in 12% of first-line patients and 15% of relapsed patients. Serious infections were diagnosed in 12% of first-line patients and 8% of relapsed patients. (Table 2)

<table>
<thead>
<tr>
<th>Therapeutic response</th>
<th>First-line (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>79</td>
<td>73</td>
</tr>
<tr>
<td>Complete response (+cCR, CRI)</td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

cCR = clinical complete response (all criteria fulfilled but bone marrow biopsy not performed); CRI = complete response with incomplete bone marrow recovery
Table 2. Severe (grade 3–4) toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>First-line (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Infections</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

Key conclusions

- Treatment of elderly and/or comorbid CLL and SLL patients with low-dose FCR demonstrated promising results despite unfavourable prognostic profiles.
- Toxicity was acceptable and manageable, with frequent serious neutropenia though relatively low serious infections.
- Longer follow-up is needed for PFS and OS data, as well as quality of life results.


Canadian perspective by Dr. Bernard Lemieux

Chronic lymphocytic leukemia (CLL) is typically a disease of the elderly. As such, patients often have comorbidities that impact fitness levels and the ability to tolerate aggressive treatment. There are a number of tools to help physicians assess patient fitness. The most commonly used tool is the Eastern Cooperative Oncology Group performance status (ECOG PS). The ECOG is a five-point scale used to evaluate how the disease is progressing, assess how it affects the patient’s daily living, determine prognosis, and determine appropriate treatment. Another tool is the significantly more detailed Cumulative Illness Rating Score (CIRS), which evaluates multi-morbidity by measuring the chronic medical illness burden in 14 systems using a five-point severity scale.

When making treatment decisions, physicians consider several factors in addition to age and comorbidities to determine whether a patient should be given more aggressive treatment. These include the patient’s wishes with respect to what side effects they can or are willing to tolerate. In some cases, older patients opt for a milder treatment knowing that CLL is incurable and quality of life may be more important than treatment efficacy. Additionally, a patient’s “entourage” (i.e., social support, family, and friends) plays an important role. Often, hematologists must rely on intuition, rather than a formal assessment to make the optimal treatment recommendations for their patients. In my practice, I start by trying to get a sense of the patient’s wishes and tolerance for side effects, and this is followed by applying the ECOG PS. While CIRS is a very thorough all-inclusive tool for assessing co-morbidities, it is often impractical to apply routinely; however, the questions of the CIRS tool generally serve as a guide rather than a formal assessment.

The combination of fludarabine, cyclophosphamide, and rituximab (FCR) is considered the treatment of choice in fit CLL patients. For patients not suitable for FCR therapy, alternatives include fludarabine and rituximab (FR), or chlorambucil monotherapy. Patient preference is also important, as quality of life may be their greatest concern. There are a number of new agents in development, such as ofatumumab and GA101, which may prove extremely useful for the treatment of CLL. These agents may be used in combination with chemotherapy or in a maintenance setting. A key objective of ongoing research in CLL is to identify treatment options that are less toxic than FCR, but more effective than chlorambucil alone.
Canadian perspective by Dr. Bernard Lemieux (cont’d)

The phase II study by Hillman, et al. examined the use of rituximab and chlorambucil (R-chlorambucil) as first-line therapy for patients with previously untreated CLL. Treatment options for elderly, frail patients with CLL who are unlikely to tolerate more aggressive therapy with FCR are limited, with chlorambucil monotherapy often being used for these patients. The addition of rituximab to chlorambucil is easy to use, appears to improve response and duration of response, and has a side effect profile similar to chlorambucil alone. The positive results of this study justify proceeding to phase III studies, which will confirm these outcomes and determine if the benefits observed translate to a survival advantage. More data will allow us to evaluate the true impact of this treatment combination; however, with rituximab's excellent track record and solid data in phase III studies for other indications, one can reasonably expect positive data in the setting of CLL.

One potential caveat to the use of this treatment combination is that chlorambucil is administered orally, while rituximab is administered by intravenous infusion. Infusions require regular hospital or clinic visits, which can be challenging for the elderly in particular, and it may be difficult to adopt this regimen unless efficacy is dramatically improved.

Del Poeta, et al. used a different approach to improve efficacy by studying induction with fludarabine combined with rituximab, followed by rituximab consolidation and maintenance. Maintenance therapy is another way to improve response and duration of response because it avoids the toxicity of chemotherapy. This study demonstrates a logical evolution of treatment options for CLL. Maintenance therapy has proven to be effective in other indolent lymphomas, so one might expect it to be effective in CLL as well. The concept of maintenance in CLL is relatively new because until recently we did not have drugs that enabled patients to achieve a complete response (CR). However, now that we can achieve CRs, maintenance therapy is the natural next step to further improve outcomes.

Rituximab is an ideal drug for maintenance therapy. It is easy to use, effective, and well tolerated. However, there are several concerns with the use of rituximab in this setting. Early data suggest that rituximab activity, particularly at the doses used in this study, may be lower in CLL than in other lymphomas, such as follicular lymphoma. Therefore, rituximab may not be the best agent for maintenance in CLL. Also, intravenous administration of rituximab may limit its use in the elderly, who may have difficulty making monthly visits to a hospital. Subcutaneous administration of rituximab is currently being studied, which may make it possible for patients to receive the drug at home. Additionally, the scheduling of rituximab with fludarabine in the induction phase might have been suboptimal.

It might have been better to administer rituximab with every dose of fludarabine in induction followed by consolidation and maintenance. Also, the use of fludarabine upfront in CLL may lead to immunosuppression and then infections may become an issue, particularly in the maintenance phase. However, these concerns are hypothetical and the efficacy and safety of this induction and consolidation/maintenance regimen need to be confirmed in phase III studies.

Seymour, et al. presented interim efficacy and safety results of a phase II study of navitoclax. Navitoclax, a Bcl-2 inhibitor, is a new agent with a different mechanism of action from current agents and appears to have promising preliminary results. Results of this study showed that there were no unexpected or unmanageable toxicities with the use of navitoclax. As monotherapy, there is some evidence of its anti-tumour activity in heavily pretreated patients, but this needs to be confirmed in phase III studies. Efficacy will likely improve if navitoclax is combined with chemotherapy, and its tolerable side effect profile suggests it will not add significant toxicity. An additional benefit of navitoclax is that it can be taken orally, which makes it suitable for maintenance therapy.

Smolej and colleagues attempted to temper the toxicity of FCR therapy using reduced doses of fludarabine and cyclophosphamide in this treatment combination. This was a sound alternative to standard dosing and results were promising. The lower dose version of FCR was less toxic than the full dose, but the true impact on efficacy remains unknown. There is a fine line between lower dose and equivalent efficacy. The incidence of neutropenia remained quite high in patients treated with reduced-dose FCR. An alternative approach might have been to drop cyclophosphamide and use FR at the full dose. In my own practice, my treatment of choice for elderly, frail patients is either FR or chlorambucil, depending on the patient’s wishes and what he/she can tolerate.

It is evident that there are varied approaches or “recipes” for effective, tolerable treatment options in elderly and comorbid CLL patients. The best approach for a physician is the one in which expectation can be clearly communicated and side effects comfortably managed. Ideally, every physician will have a core group of treatment combinations they are comfortable administering. At this time, the challenge is comparing the outcomes of phase II studies, because of the varied populations. It is clear that at some point, a phase III study for older, frailer CLL patients will be necessary, but it is very encouraging that so many options exist, ranging from new drugs and new antibodies to incorporating maintenance therapy and using reduced-dose regimens. The true efficacy of these options remains to be thoroughly evaluated in phase III studies.
Canadianizing a New Standard of Care in CLL

Treatment with rituximab in combination with fludarabine plus cyclophosphamide (FCR) has dramatically improved the outcome of patients with chronic lymphocytic leukemia (CLL). For patients who can tolerate it, first-line treatment with FCR is now considered to be the standard of care in CLL across Canada. Despite the success of the FCR regimen, a number of questions exist on its optimal administration.

The following paper is the second of a series examining key challenges faced in the administration of FCR in Canada. Future papers will address issues such as supportive care for patients receiving FCR and use of the oral formulations of fludarabine and cyclophosphamide. By addressing the challenges related to the administration of FCR, patients are more likely to complete all treatment cycles, thereby increasing efficacy and resulting in improved outcomes.

Managing hematological toxicities with FCR

Tina Crosbie, BSc Pharm, ACPR;1 James Johnston, MD (FRCPC);2 Jennifer Daley-Morris, BSc Pharm;3 Marc Geirneart, BSc Pharm2

1The Ottawa Hospital, Ottawa, Ontario; 2CancerCare Manitoba, Winnipeg, Manitoba; 3Stronach Regional Cancer Centre

Medical Writer: Anna Christofides MSc, RD, New Evidence

Background

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world, representing approximately 30% of all leukemias.1,2 Although predominantly characterized by neoplastic B-cells, CLL is clearly distinctive from other leukemic diseases and B-cell tumours.3 In CLL, an accumulation of abnormal B-lymphocytes in the blood, bone marrow, lymph nodes, and spleen causes overcrowding, suppressing the formation and function of blood and immune cells. In addition, malignant lymphocytes do not function normally, further reducing the body's ability to fight infection.

Bone marrow infiltration by CLL cells can result in a number of cytopenias, which are predictive of poor prognosis in patients with CLL.2,3 In addition, CLL is characterized by a high prevalence of autoimmune disease such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenia purpura (ITP), pure red cell aplasia (PRCA), and autoimmune agranulocytosis (AIG).

Immune incompetence is another key feature of CLL, characterized by progressive hypogammaglobulinemia and impaired ability of cell-mediated immunity to recall antigens.2 Patients with CLL are therefore at increased risk of infections, which are a common cause of morbidity and mortality.1 In CLL patients, especially those with neutropenia, bacteremia and pneumonia are commonly seen.

The addition of rituximab to fludarabine and cyclophosphamide (FCR) has dramatically improved remission duration and survival of patients with CLL, as evidenced in the landmark CLL-8 study by Hallek, et al. (2010).4 However, chemotherapeutic regimens such as FCR also increase the risk of cytopenias and opportunistic infections.1,4,5 Effective monitoring and management of cytopenias and infections is therefore of key importance in the treatment of CLL.

Given the impact of CLL and its treatment on the bone marrow and the immune system, it is important to effectively manage hematologic toxicities. Despite the recognition of this concern, strategies to manage these complications vary within and between Canadian institutions. This paper is a general discussion on the management of hematological toxicities in CLL patients treated with FCR. However, it does not reflect a true evidence-based guideline process with a systematic literature review and is not meant to be used as a consensus guideline. The management and prevention of infections through appropriate prophylaxis is beyond the scope of this paper but is an important focus for future discussions.
Selecting patients for treatment with FCR

Patient fitness and comorbidities should be considered in treatment decisions to determine whether aggressive therapies such as FCR can be tolerated. Several systems exist for determining patient fitness, two of the most common being the Eastern Cooperative Oncology Group (ECOG) Performance Status and the Cumulative Illness Rating Scale (CIRS). In determining whether a patient can be categorized as fit, a combination of these scoring systems should be used.6

In 1982, ECOG developed a set of performance status criteria that categorizes patients into one of five categories from high to low levels of physical function. (Table 1) These categories were designed to assess how the patient’s disease affects daily living.7 The ECOG Performance Status categories are also commonly used within the context of CLL to assess treatment intensity and determine whether elderly patients could be included in specific clinical trials.7

Once a fitness score has been determined based on a combination of the systems discussed, it is possible to group patients into a fit or frail group. (Table 2)

By using the methods described above to determine patient fitness, treatment decisions can be made that balance efficacy and individual patient tolerability. If patients are determined to be fit according to the above criteria, FCR is a reasonable first-line treatment option. However, if patients are identified as frail, alternative, less toxic treatment regimens should be used. Less aggressive treatment options that can be considered in frail patients include fludarabine; chlorambucil; or cyclophosphamide, vincristine, and prednisone (CVP); with or without rituximab. For patients with a CIRS score ≥6 and/or ECOG >2 but with renal dysfunction, FCR may still be appropriate in some patients (e.g., CrCl 50–70 mL/min). Fludarabine with rituximab (FR) can be considered with a reduced dose of fludarabine for patients with poor renal function. In addition, for patients falling in between the fit and frail categories, or for those requiring a less aggressive regimen, FR is also a reasonable option. By using these selection methods to eliminate frail patients, hematological toxicities may be minimized or even eliminated completely with the use of FCR.

Managing cytopenias

In determining the appropriate strategy for managing CLL patients with hematological toxicities, it is important to determine whether these are related to the disease itself or to treatment with chemotherapeutic regimens such as FCR. Prior to treatment, bone marrow suppression as a result of CLL itself can lower blood counts due to overcrowding with abnormal lymphocytes. Thus, it is important to treat the disease to restore blood counts. As treatment with FCR also causes myelosuppression, low counts seen with later treatments (cycles 4–6) may occur as a result of chemotherapy itself. At later points in the disease, delaying treatment is therefore appropriate to ensure bone marrow recovery and prevent further toxicity.

Since patients with CLL have low blood counts to begin with, standard criteria for grading hematologic toxicities cannot be applied.6 Therefore, to adequately monitor blood counts and manage cytopenias effectively, it is important to assess baseline counts prior to treatment to establish a basis for comparison.

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**Table 1. ECOG Performance Status categories**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

*Adapted from Oken, et al 1982*  
*ECOG = Eastern Cooperative Oncology Group*

**Table 2. Patient fitness types**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Description</th>
</tr>
</thead>
</table>
| Fit group | ECOG Performance Status 0–2  
CIRS ≤ 6 |
| Frail group | ECOG Performance Status 3–4  
CIRS >6 |

*CIRS = Cumulative Illness Rating Scale;  
ECOG = Eastern Cooperative Oncology Group*
Once treatment is initiated, periodic blood counts should be documented and compared to baseline levels rather than to normal lab values in order to assess progress. A grading scale of hematologic toxicities for use in CLL was developed by the International Workshop for CLL (IWCLL) and is presented in Table 3. For lower risk patients, blood counts should be monitored 1–2 times per cycle, with more extensive monitoring in earlier cycles. In higher risk patients, such as those with low platelet levels at baseline, weekly blood counts are recommended. Although most patients had hematologic impairment at baseline either as a result of their disease or prior therapy, use of fludarabine may cause cumulative myelosuppression. Since patients are already immuno-compromised, administration of fludarabine and cyclophosphamide (FC) requires careful hematologic monitoring.

Recombinant granulocyte colony-stimulating factor (rG-CSF) is a supportive care agent that stimulates neutrophil proliferation, differentiation, and activation. The 2006 American Society of Clinical Oncology (ASCO) guidelines on the use of white blood cell growth factors recommends the use of G-CSF when the anticipated frequency of febrile neutropenia exceeds 20% or in patients considered at high-risk because of comorbidities (e.g., extensive prior chemotherapy or pelvic radiotherapy, neutropenia existent prior to chemotherapy, or active infection). In addition, the protocol for the CLL-8 study mandated the use of G-CSF in the event of neutropenia with fever >38.5 °C or hypothermia with or without suspected or documented infection. In the CLL-8 study, 45% of patients treated with FCR and 23% of patients treated with FC received G-CSF during the course of their disease.

Use of growth factors may be useful in certain patients with infection or disease-related bone marrow suppression. However, when neutrophil counts are reduced after cytotoxic therapy, administering growth factors may elevate ANCs, giving physicians a false sense of security that continuing treatment can be done safely. When treatment is resumed prematurely, complete recovery may not have occurred, causing further damage to bone marrow. Further bone marrow damage can impede the ability to give subsequent treatments, resulting in a poorer prognosis for these patients. Therefore, when neutrophil counts are reduced as a result of treatment, FCR should be delayed to allow for adequate recovery before resuming therapy. Determining the cause of neutropenia is necessary to determine the correct course of action. Generally, when neutropenia occurs early in the disease course, such as between cycles 1 and 3, growth factors may be considered while waiting for bone marrow clearance. Beyond early disease, growth factors should only be used to prevent recurring infections when neutropenia is accompanied by fever.

### Table 3. Grading of hematologic toxicities in CLL

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Decrease in platelets† or Hb‡</th>
<th>Absolute Neutrophil Count§</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change to 10%</td>
<td>≥2.0 × 10^9/L (2000/mm^3)</td>
</tr>
<tr>
<td>1</td>
<td>11%–24%</td>
<td>1.5–2.0 × 10^9/L (1,500–2,000/mm^3)</td>
</tr>
<tr>
<td>2</td>
<td>25%–49%</td>
<td>≥1.0–1.5 × 10^9/L (1,000–1,500/mm^3)</td>
</tr>
<tr>
<td>3</td>
<td>50%–74%</td>
<td>≥0.5–1.0 × 10^9/L (500 and 1,000/mm^3)</td>
</tr>
<tr>
<td>4</td>
<td>≥75%</td>
<td>&lt;0.5 × 10^9/L (&lt;500/mm^3)</td>
</tr>
</tbody>
</table>

Adapted from Hallek, et al. 2008

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pre-treatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is <20 × 10^9/L (20 000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (i.e. 20 × 10^9/L [20 000/μL]) was present pre-treatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoetin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches <1.0 × 10^9/L (1000/μL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1.0 × 10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to granulocytes. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

### Managing neutropenia

Neutropenia is the most common hematologic toxicity seen in patients with cancer. The administration of cytotoxic chemotherapies, such as cyclophosphamide and fludarabine, generally results in a white blood cell nadir after 5–14 days, with recovery by days 7–21. However, high-dose chemotherapy can extend the duration and deepen the nadir of the neutropenia, increasing the risk of infection. Careful monitoring of absolute neutrophil counts (ANC) and comparison to baseline levels is therefore important to ensure neutropenia is managed appropriately.

Although cytopenias associated with cyclophosphamide are well known, treatment with fludarabine can lead to additional myelosuppression. Myelosuppression with fludarabine generally has a time to nadir of 10–14 days, with recovery between 5–7 weeks. A phase I study in solid tumour patients showed that the median time to nadir counts after treatment with fludarabine was 13 days (range: 3–25 days) for granulocytes and 16 days (range: 2–32 days) for platelets. Although most patients had hematologic impairment at baseline either as a result of their disease or prior therapy, use of fludarabine may cause cumulative myelosuppression. Since patients are already immuno-compromised, administration of fludarabine and cyclophosphamide (FC) requires careful hematologic monitoring.
Before treatment with FCR
Establish baseline blood counts and monitor 1–2 times per cycle in lower risk and weekly in higher risk patients

Neutropenia
Grade 3/4:
ANC <1.0x10⁹/L

Thrombocytopenia
Grade 3/4:
≥50% decrease in platelet count

Anemia
Grade 3/4:
≥50% decrease in Hb

Cycle 1–3 Grade 3/4
Consider using growth factors while waiting for marrow clearance due to disease

1st Grade 3/4 event
• Delay FCR for up to 2 weeks
• Once counts ≥baseline, consider starting subsequent cycles of FCR with 25% dose reductions of F and C

2nd Grade 3/4 event
• Delay FCR for up to 2 weeks
• Once counts ≥baseline, start subsequent cycles of FCR with further dose reductions of F and C

3rd Grade 3/4 event
• Delay FCR for up to 2 weeks
• Once counts ≥baseline, start subsequent cycles of FCR with further dose reductions of F and C
• If counts remain low, FCR should be discontinued

At any point during treatment
Consider platelet transfusion when counts <20,000/µL

At any point during treatment
• If Hb does not rise more than 100 g/L by 8 weeks consider ESAs
• Epoetin or darbepoetin recommended when Hb <100 g/L after treatment
• Hb can be increased to the lowest concentration needed to avoid transfusions
• Hb should not exceed 120 g/L during ESA therapy
• Iron supplementation should be given to augment response to ESAs
• Transfusions of RBCs recommended only for severe anemia with cardiac complications


ANC = absolute neutrophil count; C = cyclophosphamide; ESA = erythropoiesis stimulating agent; F = fludarabine; FCR = fludarabine, cyclophosphamide, rituximab; G-CSF = granulocyte colony-stimulating factor; Hb = hemoglobin
Appropriate upfront selection of patients for treatment with FCR should dramatically reduce the risk of cytopenias in patients with CLL. Therefore, eliminating cyclophosphamide completely to increase neutrophil counts is not recommended. To manage patients with severe neutropenia, treatment delays and dose reductions are appropriate to allow for marrow recovery. In the CLL-8 study, treatment with FCR was delayed and the dose of fludarabine and cyclophosphamide was reduced in patients with grade 3/4 neutropenia.4 (Table 4) Therefore, when the first grade 3/4 cytopenia is reported, FCR treatment should be delayed for up to two weeks until counts reach or exceed baseline levels. Once counts have recovered, treatment with FCR may be resumed, but the dose of fludarabine and cyclophosphamide should be reduced by 25%. If grade 3/4 neutropenia continues to occur, fludarabine and cyclophosphamide should continue to be reduced. If, however, severe neutropenia occurs for three or more cycles, treatment with FCR should be discontinued and less marrow suppressive rituximab combinations, such as FR or cyclophosphamide, rituximab, dexamethasone (RCD), may be considered if the patient can tolerate them and they have active disease. (Figure 1)

Managing thrombocytopenia
Before beginning treatment with FCR, patients may have thrombocytopenia as a result of marrow replacement by their leukemia; the majority have high-risk disease with platelet levels <100,000/μmL.5,6 As with neutropenia, thrombocytopenia may also occur as a result of treatment with FCR.5,15 When severe thrombocytopenia (grades 3/4) occurs after treatment with FCR, treatment delays and dose reductions of fludarabine and cyclophosphamide should be implemented as per the recommendations above for neutropenia. (Table 4 and Figure 1)

Treatment for thrombocytopenia typically involves platelet transfusions, which are commonly given when platelet levels fall below 20,000/μL.10 Common risks associated with platelet transfusions include infection, allergic reactions, transfusion-associated lung injury, and alloimmunization. In addition, refractoriness to platelet transfusion can occur due to the development of antibodies. The development of antibodies can become a significant problem for patients who become dependent upon transfusions, although leukocyte filtration can decrease the incidence of this complication.

Managing anemia
Anemia is a common consequence of cancer and its treatment, occurring in approximately 40% of patients.10 Potential causes of cancer-associated anemia may include direct tumor infiltration of bone marrow; reduced levels of endogenous erythropoietin production; an increase in inflammatory cytokines, such as tumor necrosis factor (TNF) that may directly inhibit erythropoiesis by curbing stored iron utilization; and other contributory factors, such as nutritional deficiencies, hemorrhage, and hemolysis.

The primary treatments for cancer-induced anemia include blood transfusions, erythropoiesis stimulating agents (ESA), such as epoetin alfa; darbepoetin alfa; and iron therapy.10 Decisions regarding treatment must be tailored to each patient based on the degree of anemia, clinical status, and comorbidities. For patients with severe anemia with continued symptoms such as poor cardiac or respiratory function manifesting as dyspnea, cardiac failure, or angina, treatment should include transfusion of packed red blood cells (RBCs). However, for mild to moderate anemia, blood transfusions are not recommended due to the increased risk of infection, allergic responses, transfusion-associated lung injury, and alloimmunization.

### Table 4. CLL-8 protocol for cytopenia-related dose reductions

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>FCR Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Grade 3/4 cytopenia</td>
<td>- Treatment delayed for up to 2 weeks with 25% dose reduction of fludarabine and cyclophosphamide for subsequent cycles</td>
</tr>
<tr>
<td>2nd Grade 3/4 cytopenia</td>
<td>- Treatment delayed for up to 2 weeks with further reduction of fludarabine and cyclophosphamide for subsequent cycles</td>
</tr>
<tr>
<td>3rd Grade 3/4 cytopenia</td>
<td>- Treatment delayed for up to 2 weeks - If no resolution of cytopenia, treatment should be discontinued</td>
</tr>
</tbody>
</table>

Adapted from Hallek, et al. 2010
The 2010 ASCO/ASH guidelines on treating cancer-induced anemia recommend that iron stores be checked at baseline and periodically to optimize symptom improvement.\(^1\)\(^,\)\(^2\) (Table 3 and Figure 1) The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin (Hb) concentration that has decreased to $<100\, \text{g/L}$ in order to decrease RBC transfusions. Transfusions are also an option, depending on the severity of the anemia or clinical circumstances. An optimal level at which to initiate ESA therapy in patients with anemia whose Hb is between 100–120 g/L cannot be definitively determined from the available evidence. Under these circumstances, the decision to initiate ESA treatment should be determined by clinical judgment, consideration of the risks and benefits of ESAs, and patient preferences. Hb can be increased to the lowest concentration needed to avoid transfusions, which may vary by patient and condition. However, the Hb concentration should not exceed 120 g/L during ESA therapy.\(^1\)\(^,\)\(^4\) The guidelines also state that epoetin or darbepoetin are equally effective when treatment calls for ESAs. Regardless of the supportive drug chosen, iron supplementation is advised to augment the response to ESAs.

### Autoimmune complications of CLL

Autoimmune complications occur in around 10–25% of patients with CLL at some point during their disease.\(^2\)\(^,\)\(^3\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^10\) Blood constituents are the main target, resulting in a number of disorders, including AIHA, ITP, PRCA, and AIG. Of these phenomena, AIHA is the most common.

Patients with CLL receiving FCR should be evaluated and closely monitored for signs of autoimmune cytopenias, which occur in around 6.5% of treated patients and may be confused with cytopenias related to marrow suppression.\(^1\)\(^,\)\(^9\) Typically, immune cytopenias should be suspected in patients when there is an isolated fall or delayed recovery in Hb, platelets, or neutrophils.

The development of AIHA following FCR is typically associated with a negative Coomb's test. The diagnosis of PRCA or ITP usually requires a marrow confirmation.\(^2\) These conditions usually respond to prednisone with discontinuation of FCR. Patients not responding to prednisone, or relapsing following tapering of the steroid, usually respond to cyclophosphorine or to combination treatment with RCD.\(^2\)\(^0\)

### Conclusions

CLL is a B-cell malignancy that is distinct from other leukemic diseases and B-cell tumours, with important consequences for its management. The disease itself leads to a number of cytopenias due to overcrowding of bone marrow with abnormal lymphocytes. Although treatment with FCR has improved overall and progression-free survival, cytotoxic regimens such as these can worsen cytopenias through treatment-related myelosuppression.

Upright selection of fit patients who are better able to tolerate more aggressive regimens such as FCR can effectively reduce the risk of cytopenias. Further, by using a combination of tools such as the ECOG and CIRS to categorize patients, treatment decisions can be made based on fitness level to ensure therapy is well tolerated.

Given the distinct nature of CLL from other diseases, standard criteria for grading the severity of cytopenias are not appropriate. It is therefore important to monitor blood counts before and during treatment to effectively manage toxicities. When cytopenias occur as a result of the disease itself, treatment with chemotherapy is important to reduce lymphocyte burden. However, when hematologic toxicities occur as a result of treatment, dose delays and reductions may be necessary to allow adequate recovery of bone marrow. Given the impact of hematological toxicities on adherence to treatment, effective management is crucial to ensure optimal treatment response and remission.

---

APPENDIX A: Calculating the fourteen-system modified Cumulative Index Rating Scale (CIRS)

<table>
<thead>
<tr>
<th>Patient name:</th>
<th>Diagnosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td>Medical details:</td>
</tr>
<tr>
<td>Doctor:</td>
<td></td>
</tr>
<tr>
<td>Hospital ID number / HC #:</td>
<td></td>
</tr>
</tbody>
</table>

### Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No problem affecting that system</td>
</tr>
<tr>
<td>1</td>
<td>Current mild problem or past significant problem</td>
</tr>
<tr>
<td>2</td>
<td>Moderate disability or morbidity and/or requires first-line therapy</td>
</tr>
<tr>
<td>3</td>
<td>Severe problem and/or constant and significant disability</td>
</tr>
<tr>
<td>4</td>
<td>Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment</td>
</tr>
</tbody>
</table>

### Ratings

#### Rated 0
- No problems or healed minor injuries
- Past childhood injuries
- Minor surgery (e.g., amygdalectomy)
- Uncomplicated healed fractures
- Other past problems healed without sequel

#### Rated 1
- Current medical problem with mild discomfort or disability, or occasional exacerbations
- Minor impact on morbidity
- Past significant medical problems not currently an issue
- Major surgery (e.g., hysterectomy)

#### Rated 2
- Medical condition that requires daily treatment (first-line therapy) (e.g., steroids – asthma, H₂ blockers – acid reflux)
- Severe problem
- Moderate disability or morbidity

#### Rated 3
- Chronic conditions that are not controlled with first-line therapy (e.g., B₂ overuse – asthma, symptomatic angina, vaccines for allergic rhinitis)
- Constant significant disability
- Severe problem

#### Rated 4
- Extremely severe problem
- Any acute condition that require immediate treatment (severe bronchospasm, unstable angina)
- Organ failure (end-stage renal disease/dialysis, O₂ for COPD)
- Severe sensory impairment (blindness, deafness, wheelchair-bound)
- Quality of life severely affected, severe functional impairment

### Rating malignancies

#### Rated 1
- Cancer diagnosis without evidence of recurrence in past 10 years, and skin cancer sporadic in past without recurrence or sequel (other than melanoma)

#### Rated 2
- No evidence of recurrence or sequel in past 5 years

### Fourteen-system modified version of CIRS

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>RATING/SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Vascular</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Hematological</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0 1 2 3 4</td>
</tr>
</tbody>
</table>

### Smoking Scale

<table>
<thead>
<tr>
<th>Smoking Level</th>
<th>Pack Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rated 1</td>
<td>Up to 20</td>
</tr>
<tr>
<td>Rated 2</td>
<td>21-40</td>
</tr>
<tr>
<td>Rated 3</td>
<td>Over 40</td>
</tr>
</tbody>
</table>

### Subtotal

New Evidence in Oncology | August 2011 27
Patient name: ____________________________  Date: ____________________________

**Ophthalmological/otorhinolaryngology**
- Any problems with eyes (glaucoma, cataract, loss of vision), ears, nose, throat or voice issues (loss of hearing, vertigo/dizziness unless neurological)
- Any medications taken for above

**Upper gastrointestinal**
- Any problem with stomach and/or digestion (esophagus, duodenum)
- Any medications taken for above
- Surgery for stomach or esophagus

**Lower gastrointestinal**
- Any intestinal problems (intestinal hernia, constipation, incontinence or anal problems)
- Any medications taken for above
- Abdominal surgery

**Hepatic/pancreatic**
- Any liver or pancreas problems
- Any medications taken for above
- Surgery for liver or pancreas (cholecystectomy rated here)

**Renal**
- Any kidney problems (impairment in function, infections)
- Any medications taken for above
- Surgery for kidneys

**Genitourinary**
- Any urinary problems (lithiasis, incontinence)
- Any medications taken for above
- Surgery for bladder or renal lithiasis

**Musculoskeletal & tegumental**
- Any problems in the skin, joints, bones, muscles (arthritis, osteoporosis, carpal tunnel, fibromyalgia and any other skin/musculoskeletal problem)
- Any medications taken for above (anti-inflammatory, infiltrations, creams)

**Neurological**
- Any neurology problems (cerebrovascular disease, accidents, peripheral neuropathy, headaches)
- Any medications taken for above
- Surgery for these problems

**Endocrine, metabolic, breast**
- Any problems of thyroid, obesity, diabetes, or hormonal problems
- Obesity ____________________________ 
  Rated 1 - BMI ≥ 30
- Any medication or surgery for any of these problems
  Rated 2 - BMI ≥ 30 + meds or moderate disability
- Any problems with breasts (dysplasia, cancer)
  Rated 3 - BMI ≥ 45
- Surgery for these problems
- Menopause/andropause, any hormone ____________________________ 
  Rated 0 – without hormonotherapy or symptoms
  Rated 1 – symptomatic or with hormonotherapy

**Psychiatric**
- Any problems of depression, anxiety, alcohol or drug abuse, or other problems
- Personality problems/disorders
- Any medications taken for above

**TOTAL SCORE**
- Only one score is given for each system
- Total score = sum of all scores

Adapted from Linn BS, et al, and Hudon C, et al.1-3

**References:**

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**Subtotal from front**

<table>
<thead>
<tr>
<th>System</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmological/otorhinolaryngology</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Lower gastrointestinal</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hepatic/pancreatic</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal &amp; tegumental</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Neurological</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Endocrine, metabolic, breast</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
New Approaches to Treatment in Follicular Lymphoma

When making treatment decisions for patients with follicular lymphoma (FL), an indolent and usually incurable disease, quality of life (QoL) is a high priority for both the patient and the physician. Treatment has traditionally consisted of either employing a watch-and-wait strategy, or using single-agent regimens until disease progression to the point of requiring more aggressive therapy.

With the development of new treatment regimens and the approach to improve survival in FL, physicians believe that first-line treatment should be more aggressive in order to achieve this goal. This is supported by the recent observation that improved survival is at least in part dependent on the quality of response to first-line treatment. In patients requiring therapy, immunochemotherapy is the standard of care. New therapeutic strategies currently in development include varying both the chemotherapy and the antibody components in immunochemotherapy. Promising agents include bortezomib combined with rituximab instead of the standard chemotherapy combinations of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); or fludarabine plus cyclophosphamide (FC).

Alternately, new antibodies such as GA101 could be combined with the classic chemotherapy regimens. Data from studies examining the above issues in FL were presented at ICML and EHA 2011:

- The preliminary results of a phase III study presented at ICML 2011 demonstrated that patients who were treated with rituximab maintenance instead of undergoing watchful waiting had improved emotional wellbeing, and QoL evaluations showed a benefit for rituximab therapy.
- A phase III study comparing bortezomib-rituximab with rituximab presented at EHA 2011 demonstrated that bortezomib-rituximab was tolerable and feasible, and resulted in improved outcomes. Furthermore, this study supported the notion that achieving higher quality responses to previous treatment was associated with greater clinical benefit in both treatment arms.
- Preliminary results from a phase Ib study combining a novel type II monoclonal antibody against CD20 (GA101) at high and low doses with chemotherapy were presented at EHA 2011 and indicated that G-CHOP and G-FC are safe and highly effective treatments for patients with relapsed FL.

Preliminary results of QoL analyses from the intergroup phase III randomized trial of rituximab vs. watch and wait approach in patients with FL

Background
Little is known about the quality of life (QoL) of patients with advanced stage asymptomatic follicular lymphoma (FL) who are not treated immediately but rather undergo watchful waiting. This study by Ardeshna and colleagues was designed to compare immediate treatment with rituximab with watchful waiting. It was powered for both clinical outcome and QoL, and the results were presented at ICML 2011.1

Study design
• Eligible patients with advanced stage, asymptomatic, non-bulky FL were randomized between watchful waiting, rituximab induction (four weekly doses), and rituximab induction followed by rituximab maintenance over two years (four weekly doses followed by one dose every two months for two years).
• QoL was assessed before and after randomization. If no new therapies were initiated, QoL was assessed one month after randomization and then every two months for two years, followed by every six months for two years.
• QoL questionnaires used were:
  • Functional Assessment of Cancer Therapy (FACT-G) with four additional questions relating to worries about:
    – Their disease becoming more aggressive;
    – Requiring therapy;
    – Being unable to support themselves or their family;
    – Having difficulty planning for the future.
  • Hospital Anxiety and Depression Scale (HADS)
  • Mental Adjustment to Cancer Scale
  • Impact of Event Scale – revised
  • Illness Impact Bank
  • Illness Coping Style
• The primary aim was to determine if at seven months after randomization:
  • Immediate treatment with rituximab increased functional wellbeing;
  • Deferring treatment results in increased anxiety and depression;
  • Increased clinic visits and the side effects related to the administration of rituximab negatively impacted wellbeing.
• The secondary aims were the same at 13, 25, and 37 months.
• Except for HADS subscale, all subscale scores were standardized on a 100-point scale, with 100 indicating perfect health.
• A change of five to10 points was regarded as a minimal clinically important difference, and a p-value of <0.01 was considered to be statistically significant.
• At the time of presentation, data had been analyzed for baseline, month 7, and month 13.

Key findings
• Between September 2004 and May 2009, 463 patients were randomized in this study.
• 456 of these patients participated in the QoL portion of this study.
• Baseline QoL was similar between arms: mean scores were 89, 84, 73, and 80 for physical, social/family, emotional, and functional wellbeing, respectively.
• At baseline, 27% of patients had borderline or case anxiety, and 9% had borderline or case depression.
• At months 7 and 13, emotional wellbeing significantly improved in all arms with a mean difference greater than five.
• The greatest improvement was in rituximab maintenance group. (Figure 1)
• Anxiety was unchanged in the watchful waiting and rituximab induction arms, but significantly reduced in the rituximab maintenance arm from 11.0% (baseline) to 6.6% by month 13 (p = 0.00005). (Table 1)

• Depression was unchanged from baseline to month 7 or month 13.

• Mental adjustment to cancer improved significantly from baseline to month 7 or month 13 in the rituximab maintenance arm and patients felt more in control of their situation, but this was not observed in the rituximab induction or watchful waiting arms. (Table 2)

• There was a trend for patients receiving rituximab maintenance to be less worried about their disease becoming more aggressive at month 7 and this trend became highly significant at month 13.

• At month 7, patients in the watchful waiting arm were more likely to be worrying about requiring treatment (or more treatment) than patients receiving rituximab maintenance.

• Patients receiving rituximab maintenance were significantly less worried about supporting themselves or their family by month 13 than patients in watchful waiting.

• In terms of difficulty in planning for the future, there were some improvements in all treatment arms from baseline to month 7 or month 13, but these were not significant.

### Table 1. HADS – anxiety

<table>
<thead>
<tr>
<th></th>
<th>Baseline (%)</th>
<th>Month 7 (%)</th>
<th>Month 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Watchful waiting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>71.3</td>
<td>76.5</td>
<td>77.4</td>
</tr>
<tr>
<td>Borderline anxiety</td>
<td>10.8</td>
<td>10.6</td>
<td>13.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17.8</td>
<td>12.9</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Rituximab induction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>79.2</td>
<td>75.4</td>
<td>77.8</td>
</tr>
<tr>
<td>Borderline anxiety</td>
<td>11.7</td>
<td>15.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9.1</td>
<td>8.8</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Rituximab maintenance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>71.1</td>
<td>79.0</td>
<td>86.1</td>
</tr>
<tr>
<td>Borderline anxiety</td>
<td>17.9</td>
<td>12.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.0</td>
<td>8.8</td>
<td>6.6</td>
</tr>
</tbody>
</table>

### Table 2. Mental adjustment to cancer

<table>
<thead>
<tr>
<th></th>
<th>Change from baseline to month 7</th>
<th>Change from baseline to month 13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Watchful waiting</strong></td>
<td>-3.49</td>
<td>+1.56</td>
</tr>
<tr>
<td></td>
<td>p = 0.17</td>
<td>p = 0.50</td>
</tr>
<tr>
<td><strong>Rituximab induction</strong></td>
<td>-0.79</td>
<td>-0.22</td>
</tr>
<tr>
<td></td>
<td>p = 0.78</td>
<td>p = 0.94</td>
</tr>
<tr>
<td><strong>Rituximab maintenance</strong></td>
<td>+8.53</td>
<td>+9.06</td>
</tr>
<tr>
<td></td>
<td>p &lt;0.0001</td>
<td>p &lt;0.0001</td>
</tr>
</tbody>
</table>
Key conclusions

■ At baseline, the physical, social, and functional wellbeing is high in all patients, while emotional wellbeing is relatively reduced.
  • There is an increase in case anxiety relative to the normal population, the cause of which was likely worry about the disease becoming more aggressive and the need for treatment.
  • There is also an increase in case depression relative to the normal population.

■ The negative impact of the diagnosis of FL lessens with time.

■ Emotional wellbeing and additional concerns improved, and this was greater in the rituximab maintenance group compared with watchful waiting. Patients on watchful waiting were more likely that patients on rituximab maintenance to:
  • Be worried about the disease becoming more aggressive;
  • Be worried about the need for therapy;
  • Be worried about their ability to support themselves or their family;
  • Not feel in control of their situation;
  • Have negative associations with hospital visits;
  • Avoid thinking about or learning about their illness;
  • Have reduced improvement in emotional wellbeing.

■ None of the QoL scales used in this study showed a benefit for watchful waiting over rituximab induction or rituximab maintenance.


Bortezomib-rituximab results in improved PFS and response rates vs. Rituximab, and quality of response is associated with improved outcomes, in patients with relapsed FL

Background
Outcomes in patients with follicular lymphoma (FL) have improved in recent years because of the introduction of new therapies, and the quality of response to first-line therapy is associated with improved survival.\(^1\) Rituximab is approved for relapsed/refractory FL and it is a widely used treatment in newly diagnosed and relapsed FL.\(^2\) Bortezomib has shown activity as a single agent in heavily pre-treated indolent lymphoma patients.\(^3\) In combination with rituximab, bortezomib has shown activity in a randomized phase II study in FL and other non-Hodgkin lymphoma subtypes.\(^4,5\)

In this study, Coiffier and colleagues report on the overall efficacy and safety results of the international, multicentre, phase III LYM3001 study that compared bortezomib-rituximab with rituximab alone in patients with relapsed or refractory rituximab-naïve or rituximab-sensitive FL. Additionally, analyses were conducted to determine the impact of quality of response to treatment on outcomes. The results were presented at EHA 2011.\(^6\)

Study design
  • Patients with grade 1 or 2 measurable, relapsed FL with a time to progression (TTP) of six or more months for prior rituximab-containing therapy were enrolled.
  • Patients were randomized in a one-to-one ratio to receive five five-week treatment cycles consisting of bortezomib (1.6 mg/m\(^2\) on days 1, 8, 15, 22, all cycles) plus rituximab (375 mg/m\(^2\), days 1, 8, 15, 22, cycle 1, and day 1, cycles 2–5), or rituximab alone on the same schedule.
• The primary endpoint was progression-free survival (PFS).
• Secondary endpoints included overall response rate (ORR), complete response (CR)/unconfirmed CR (CRu) rates, duration of response (DOR), TTP, and one-year overall survival (OS), as well as safety and tolerability.

**Key findings**

**Patients**

• A total of 676 patients were enrolled to receive bortezomib-rituximab (n = 336) or rituximab alone (n = 340).

• The baseline characteristics were generally well balanced between the study arms.
  ◦ The median age was 57 years in the bortezomib-rituximab arm (range: 24–83 years) and 57 years in the rituximab arm (range: 21–84 years).
  ◦ 43% and 44% had received prior rituximab, respectively.

• Patients in both arms received a median of five cycles of therapy (range: 1–5 cycles).
  ◦ 71% and 72% of the patients in the bortezomib-rituximab and rituximab arms, respectively, completed all five cycles.
  ◦ 17% and 23% of patients, respectively, discontinued study therapy prior to completing all five cycles due to disease progression.

**Efficacy**

• After a median follow-up of 33.9 months, the median PFS was 12.8 months for bortezomib-rituximab vs. 11.0 months with rituximab. (Figure 1)

• PFS was evaluated in prespecified subgroups and bortezomib-rituximab had the greatest clinical benefit in patients younger than 65 years, those receiving second- or third-line therapy, those who were rituximab-naïve, those who had more than one year since their last therapy, and those with adverse prognostic factors.

• The ORR (CR/CRu + PR) was 63% vs. 49% ($p < 0.001$) in the bortezomib-rituximab and rituximab arms, respectively, including 25% vs. 18% CR/CRu ($p = 0.035$). (Table 1)

• Median DOR was 16.0 and 13.8 months, with 50% and 32% of patients in the bortezomib-rituximab arm and 38% and 23% in the rituximab arm having durable responses for six and 12 months, respectively. (Table 1)

• In both arms, PFS was significantly longer in patients who achieved CR/CRu vs. PR vs. no response (NR).
  ◦ In the bortezomib-rituximab arm the median PFS was 32.6, 13.6, and 4.5 months, respectively;
  ◦ In the rituximab arm the median PFS was 33.1, 14.1, and 4.7 months ($p \leq 0.01$ for all comparisons). (Figure 2)
Figure 2. Progression-free survival by treatment arm and response to treatment

Table 1. Response rates and durability of response

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib-rituximab (n = 315)</th>
<th>Rituximab (n = 324)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>63</td>
<td>49</td>
<td>0.569 (0.415–0.780)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>25</td>
<td>18</td>
<td>0.665 (0.455–0.973)</td>
<td>0.035</td>
</tr>
<tr>
<td>PR</td>
<td>38</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>25</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>16.0 (12.6–20.9)</td>
<td>13.8 (11.8–16.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median DOR (CR/CRu)</td>
<td>28.6 (21.6–NE)</td>
<td>30.9 (14.2–NE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durable response (≥6 months) rate, %</td>
<td>50</td>
<td>38</td>
<td>0.608 (0.444–0.833)</td>
<td>0.002</td>
</tr>
<tr>
<td>Durable (≥6 months) CR/CRu</td>
<td>24</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durable response (≥12 months) rate, %</td>
<td>32</td>
<td>23</td>
<td>0.636 (0.448–0.904)</td>
<td>0.012</td>
</tr>
<tr>
<td>Durable (≥12 months) CR/CRu</td>
<td>18</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval; CR = complete response; CRu = unconfirmed complete response; DOR = duration of response; NE = not evaluable; ORR = overall response rate; PR = partial response
Similarly, higher quality of response was associated with longer TTP, time to next treatment (TTNT) and treatment-free interval (TFI) in both treatment arms. (Table 2)

The median TTP was 13.3 vs. 11.3 months, the median TTNT was 23.0 vs. 17.7 months and the median TFI was 17.7 vs. 13.0 months in the bortezomib-rituximab and rituximab arms, respectively. (Table 2)

The one year OS rates were 90.1% and 90.5% with bortezomib-rituximab vs. rituximab, respectively. (Table 2)

Safety

The rates of adverse events (AEs), grade ≥3 AEs, serious AEs (SAEs), dose reductions, and treatment withdrawals were higher in the bortezomib-rituximab arm than in the rituximab arm.

In the bortezomib-rituximab and rituximab arms, 46% and 21% of patients had grade ≥3 AEs, 18% and 11% had SAEs, and 16% and 1% had peripheral neuropathy (PN; 3% and 0% were grade ≥3; most of which were reversible), respectively.

**Table 2. Outcomes by treatment arm: overall and by response to treatment**

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib-rituximab (n = 336)</th>
<th>Rituximab (n = 340)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP – ITT, months (95% CI)</td>
<td>13.3 (11.5–15.9)</td>
<td>11.3 (9.2–12.3)</td>
<td>0.808 (0.668–0.977)</td>
<td>0.027</td>
</tr>
<tr>
<td>TTP, patients with CR/CRu</td>
<td>32.6</td>
<td>33.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TTP, patients with PR</td>
<td>13.7</td>
<td>14.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TTP, patients with NR</td>
<td>4.6</td>
<td>4.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median TTNT – ITT, months (95% CI)</td>
<td>23.0 (19.7–28.0)</td>
<td>17.7 (15.5–21.3)</td>
<td>0.799 (0.657–0.971)</td>
<td>0.024</td>
</tr>
<tr>
<td>TTNT, patients with CR/CRu</td>
<td>NE</td>
<td>NE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TTNT, patients with PR</td>
<td>28.0</td>
<td>23.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TTNT, patients with NR</td>
<td>9.1</td>
<td>7.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median TFI – ITT, months (95% CI)</td>
<td>17.7</td>
<td>13.0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TFI, patients with CR/CRu</td>
<td>NE</td>
<td>NE</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TFI, patients with PR</td>
<td>22.7</td>
<td>18.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TFI, patients with NR</td>
<td>4.4</td>
<td>3.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1-year OS rate – ITT, % (95% CI)</td>
<td>90.1 (86.9–93.4)</td>
<td>90.5 (87.4–93.7)</td>
<td>0.971* (0.712–1.325)</td>
<td>0.854</td>
</tr>
</tbody>
</table>

*HR for OS between arms*  
95% CI = 95% confidence interval; CR = complete response; CRu = unconfirmed complete response; HR = hazard ratio; ITT = intent to treat; NE = not evaluable; NR = no response; OS = overall survival; PR = partial response; TFI = treatment-free interval; TTNT = time to next treatment; TTP = time to progression.

**Key conclusions**

- Bortezomib-rituximab resulted in improvements in PFS, ORR, CR/CRu rates, DOR, and other outcomes compared with rituximab alone.
- The toxicity of the treatment was acceptable and though AE rates were higher with bortezomib-rituximab than with rituximab alone, this did not affect the feasibility of treatment.
- Achievement of CR/CRu vs. PR vs. NR was associated with greater clinical benefit in both arms.
- The longer PFS and TTNT in the bortezomib-rituximab arm were driven by the additional responses with bortezomib-rituximab vs. rituximab, notably higher rates of durable response, CR/CRu, and durable CR/CRu.
- Further studies have begun to build on the bortezomib-rituximab combination.

**References:**  
Interim results from a phase Ib study of the anti-CD20 obinutuzamab (GA101) in combination with FC or CHOP in relapsed/refractory FL

Background
Obinutuzumab (GA101) is a novel type II, glycoengineered, humanized monoclonal anti-CD20 antibody that increases antibody-dependent cellular toxicity (ADCC), directs cell death activity, and lowers complement-dependent cytotoxicity (CDC) compared with type I antibodies including rituximab. GA101 has been shown to be more effective than rituximab in depleting B-cells from whole blood and lymphoid tissue, and in inhibiting the growth of human lymphomas in animal xenograft models, both as a single agent and in combination with chemotherapy. It has also shown efficacy and safety in single-agent studies in non-Hodgkin lymphoma (NHL) and chronic lymphocytic lymphoma (CLL).

Davies and colleagues have undertaken the first study to evaluate the safety and efficacy of combining GA101 with chemotherapy, and interim results of this study were presented at EHA 2011.

Study design
- BO21000 is a phase Ib study of GA101 in combination with fludarabine and cyclophosphamide (G-FC) or cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) in patients with relapsed or refractory follicular lymphoma (FL).
- Patients received either four to six cycles of G-FC every 28 days, or six to eight cycles of G-CHOP every 21 days.
- After stratification to G-FC or G-CHOP, patients were randomized between two dose regimens of GA101, either 400 mg on days 1 and 8 of cycle 1 and 400 mg on day 1 for subsequent cycles, or 1,600 mg GA101 on days 1 and 8 of cycle 1 and 800 mg on day 1 for subsequent cycles.
- Patients who responded to therapy were offered maintenance treatment with GA101 at the induction dose (400 mg or 800 mg) every three months for a maximum of two years, or until progression.
- The primary objective was safety.
- The secondary or exploratory objective was preliminary efficacy.

CR = complete response; FL = follicular lymphoma; G-CHOP = GA101, cyclophosphamide, doxorubicin, vincristine and prednisone; G-FC = GA101, fludarabine and cyclophosphamide; PR = partial response; q3m = every three months
Key findings

- 28 patients were treated with G-FC and 28 were treated with G-CHOP. (Table 1)

At this interim analysis, all 28 G-FC patients and 17 of 28 G-CHOP patients completed induction treatment.

The incidence and severity of adverse events (AEs) during the induction phase were similar in both treatment dose groups with no evidence of increased toxicity with the higher dose of GA101.

The majority of IRRs were grade 1 or 2, with only 7% of patients in both arms experiencing grade 3 or 4 IRRs.

- 15 serious AEs (SAEs) were reported in the G-FC group and six (in five patients) were reported in the G-CHOP group. (Table 2)

There were no treatment- or infection-related deaths.

- Two deaths were reported in the G-FC arm, secondary to progression in one patient and from underlying Parkinson’s disease in the other.
- Of the 137 doses of G-FC delivered, 10 doses in nine patients were delayed due to an AE.
- Seven of these patients also had a dose reduction.
- Three additional patients had a dose reduction only.
- Of the 181 doses of G-CHOP delivered, six doses in five patients were delayed due to an AE.
- Five of these patients also had a vincristine dose reduction due to neuropathy.
- One patient each had dose reductions of prednisone, cyclophosphamide, and cyclophosphamide/doxorubicin.

Reasons for the six early withdrawals in the G-FC arm were: AEs (n = 5) and insufficient response (n = 1).

No patients have withdrawn from the G-CHOP arm to date.

In the G-FC arm, 26/28 patients (93%) responded at the end of treatment, with one patient having progressive disease and one withdrawing from the study during cycle 1. (Table 3)

In the G-CHOP arm, 16/17 patients (94%) with a response assessment responded at the end of treatment. (Table 3)

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>G-CHOP (n = 28)</th>
<th>G-FC (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>62.5 (32–75)</td>
<td>61.0 (45–77)</td>
</tr>
<tr>
<td>Clinical stage at progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II/III–IV, n (%)</td>
<td>9 (32)/9 (68)</td>
<td>5 (18)/23 (82)</td>
</tr>
<tr>
<td>FLIPI, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>8 (29)</td>
<td>8 (29)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>15 (54)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>High</td>
<td>5 (18)</td>
<td>13 (46)</td>
</tr>
<tr>
<td>Prior treatment lines, median (range)</td>
<td>1.0 (1–3)</td>
<td>2.0 (1–7)</td>
</tr>
<tr>
<td>Prior rituximab treatment lines, median (range)</td>
<td>1.0 (0–2)</td>
<td>1.0 (0–3)</td>
</tr>
<tr>
<td>Bone marrow involvement, n (%)</td>
<td>7 (25)</td>
<td>7 (26)*</td>
</tr>
<tr>
<td>Bulky &gt;7cm, n (%)</td>
<td>9 (32)</td>
<td>5 (18)</td>
</tr>
</tbody>
</table>

*Bone marrow results available for n = 27

FLIPI = follicular lymphoma international prognostic index; G-CHOP = GA101, cyclophosphamide, doxorubicin, vincristine and prednisone; G-FC = GA101, fludarabine and cyclophosphamide

Table 2. Serious adverse events

<table>
<thead>
<tr>
<th>G-CHOP</th>
<th>G-FC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>Low dose</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Neutropenia/fever</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>Stomatitis necrotizing</td>
</tr>
<tr>
<td>Infection</td>
<td>Anemia</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td>Neutropenic sepsis (two episodes in the same patient)</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Cystitis</td>
<td>Neutropenic sepsis</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

G-CHOP = GA101, cyclophosphamide, doxorubicin, vincristine and prednisone; G-FC = GA101, fludarabine and cyclophosphamide
Table 3. Response at the end of induction treatment

<table>
<thead>
<tr>
<th></th>
<th>G-CHOP</th>
<th></th>
<th>G-FC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>Low dose (n = 10)</td>
<td>High dose (n = 7)</td>
<td>Total (n = 17)</td>
<td>Low dose (n = 15)</td>
</tr>
<tr>
<td>ORR</td>
<td>9 (90)</td>
<td>7 (100)</td>
<td>16 (94)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>CR</td>
<td>3 (30)</td>
<td>5 (71)</td>
<td>8 (47)</td>
<td>11 (79)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (60)</td>
<td>2 (29)</td>
<td>8 (47)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (10)</td>
<td>–</td>
<td>1 (6)</td>
<td>–</td>
</tr>
<tr>
<td>PD</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*One patient in the high dose group withdrew from treatment and did not have a response assessment (classified as a non-responder)

CR = complete response; G-CHOP = GA101, cyclophosphamide, doxorubicin, vincristine and prednisone; G-FC = GA101, fludarabine and cyclophosphamide; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Key conclusions

- These preliminary results indicate that G-CHOP and G-FC combinations may be delivered safely and are highly effective treatments in patients with relapsed FL.
- The overall and complete response rates to GA101 plus chemotherapy was high, and for G-CHOP, the higher dose of GA101 achieved a numerically higher complete response rate compared with the lower dose.
- Importantly, G-CHOP can be delivered at the pre-specified three-weekly intervals without the need for dose reductions or delays.
- There is no evidence for increased toxicity at higher doses of GA101.
- Based on these promising results, GA101 will be studied in combination with CHOP and other chemotherapies in a randomized phase III study against the standard of care, R-CHOP.

References:
The study by Ardeshna and colleagues is a unique study, which performed a detailed quality of life (QoL) comparison between patients undergoing watchful waiting vs. early treatment with rituximab for advanced stage, asymptomatic, non-bulky follicular lymphoma (FL). This is a very comprehensive evaluation of multiple aspects of QoL. They identified a subset of patients who were uncomfortable with a watchful waiting approach, in which initiating standard therapy with rituximab plus chemotherapy may be justified. In these patients, the lesser toxicity associated with rituximab monotherapy (administered either as four weekly doses or four weekly doses followed by maintenance therapy) may offer a reasonable alternative.

Based on the preliminary information available from this study, it does appear that for some patients, early rituximab treatment would be beneficial both in terms of delaying time to definitive therapy and improving certain aspects of QoL. Early treatment appears to be well tolerated with minimal concern for significant toxicity, but longer follow-up is needed to assess long-term safety as well as the impact on response to future therapy. While early rituximab treatment in this setting may change treatment practice, at the time of analysis, there is no overall survival (OS) advantage, so watchful waiting remains a viable option.

It is noteworthy that the rituximab induction arm of this study appeared to provide benefit that was closely comparable to the maintenance arm. It is unfortunate that this arm was prematurely closed, as it supports the use of upfront rituximab at a significantly reduced cost compared with maintenance therapy. One major barrier to implementing early rituximab therapy in advanced-stage, asymptomatic, non-bulky FL includes funding approval and access in this setting. However, due to the significant benefit achieved in delaying definitive treatment, this approach is associated with long term cost savings.

Coiffier, et al. evaluated the combination of bortezomib plus rituximab compared with rituximab monotherapy in patients with relapsed FL in a phase III randomized controlled trial. This study demonstrated a modest improvement in progression-free survival (PFS) but no OS benefit when bortezomib was added to rituximab. The bortezomib-rituximab arm was associated with greater toxicity compared with the rituximab monotherapy arm, including a higher rate of serious adverse events (SAEs), particularly peripheral neuropathy. In this setting, the marginal clinical benefit achieved may not warrant the additional toxicity. However, based on bortezomib’s mechanism of action, earlier use in the front-line setting or in combination with chemotherapy may prove to be more advantageous and should be further investigated.

The novel type II monoclonal anti-CD20 antibody, GA101 was studied by Davies, et al. in a phase Ib study. This study was designed to address the safety of GA101 at two dose levels in combination with two different multi-agent chemotherapy regimens, CHOP or FC, in relapsed/refractory FL. To date, preclinical and early clinical data examining the safety and efficacy of GA101 have not identified any unexpected toxicities compared with rituximab. It appears to be a promising agent that may be superior to rituximab; however, this needs to be evaluated in larger comparative trials. This phase Ib study demonstrates that GA101 can be safely added to chemotherapy regimens, including CHOP and FC. Complete response rates appear to be higher in the high dose cohort, with no apparent increase in toxicity, but the dosing strategy remains to be optimized in future studies. Based on these promising data, the next step will be to compare GA101 head-to-head with rituximab to evaluate its potential clinical benefit.
Diffuse Large B-cell Lymphoma

New Treatment Options for Patients with DLBCL

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma (NHL), accounting for 25–30% of all cases of NHL. Significant progress in the management of patients with DLBCL has been made in the last decade with the addition of rituximab to chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Despite this progress, certain issues continue to be a challenge for physicians. These issues include patients with resistant disease, high-risk patients with poor prognostic factors, and the elderly who tend to have worse outcomes to therapy than younger patients.

These issues drive the development of new treatment approaches and novel agents to improve outcomes for patients with DLBCL. Data from recent advances in this field were presented at EHA 2011 and ICML 2011:

• At ICML 2011, an update of the ongoing experience of treating limited-stage DLBCL patients according to a positron emission tomography (PET)-based algorithm was presented. This study concluded that most patients will be PET-negative after three cycles of R-CHOP and have an excellent outcome following abbreviated R-CHOP alone, while PET-positive patients who receive involved-field radiotherapy (IFRT) have a high rate of distant relapse.

• A phase II study of CT-011 in DLCBL patients presented at ICML 2011 provides the first signal of clinical efficacy by demonstrating improved progression-free survival (PFS) and overall survival (OS) after autologous stem cell transplantation (AuSCT).

• Preliminary results from a phase II study combining R-CHOP and enzastaurin were presented at ICML 2011 and indicated that the combination improved PFS and complete response (CR) rates for patients with intermediate- or high-risk DLBCL with no additional toxicity compared with R-CHOP alone.

• A retrospective study presented at EHA 2011 examined the clinical characteristics of very elderly DLBCL patients and their chemotherapy use. Encouraging results were observed, suggesting that the majority of very elderly patients with DLBCL should receive an adjusted R-CHOP-like chemotherapeutic regimen with curative intent rather than palliative treatments.

Treatment of limited-stage DLBCL can be effectively tailored using a PET-based approach

**Background**

Since 2005, patients in British Columbia (B.C.) with limited-stage diffuse large B-cell lymphoma (DLBCL) have been treated according to a positron emission tomography (PET)-based algorithm. Following three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), patients undergo 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scan. Those who are PET-negative receive one additional cycle of R-CHOP and those who are PET-positive receive involved-field radiotherapy (IFRT). Sehn and colleagues presented an update of this ongoing experience at ICML 2011.¹

**Study design**

- The goal of this study was to review the outcomes of all patients in the B.C. Cancer Agency Lymphoid Cancer database treated with the PET-based algorithm.
- The database was used to identify all patients with limited-stage DLBCL treated with this PET-based approach between March 2005 and June 2010.
- Patients with primary CNS, primary testicular, and transformed lymphoma were excluded.
- FDG-PET/CT scans were performed at a single centre 14–21 days after three cycles of the standard three-weekly schedule of R-CHOP.

**Key findings**

- A total of 134 patients were identified and their clinical characteristics were as follows:
  - Median age was 64 years (range: 22–88 years);
  - 57% were male;
  - 57% had stage I disease; 43% had stage II disease;
  - 3% had performance status (PS) >1;
  - 11% had elevated lactate dehydrogenase (LDH);
  - 51% had at least one extranodal site;
  - 32% had mass size ≥5 cm;
  - 20% had a stage-modified international prognostic index (IPI) risk score of 0. 49% had an IPI of 1; 23% had an IPI of 2; and 8% had an IPI of 3–4.
- The median follow-up was 30 months (range: 3–68 months).
- After three cycles of R-CHOP, the PET results were as follows:
  - PET-negative = 103 patients (77%);
  - PET-positive = 30 patients (22%);
  - PET-indeterminate = one patient (1%).
- Elevated serum LDH and mass size ≥5 cm were predictive of PET status (p = 0.02 and 0.001, respectively), whereas stage-adjusted IPI was of borderline significance (p = 0.08).

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¹ Sehn LH, et al. ICML 2011: Abstract 028

IFRT = involved-field radiotherapy; PET = positron emission tomography; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
• Of the 103 PET-negative patients, 100 completed treatment with one additional cycle of R-CHOP, two patients received IFRT due to physician choice, and one patient died of toxicity before receiving any further treatment.
  ◦ Seven of the 103 PET-negative patients had relapsed disease (three initially localized at the original site, two local and distant, and two distant only).
  ◦ Three of the PET-negative relapses were delayed, occurring between 2.5 and four years after the initial diagnosis.
• 29 out of 30 PET-positive patients received IFRT and one patient received one additional cycle of R-CHOP alone due to concern about toxicity.
  ◦ Nine of the 30 PET-positive patients had relapsed disease, all with disease distant from the original site and one patient with follicular lymphoma.
  ◦ Four patients have died from their disease.
• The one patient with an indeterminate PET scan completed therapy with IFRT and remains in remission.
• The three-year estimated time-to-progression (TTP) was 85% for the entire group of patients and 92% and 60% for PET-negative and PET-positive patients, respectively. (Figure 1)
• The three-year overall survival (OS) was 93% for the entire group of patients, and 96% for PET-negative and 83% for PET-positive patients, respectively. (Figure 2)
• Univariate analysis revealed that age, stage, PS, and PET status were significant predictors of TTP.
• In a multivariate analysis where age, stage, PS, LDH, presence of extranodal involvement, mass size ≥5 cm, and PET status were controlled for, only age, PS, and PET status remained independent predictors of TTP.

Key conclusions
■ The majority of patients with limited-stage DLBCL will be PET-negative after three cycles of R-CHOP and have an excellent outcome following abbreviated R-CHOP alone, although delayed relapses have been observed.
■ PET-positive patients who complete therapy with IFRT have a high rate of distant relapse and alternative approaches may be warranted in this subgroup.

A phase II study of CT-011 after AuSCT in recurrent/refractory DLBCL

Background
CT-011 is a humanized anti-program death-1 (PD-1) antibody. It blocks PD-1 function and enhances the activities of natural killer (NK) and T-cells against PD-L1-positive tumours isolated from cancer patients. It also induces effective immune-mediated tumour regression in experimental human and murine tumour models.

Gordon and colleagues hypothesized that CT-011 can elicit tumour-immune control leading to favourable clinical outcomes in diffuse large B-cell lymphoma (DLBCL) patients by delaying recurrence after autologous stem cell transplantation (AuSCT). The results of their study were presented at ICML 2011.1

Study design
- Patients were eligible for this study if they had recurrent/refractory DLBCL that was chemosensitive in pre-transplant salvage therapy, and an ECOG performance status (PS) of 0–1.
- Three doses of CT-011 were given at 1.5 mg/kg every six weeks 30–90 days following AuSCT, and patients were followed for a total of 18 months.
- The primary endpoint was progression-free survival (PFS) at 16 months after the first dose of CT-011 (approximately 18 months after AuSCT).
- Secondary endpoints included overall survival (OS), event-free survival (relapse, second cancer, or death), toxicity, safety, and biological and cellular correlates.

Key findings
- 72 patients were enrolled in this study and 71 were evaluable.
  - The median age was 57 years (range: 19–80 years);
  - 70 patients (97%) had prior rituximab treatment and six patients (8%) had radiation post-transplant.
  - 43 pre-transplant patients (47%) had international prognostic index (IPI) scores of 3 or 4, and 42 patients (58%) had marrow involvement.
- Toxicity included 14 patients with grade 3–4 neutropenia and six patients with thrombocytopenia.
- There were no grade 3–4 non-hematological toxicities.
- At the time of this analysis, 56 patients were followed for at least 18 months.

Table 1. Most frequent adverse events

<table>
<thead>
<tr>
<th>Adverse event, n (% of total events)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 (4.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (3.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (3.2)</td>
</tr>
<tr>
<td>WBC count decrease</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (2.2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>8 (2.1)</td>
</tr>
</tbody>
</table>
The estimated 18-month PFS was 70% (95% CI: 57–79). (Figure 1)

The estimated 18-month OS was 84% (95% CI: 72–91). (Figure 2)

Increases in circulating CD8+ central memory cells (CD8+ CD62L+ CD127+) were seen as early as 24 hours following the first dose of CT-011. (Figure 3)
  - This increase was subset specific, as other memory T-lymphocytes did not increase.
  - This increase was attributable to PD-1 blockade and the enhancement of CD8+ PD-1+ cell survival.

CD4-positive effector memory cells (CD4+ CD45RO+ CD62L-CCR7-) increased six weeks following the first CT-011 dose.
  - The increase may be subset specific as it was not observed in other subsets of CD8 or CD4 memory cells.

Increases in interleukin (IL)-7α receptor (CD127) expression in CD4 memory cell subsets were observed as early as 24 hours following the first CT-011 dose.
  - No changes were observed for L-selectin (CD62L), a homing receptor for leukocytes, in all tested subsets following CT011 treatment.

There were no observed changes in the peripheral levels of interferon gamma (IFNγ) or tumour necrosis factor alpha (TNFα), which excludes the occurrence of the hypothetical cytokine storm.

No anti-CT-011 antibodies have been detected in the sera of any of the patients treated with CT-011 in this study throughout the treatment period, as well as one and four months after the last dose of CT-011.
**Figure 2. Preliminary overall survival after CT-011 following AuSCT**

![Graph showing preliminary overall survival after CT-011 following AuSCT](image)

Study 18 months OS 0.84 (95% CI: 0.72–0.91)

*Historical control is the median of:

95% CI = 95% confidence interval; AuSCT = autologous stem cell transplantation; OS = overall survival

**Figure 3. Increase in circulating CD8+ central memory cells**

![Graph showing increase in circulating CD8+ central memory cells](image)

** Median ABS (×10⁶/mm³)

- CD8+/CD62L+/CD127+:
  - Initial: 70, n = 62
  - Follow-up: 117, n = 47
  - Increase: +47%

- CD4+/CD45RC+/CD62L+/CCR7+:
  - Initial: 200, n = 62
  - Follow-up: 260, n = 47
  - Increase: +38%

- CD14+/B7-H1+:
  - Initial: 30, n = 62
  - Follow-up: 50, n = 47
  - Increase: +103%

** p ≤ 0.01 by Wilcoxon matched paired test
**Key conclusions**

- Compared with historical control data, CT-011 resulted in improved PFS and OS in patients with recurrent/refractory DLBCL after AuSCT.
- There was acceptable toxicity and CT-011 was well tolerated.
- Cellular and biological data suggest peripheral increases in specific subsets of memory T-cells and upregulation of the IL7α receptor, which is pivotal for survival and maturation of memory lymphocytes.
- The subset-specific increases in CD8+ central memory cells and CD4+ effector memory cells are consistent with CT-011’s mechanism of action in enhancing the survival, function, and trafficking of memory lymphocytes *in vitro*.
- These data provide the first signal of clinical efficacy of an anti-PD-1 antibody in DLBCL and suggest that randomized phase III trials are warranted.


Hainsworth JD, et al. ICML 2011: Abstract 074

**Randomized phase II study of R-CHOP plus enzastaurin vs. R-CHOP in the first-line treatment of patients with intermediate and high-risk DLBCL: Preliminary analysis**

**Background**

Enzastaurin (ENZ) is an oral serine/threonine kinase inhibitor that targets protein kinase Cβ (PKCβ), an enzyme that plays a pivotal role in normal B-cell signaling and survival. At clinically achievable concentrations, ENZ induces apoptosis and suppresses the proliferation of various tumour cell lines including lymphomas.1 Its clinical activity has been demonstrated in patients with diffuse large B-cell lymphoma (DLBCL).2

At EHA 2011, Hainsworth and colleagues presented the results of a study that compared first-line treatment with R-CHOP plus ENZ to standard R-CHOP.3

**Study design**

- DLBCL patients were required to have intermediate- or high-risk international prognostic index (IPI) scores (2–5).
- Patients were randomized in a three-to-two ratio to receive six 21-day cycles of either R-CHOP plus ENZ therapy (arm A), or R-CHOP alone (arm B).
- After six cycles, responders in arm A could continue single-agent ENZ as maintenance therapy, with response evaluations conducted every eight weeks.
- A 1,125 mg oral loading dose of ENZ was given on day 2 of each cycle followed by 500 mg ENZ daily.
- Response was evaluated (according to 1999 International Working Group criteria) every eight weeks and complete restaging was performed at the end of cycle 6.
- The primary endpoint was progression-free survival (PFS).
- Secondary objectives included overall response rates (ORR; complete response [CR] and partial responses [PR]), overall survival (OS), and safety.
- This preliminary analysis was performed after all patients had completed R-CHOP chemotherapy, and had been followed for at least one year.

**Key findings**

- 57 patients were enrolled in arm A and 43 were enrolled in arm B.
• Patient characteristics were comparable in both arms.
  ᵅ A total of 65 patients (65%) had either high-intermediate (44%) or high (21%) IPI risk scores.
• The median PFS has not yet been reached; however, the one-year PFS rate for arm A was 73% (CI: 0.60–0.85) and 52% in arm B (CI: 0.35–0.69). (Figure 1)
• Patients in arms A or B with an IPI risk score of 2 did not have a statistically significant difference in PFS, however patients treated in arm A with an IPI risk score of 3–5 had a significantly better PFS than patients in arm B with an IPI risk score of 3–5. (Figure 2)
• The two-year OS rates were not significantly different for arm A (75%) and arm B (68%). (Figure 3)
• ORR for arms A and B were 80.4% and 83.3%, respectively, and CR rates (CR + CRu) were 35.7% and 26.2%. (Table 1)
• The most frequently observed grade 3–4 adverse events (AEs) were neutropenia (46% vs. 46% in arms A and B, respectively) and leukopenia (19% vs. 21%). (Table 2)
• In arm A, four patients died (two from sepsis, one from pulmonary embolism, and one from acute respiratory distress syndrome), and in arm B two patients died (both from sepsis).

Figure 1. Progression-free survival

![Figure 1. Progression-free survival](image1)

Figure 2. Progression-free survival by IPI score

![Figure 2. Progression-free survival by IPI score](image2)
**Table 1. Response rates**

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP + ENZ n = 56</th>
<th>R-CHOP n = 42</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>14 (25.0)</td>
<td>10 (23.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>CRu</td>
<td>6 (10.7)</td>
<td>1 (2.4)</td>
<td>0.233</td>
</tr>
<tr>
<td>PR</td>
<td>25 (44.6)</td>
<td>24 (57.1)</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>3 (5.4)</td>
<td>1 (2.4)</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
<td>-</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>8 (14.3)</td>
<td>5 (11.9)</td>
<td>-</td>
</tr>
<tr>
<td>PET negative*</td>
<td>25/41 (61%)</td>
<td>18/28 (64%)</td>
<td>0.806</td>
</tr>
</tbody>
</table>

Values are expressed as number (percent) of patients with the indicated best response

* Number of PET negative over number of post-induction PET scans

* CR = complete response; CRu = unconfirmed complete response; ENZ = enzastaurin; PD = progressive disease; PET = positron emission tomography; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SD = stable disease

**Table 2. Grade 3 or 4 treatment-related toxicity**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>R-CHOP + ENZ n = 57</th>
<th>R-CHOP n = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26 (46)</td>
<td>20 (46)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11 (19)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9 (16)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (12)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (9)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections (non-neutopenic)</td>
<td>3 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (14)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (4)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Values are expressed as number (percent) of patients

ENZ = enzastaurin; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
Key conclusions

- This preliminary analysis suggests an improvement in PFS and CR for patients with intermediate- or high-risk DLBCL treated with R-CHOP plus ENZ when compared with R-CHOP alone.
- No difference in OS was observed at the time of analysis, but continued monitoring is ongoing.
- Toxicity profiles were comparable between the two treatment arms.
- A final analysis will be conducted after all patients have been followed for at least two years.

References:


Lower dose intensity chemoimmunotherapy in very elderly patients with DLBCL

**Background**

The optimal treatment of very elderly patients with diffuse large B-cell lymphoma (DLBCL) has not been well established. Many patients have received chemotherapy without anthracyclines and this may adversely affect outcomes. The combination of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has greatly improved the prognosis of DLBCL. The administration of rituximab in very elderly patients might permit dose reductions in the chemotherapy regimen without significant loss in efficacy.

At EHA 2011, Vassilakopoulos and colleagues described the clinical characteristics of very elderly patients with DLBCL, the actual delivered doses of chemoimmunotherapy drugs in routine clinical practice, and the final outcomes in these patients.1

**Study design**

- This was a retrospective study conducted in five medical centres.
- Comparisons were made amongst the following age groups: very elderly (≥80 years), elderly (61–70 years), and younger (≤60 years).
- Among 579 patients with DLBCL treated with R-CHOP or similar regimens, 56 were older than 80 years (10%).
- Clinical and laboratory characteristics of these patients were studied and compared with the 523 patients younger than 80 years, who were treated during the same period.
- The parameters evaluated included: gender, international prognostic index (IPI) risk factors, B-symptoms, anemia, lymphocytopenia, albumin, progression-free survival (PFS), and overall survival (OS).
- Additionally, the investigators studied the relative dose intensity (RDI) of the four drugs (except corticosteroids) that was actually delivered to the very elderly patients.
  - The reference points were the doses and time intervals of standard R-CHOP given every 21 days.
  - Endpoints included event-free survival (EFS) including any event of relapse, progression or toxic death, and OS including death for any reason.

**Key findings**

- The median age of the very elderly patients was 82.5 years (range: 80–91 years).
- The frequency of adverse prognostic factors (high IPI, poor revised IPI [R-IPI], low serum albumin, severe lymphocytopenia) was significantly higher in very elderly patients compared with the younger patient group (≤60 years), but the difference was mainly due to the favourable prognostic profile of the younger patient group.
  - In contrast, the characteristics of patients aged 61–79 and ≤80 years were similar.
• The five-year EFS was 81%, 68%, and 62% ($p = 0.0005$) in the group of ≤60, 61–79, and ≥80 year-old patients, respectively ($p = 0.12$ for 61-79 vs. ≥80). (Figure 1)

• The corresponding five-year OS was 90%, 65%, and 55% for the three groups, respectively ($p < 0.0001$, but $p = 0.048$ for 61–79 vs. ≥80). (Figure 2)

• In a multivariate analysis of PFS, age ≥80 years had no independent prognostic significance when IPI and lymphocytopenia were taken into account.

• On the contrary, age ≥80 years was an independent prognostic factor for OS with a relative risk of 2.9 ($p < 0.001$) and 2.1 ($p = 0.01$) compared with patients <80 years or 61–79 years, respectively.

• Among patients ≥80 years old who received more than one cycle of anthracycline-based chemotherapy, the median RDI for rituximab was 85% (interquartile range [IQR]: 78–99%), 76% for cyclophosphamide (IQR: 67–86%), 60% for anthracycline (IQR: 50–69%), and 64% for vincristine (IQR: 50–76%). (Figure 3)

• Moreover, six out of 56 patients did not receive anthracyclines, and two received only one cycle.
Figure 3. Relative dose intensity of chemotherapy drugs

Key conclusions

- Anthracycline-containing chemotherapy results in prolonged survival in >50% of DLBCL patients who are older than 80 years.
- These results are very encouraging, even though RDI for chemotherapeutic drugs was reduced in clinical practice.
- Very advanced age (≥80 years) was an independent prognostic factor for OS but not EFS.
- These observations suggest that the majority of very elderly patients with DLBCL should not be treated with palliative approaches, but they should receive an adjusted R-CHOP-like chemotherapeutic regimen with curative intent.


Canadian perspective by Dr. Douglas Stewart

Sehn and colleagues retrospectively evaluated a positron emission tomography (PET)-based approach to tailor treatment for limited-stage diffuse large B-cell lymphoma (DLBCL) at their centre. The study suggests encouraging results for patients who were PET-negative following three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). When treated with a fourth and final cycle of R-CHOP, they had a three-year progression-free survival (PFS) rate of 92%. On the other hand, PET-positive patients had a three-year PFS of 60%. Further study may be needed to determine the best treatment approach for these patients, as involved-field radiotherapy (IFRT) alone is insufficient. Findings of the study are very interesting and provide a rationale for further prospective multi-centre studies to confirm results.

When treating patients with limited-stage DLBCL, patient age and disease location need to be considered. Older patients, especially those with disease in the neck or axillary region, are often treated with three cycles of R-CHOP followed by IFRT. A PET-guided approach has traditionally not been employed for these elderly patients who usually prefer to limit chemotherapy exposure, and for whom long-term effects of radiation are of less concern. In younger patients, especially those with disease in their chest, abdomen, or pelvic region, PET-guided therapy may be particularly beneficial. IFRT is used more sparingly in younger patients, particularly in anatomical areas of concern due to the potential long-term adverse effects of premature cardiac disease and secondary malignancies. The study by Sehn and colleagues suggests that young patients with good prognosis limited-stage DLBCL who are PET-negative following three cycles R-CHOP can safely be treated with one additional cycle of R-CHOP and avoid IFRT. Until stronger evidence exists from prospective randomized controlled studies, other patients who are PET-positive following
initial R-CHOP or have multiple adverse international prognostic index (IPI) risk factors should probably receive a full six cycle course of R-CHOP, potentially then followed by IFRT to initial disease sites.

Despite significant advances in first-line therapies for DLBCL, a number of patients have refractory disease and poor outcomes. These patients, if eligible, are often candidates for autologous stem cell transplantation (AuSCT). In selecting patients for AuSCT, a number of factors need to be considered. These include time to relapse, IPI score at relapse, sensitivity to salvage therapy, and severity of comorbidities. There is currently no standard post-transplant treatment despite the fact that AuSCT cures less than 50% of relapsed DLBCL patients. Gordon, et al. studied the novel immunotherapy agent CT-011 in a phase II setting in refractory or recurrent DLBCL patients who received AuSCT. This study evaluated toxicity, PFS, and correlative biological data in an immune cell subset. Biological factors were not correlated to PFS, which may have yielded interesting findings if patients who had an increase in the biological factors also experienced a longer PFS. This is a preliminary study and the authors managed to achieve a proof of concept, with encouraging outcomes. A phase III trial to investigate this strategy fully is therefore warranted.

Hainsworth, et al. evaluated the integration of enzastaurin with the established standard R-CHOP therapy as first-line treatment for intermediate- or high-risk DLBCL in a randomized phase II study. The key strength of this study is the randomization component of the study design. The results are encouraging, with a strong trend toward improved PFS, especially in high IPI patients, without significantly increased toxicities. The rate of febrile neutropenia, though higher in the enzastaurin R-CHOP arm, is still less than 20% and infection rates were similar between groups. Other approaches that have been studied to intensify R-CHOP-like therapy include R-CHOP followed by AuSCT; the Groupe d’Étude des Lymphomes de l’Adulte (GELA) approach of chemotherapy followed by high-dose sequential chemotherapy consolidation; and the addition of etoposide to R-CHOP (R-CHEOP). All of these approaches result in considerable increases in toxicity. The addition of enzastaurin to R-CHOP is attractive because enzastaurin is an oral agent and it does not appear to add significant toxicity. If this treatment combination does improve PFS for high-risk patients, this will be an important option in DLBCL. Preliminary data need to be confirmed with longer follow-up and with a randomized controlled phase III study.

Very elderly patients with DLBCL require particular attention and a thorough evaluation is needed to determine if they are suitable candidates for standard treatment regimens or if palliative approaches are more appropriate. Very elderly patients have a number of comorbidities and competing causes of death. In addition, physicians need to respect the wishes of the patients, as some may not want treatment for their lymphoma. Less aggressive chemotherapy is usually offered if organ function and performance status are compromised. Vassilakopoulos, et al. evaluated the use of lower intensity chemotherapy in very elderly patients with DLBCL in a retrospective study. This study provides support for the current treatment approach and demonstrates that decreasing the dose of R-CHOP can result in good outcomes for some patients. In treating the very elderly in my own practice, I tend to include more pre-treatment testing, including echocardiograms and other organ assessments. I then try the standard regimen of R-CHOP, while employing more rigorous supportive care, including growth factor support. I also monitor these patients regularly by having them return to the clinic for interim assessments and blood counts and, if necessary, dose reductions are implemented. The findings of this study are important because there are few alternate options for very elderly DLBCL patients. One option might be to substitute etoposide for adriamycin if the patient has cardiac issues, which are more common in the elderly, but this is not widely accepted. It is encouraging that patients can do well on reduced-dose R-CHOP.
Introducing a new star

Lundbeck in Oncology

At Lundbeck, we’ve been pioneers in bringing new treatments to Canada to help people living with psychiatric and neurological disorders.

Now we are focusing some of our brightest stars on providing new treatments for many patients who suffer from cancer.

We believe in being open to new knowledge and alternative solutions. But most of all, our sense of humanity defines how we reach out to another human being and the world around us.
Other Lymphomas

Optimizing Therapies and Outcomes for NHL

Combined immunochemotherapy continues to be the standard of care for both first-line and relapsed/refractory non-Hodgkin lymphoma (NHL). However, several unanswered questions remain, such as how to select the optimal first-line and salvage treatments, and the role of maintenance therapy, particularly in the elderly. Intensive research has continued to focus on elucidating the biological mechanisms of various NHL subtypes, identifying new molecular targets, and optimizing existing therapies.

Maintenance therapy with rituximab improves outcomes in patients with follicular (FL) and other indolent lymphomas, both in the first-line and relapsed and refractory settings.

GA101 is a type II anti-CD20 monoclonal antibody that is in early-stage clinical trials. Preclinical in vitro data have demonstrated cytotoxicity superior to rituximab, and phase I data have been promising. It is currently being evaluated as a single agent in phase II studies and in combination with chemotherapy in a phase Ib study.

Lenalidomide has also shown promise in the treatment of patients with indolent lymphomas. Single-agent therapy in patients with relapsed or refractory lymphoma achieved a modest but durable overall response rate (ORR). Recently it has been studied in combination with rituximab, and outcomes seemed to be improved without significant increases in toxicity.

Studies evaluating the above treatment approaches in NHL were presented at EHA 2011 and ICML 2011:

- Preliminary results presented at EHA 2011 from a large multicentre randomized controlled trial examined the role of rituximab maintenance therapy in elderly patients with mantle cell lymphoma (MCL). This study demonstrated that long-term rituximab had a low toxicity profile and that rituximab maintenance following R-CHOP induction should be considered the new standard for elderly patients with MCL.

- A phase II study of GA101 monotherapy at two dose levels in heavily pretreated relapsed/refractory aggressive NHL was presented at ICML 2011. Investigators demonstrated that this agent can be administered safely, even at higher doses, and shows promising efficacy in this group of patients, warranting further study.

- At ICML 2011, a phase II study evaluated lenalidomide and rituximab in patients with untreated, advanced indolent NHL. The study demonstrated that front-line therapy with lenalidomide and rituximab produced excellent ORR and complete response (CR) rates, particularly in FL patients with a high tumour burden, and is safe with a manageable side-effect profile.

References:

Rituximab maintenance significantly prolongs duration of remission in elderly patients with mantle cell lymphoma (MCL)

**Background**
Following induction therapy in elderly patients with mantle cell lymphoma (MCL), maintenance with interferon-alpha (IFN-α) has been suggested to be effective, but toxicity is a concern. Rituximab maintenance therapy has shown promising results in other lymphomas such as follicular lymphoma due to its low toxicity, making it an ideal candidate for study in MCL.

The European MCL Elderly trial studied maintenance therapy with rituximab vs. IFN-α after induction with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or fludarabine, cyclophosphamide, and rituximab (FCR). At EHA 2011, Kluin-Nelemans, et al. reported their preliminary findings.1

**Study design**
- Patients older than 60 years with stage 2–4 MCL who were not eligible for high-dose therapy were included in this study.
- Initially, patients were randomized between eight cycles of R-CHOP every three weeks or six cycles of FCR every four weeks.
- Subsequently, patients who responded (achieved a complete response [CR or unconfirmed CR (CRu) or partial remission [PR]) underwent a second randomization between maintenance with rituximab 375 mg/m² every two months or interferon-alpha 2a or 2b (IFN-α) (regular IFN weekly 3x3 MIU or pegylated IFN 1x1 μg/kg).
  - The second randomization was stratified for induction regimen, study group, age, international prognostic index (IPI), and response (CR/CRu vs. PR).
  - Both maintenance regimens were continued until progression.

**Key findings**
- Eight countries participated in this trial and randomization was closed in October 2010.
- 87% responded to R-CHOP and 78% responded to FCR.
- Out of 310 responding patients who were randomized for maintenance, data from 248 patients are currently evaluable.
- In the rituximab maintenance group, the median age was 70 years, 68% of the patients were male, 84% had stage 4 disease, 44% were intermediate-risk MCL international prognostic index (MIPI), and 48% were high-risk MIPI.
- 60% of patients had a CR/CRu upon induction therapy and 58% received R-CHOP induction.
- Patient characteristics were generally well balanced between the rituximab and IFN maintenance groups.

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**Study design**

<table>
<thead>
<tr>
<th>Newly diagnosed MCL, &gt;60–65 years; performance 0–2, Stages II–IV</th>
<th>RANDOMIZED</th>
<th>8 x R-CHOP</th>
<th>RANDOMIZED</th>
<th>IFN-α maintenance (3 x 3 MIU/week) or Peg-IFN (1ug/kg week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>CRu</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 x FCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rituximab maintenance (every 2 months)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; CRu = unconfirmed complete response; FCR = fludarabine, cyclophosphamide, and rituximab; IFN-α = interferon-alpha 2a or 2b; MCL = mantle cell lymphoma; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
• After a median follow-up of 33 months, patients randomized for rituximab maintenance had a significantly longer remission duration compared with IFN-α (77 vs. 24 months; \( p = 0.0109 \); HR = 0.54. (Figure 1)

• Patients who were randomized for rituximab maintenance and received R-CHOP as induction therapy had a significantly longer remission duration compared with IFN-α (51 vs. 24 months; \( p = 0.0005 \)).

• The difference was not significantly different for patients who received FCR as induction therapy (77 vs. 26 months, \( p = 0.11 \)), than for rituximab and IFN-α maintenance, respectively.

• Overall survival (OS) was not different between the two maintenance arms (Figure 2) but patients who were induced with R-CHOP had a longer OS than those induced with FCR (64 vs. 40 months, \( p = 0.0072 \)).

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**Figure 1. Remission duration during maintenance (per protocol analysis)**

![Figure 1](image1.png)

**Figure 2. Overall survival**

![Figure 2](image2.png)
• Grade 3–4 hematologic toxicity was higher in the IFN-α maintenance arm than in the rituximab maintenance arm (leukocytopenia 36% vs. 17%; thrombocytopenia 16% vs. 7%).

• Non-hematologic grade 3–4 toxicity was rare, except for infections (7% in the IFN-α arm vs. 7% in the rituximab arm). (Figure 3)

• FCR followed by rituximab resulted in the highest infection rate (all grades 48% vs. 30%).

• 80% of patients on IFN-α stopped maintenance even though they had not progressed, compared with 34% on rituximab ($p < 0.001$).

• Patients who responded after induction but did not receive any maintenance therapy for various reasons (mainly based upon the patient’s decision or ongoing cytopenia after induction; $n = 106$) had a poor outcome (median remission duration 26 months; three-year OS 52%).

Figure 3. Adverse events

**Key conclusions**

■ This large, multicentre, randomized controlled trial with two randomization phases for fit elderly MCL patients demonstrated that long-term rituximab had a low toxicity profile.

■ Rituximab maintenance following R-CHOP induction should be considered the new standard for elderly patients with MCL, to which new regimens should be compared.

Results from a phase II study of GA101 monotherapy in relapsed/refractory aggressive NHL

**Background**

GA101 is currently being studied in clinical trials. At ICML 2011, Cartron and colleagues presented the results from a phase II study of patients with relapsed/refractory non-Hodgkin lymphoma (NHL) being treated with GA101 monotherapy.1

**Study design**

- Patients with CD20+ aggressive NHL were randomized to receive GA101 at a low dose or a high dose in a phase II study.
- GA101 monotherapy was given on days 1, 8, 22, and subsequently every 21 days for total of nine infusions.
- In the low-dose cohort, GA101 was given at a dose of 400 mg for all infusions.
- In the high-dose cohort, GA101 was given at a dose of 1,600 mg on days 1 and 8, followed by 800 mg thereafter.
- The primary endpoint was end of treatment response (EOR), assessed four weeks after the last infusion.
- The secondary objectives included safety and pharmacokinetics.

**Key findings**

- 40 patients were randomized in this study.
  - The low dose group had 21 patients, 10 with diffuse large B-cell lymphoma (DLBCL) and 11 with mantle cell lymphoma (MCL).
  - The high dose group had 19 patients, 15 with DLBCL and four with MCL.
- The EOR was 24% (5/21) in the low dose cohort and 32% (6/19) in the high dose cohort. (Figure 1)
- For DLBCL patients, EOR was 32% and for MCL patients EOR was 27%. (Figure 2)
- 63% of patients were previously refractory to a rituximab-containing regimen, and of the 13 refractory patients in the low dose cohort, one patient achieved partial response (PR; 8%).
- The median observation time was 7.7 months (range: 0.3–14.6 months).
- The median response duration was:
  - 8.6 months in the low dose cohort (range: 5.5–9.1 or more months with three continued responses).
  - Not reached in the high dose cohort (range: 3.1–11.2 or more months with four continued responses).
- Progression-free survival (PFS) is shown in Figure 3.
  - Of the 12 refractory patients in the high dose cohort, three patients achieved PR (25%).
- The most common adverse events (AEs) were infusion-related reactions.
  - Low dose cohort = 81% of patients, all grades.
  - High dose cohort = 68% of patients, all grades.
- During treatment, related grade 3–4 hematological AEs were anemia (n = 3 in the low dose cohort) and thrombocytopenia (n = 3 in the low dose cohort).
- Ten patients had at least one grade 1–2 infection (five in each cohort) with no grade 3–4 infections reported. (Table 1)
- Pharmacokinetic sampling was carried out to study the plasma concentration profile of GA101.
- Preliminary results show that MCL patients in the high dose group (n = 4) and in the low dose group (n = 11) had lower plasma concentrations compared with DLBCL patients.

Table 1. Adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>400/400 mg, n (%)</th>
<th>1,600/800 mg, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>17 (81)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Asteinor</td>
<td>4 (19)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (19)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (14)</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (14)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (14)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3 (14)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (24)</td>
<td>-</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

Adverse events occurring in ≥10% of all patients, or at grade 3–4 in >1 patient during treatment
Key conclusions

■ GA101 monotherapy is well tolerated with no unexpected AEs and no increased toxicity in the higher dose cohort.

■ GA101 shows promising efficacy in heavily pre-treated NHL patients with aggressive disease.

■ There was no clear dose response relationship but pharmacokinetic data suggest that the high dose group offers a better exposure to GA101 than the low dose group.

■ Trials are currently ongoing to explore GA101 plus chemotherapy.


Fowler N, et al. ICML 2011: Abstract 137

Lenalidomide plus rituximab is a highly effective and well-tolerated biologic therapy in untreated indolent B-cell NHL

Background
At ICML 2011, Fowler and colleagues presented their findings of a phase II study evaluating the efficacy and safety of lenalidomide and rituximab in patients with untreated, advanced indolent non-Hodgkin lymphoma (NHL).1

Study design
• This was a single institution phase II study.
• The planned enrollment was 50 patients with grade 1–2 follicular lymphoma (FL), 30 patients with small lymphocytic lymphoma (SLL), and 30 patients with marginal zone lymphoma.
• Patients with untreated indolent NHL received 20 mg/day of lenalidomide on days 1–21 and 375 mg/m² rituximab on day 1 of each 28-day cycle for six cycles.
• Prophylactic growth factors were not used.
• Response was assessed every three cycles using 1999 International Working Group Criteria and the groups were analyzed for response and toxicity independently.
• The primary endpoint was overall response rate (ORR) (complete response [CR] plus partial response [PR]).
Secondary endpoints were progression-free survival (PFS), overall survival (OS), safety and tolerability, as well as effect on tumour and immune microenvironment.

**Key findings**

- 100 patients were enrolled with a median age of 58 years (range: 34–84 years) and 51% were male.
- 93 patients were evaluable for response.
- Histologies included: 24 patients with SLL, 49 patients with FL, and 27 patients with marginal zone lymphoma.
- The ORR for all patients was 91%, with 65% attaining CR. (Table 1)
- 25 patients (27%) had a PR, and stable disease was noted in six (6%). (Table 1)
- ORR and CR rates were impressive in FL, with 38/45 (85%) evaluable patients attaining a CR. (Table 1)
- At study entry 80% of FL patients had a follicular lymphoma international prognostic index (FLIPI) score of ≥2 and 50% met Groupe d’Etude des Lymphomes Folliculaires (GELF) criteria for high tumour burden.
- Responses were high regardless of FLIPI or GELF criteria.
- The 24-month PFS was 86% for the entire group of patients (Figure 1) or 83% for FL patients, 88% for SLL patients, and 95% for marginal zone lymphoma patients. (Figure 1)
- The most common grade ≥3 non-hematologic toxicitities included rash (eight patients), muscle pain (seven patients), thrombosis (three patients), and fatigue (three patients).
- Grade ≥3 neutropenia and thrombocytopenia occurred in 27% and 4% of patients, respectively.
- Six patients stopped treatment due to adverse events, all occurring during the first two cycles, including two patients with grade 3 rash, one with arterial thrombosis, two infusion reactions, and one with a transient episode of respiratory failure during the first cycle.

**Table 1. Response rates**

<table>
<thead>
<tr>
<th></th>
<th>SLL (n = 24)</th>
<th>Marginal zone (n = 24)</th>
<th>FL (n = 45)*</th>
<th>Evaluable (n = 93)</th>
<th>ITT (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>20 (83)</td>
<td>21 (88)</td>
<td>44 (98)</td>
<td>85 (91)</td>
<td>85 (85)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>6 (25)</td>
<td>16 (67)</td>
<td>38 (85)</td>
<td>60 (65)</td>
<td>60 (60)</td>
</tr>
<tr>
<td>PR</td>
<td>14 (59)</td>
<td>5 (21)</td>
<td>6 (13)</td>
<td>25 (27)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (8)</td>
<td>3 (13)</td>
<td>1 (2)</td>
<td>6 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (8)</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Seven patients were not evaluable for response: five due to adverse events in cycle 1, one due to non-compliance and one due to withdrawal of consent.

CR = complete response; CRu = unconfirmed complete response; FL = follicular lymphoma; ITT = intent to treat; ORR = overall response rate; PD = progressive disease; SD = stable disease; SLL = small lymphocytic lymphoma

**Key conclusions**

- The biologic agents lenalidomide and rituximab as front-line therapy produce excellent OR and CR rates in previously untreated indolent NHL.
- Response rates remain high in FL patients despite a high tumour burden.
- The toxicity profile of this combination is mild with manageable hematological side effects.
- Correlative studies are ongoing to further define the effects on the immune microenvironment.
- Phase III randomized trials in previously untreated FL are planned.

The MCL Elderly study by Kluin-Nelemans, et al. is a large randomized controlled trial (RCT) of rituximab maintenance in elderly patients with mantle cell lymphoma (MCL) conducted by the well-respected cooperative group, the European MCL Network. The study was well designed, but a few factors need to be considered when interpreting results. The use of two different induction protocols (rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] and fludarabine, cyclophosphamide, rituximab [FCR]) in the double randomization design may complicate the interpretation of efficacy results for rituximab maintenance. Furthermore, the study was only powered to look at progression-free survival (PFS), but overall survival (OS) is the more important outcome. The rationale for this study is sound. Rituximab maintenance has proven efficacy in follicular lymphoma (FL), which is a good reason to study it in other B-cell subtypes like MCL. Young, healthy patients with MCL tend to receive aggressive treatments such as R-CHOP followed by stem cell transplantation (SCT). Almost half of MCL patients, however, are older and ineligible for SCT. Since MCL tends to be fairly resistant to chemotherapy at relapse, maintenance therapy to prolong initial remission is especially important.

When examining results of the MCL Elderly study, the benefit of maintenance therapy appears greater in the R-CHOP arm than in the FCR arm; however, this may change with longer follow-up. FCR was not as well-tolerated as R-CHOP, with more complications and greater mortality observed in the FCR induction arm. The difference in the efficacy of the induction arms has an impact on the efficacy of rituximab maintenance, especially with the short follow-up period at the time of this report. Nonetheless, this study supports using rituximab maintenance until progression following induction therapy with R-CHOP in MCL. Increases in PFS and OS were observed and if, with longer follow-up, these data stay the same, the results will definitely change the standard of care. Maintenance therapy consisting of eight doses of rituximab is currently being used in Alberta for MCL, while this study used maintenance rituximab every two months until progression. This potential change in the administration of rituximab maintenance will require consideration by funding agencies.

Cartron, et al. studied the safety and efficacy of GA101 monotherapy in relapsed/refractory aggressive non-Hodgkin lymphomas (NHL). This was a small study demonstrating that GA101 has promising activity and a good safety profile in these patients. Because the response rate is low and the PFS is short with GA101 monotherapy, it is worth investigating this agent further in combination with chemotherapy or other agents, or as maintenance therapy. There was no clear dose response relationship, but the pharmacokinetic data suggest that the higher dose studied offers a better exposure to GA101. This, combined with the lack of additional toxicity at the higher dose, suggests that the higher dose should be used in attempt to achieve better outcomes.

The high response rates in the phase II study by Fowler, et al. of lenalidomide and rituximab in previously untreated indolent B-cell NHL are very encouraging. This was a prospective study that included three different lymphoma histologies. It is, however, difficult to draw firm conclusions from phase II studies, particularly since response rates are more subjective. Response rates differ from study to study, due to differences in patient selection and application of response criteria. However, the toxicity profile of lenalidomide plus rituximab was mild, with manageable hematological side effects. In myeloma, thromboembolism, deep vein thrombosis, and cytopenias have been reported, suggesting the need for future studies that examine these side effects. This phase II study certainly provides a solid rationale for the development of phase III RCTs examining lenalidomide plus rituximab, compared with the current standard of care.
New Evidence: Please describe the rationale for your study.

Dr. Dreyling: Although the current treatment for mantle cell lymphoma (MCL) is effective and achieves initially high response rates (RRs), maintaining response is difficult and patients tend to progress quickly. In follicular lymphoma (FL), the response duration is around five to eight years following induction treatment with rituximab plus chemotherapy (R-chemo). In contrast to FL, patients with MCL tend to relapse quickly within a period of two to three years, even after achieving a complete response (CR) and minimal residual disease (MRD) negativity following induction.

In order to maintain remission, there is therefore a need for post-induction treatment in patients with MCL. Previous studies have shown maintenance treatment with interferon prolongs remission; however, interferon is not well tolerated. Because a large proportion of patients with MCL are elderly, it is important to identify a maintenance treatment that can be more easily tolerated.

Maintenance treatment with rituximab (R-maintenance) has been examined in a number of studies in FL, where it has shown to be effective with a favourable side-effect profile.1 We therefore decided to perform a study comparing maintenance treatment with rituximab and interferon in patients responding to induction with R-chemo.

New Evidence: What makes rituximab a good candidate for maintenance treatment?

Dr. Dreyling: In FL, R-maintenance has shown to be a well tolerated and effective treatment strategy. It is therefore worth investigating the role of R-maintenance in MCL, given the short duration of remission and typically elderly patient population seen with this disease.

The role of R-maintenance in MCL was unclear based on results from previous studies. A study by Ghielmini, et al. used extended treatment with rituximab as first-line and second-line treatment for MCL.2 After induction treatment with the standard schedule of rituximab, patients who responded at 12 weeks were randomly assigned to no further treatment or prolonged rituximab administration every eight weeks for four courses. However, results showed no benefit of R-maintenance vs. observation alone in these patients.

In contrast to these results, a study performed by our group in relapsed MCL did show a benefit of R-maintenance vs. observation after induction treatment with R-FCM.3 Further research is therefore needed to determine whether R-maintenance is beneficial in elderly patients with MCL.

Commentary

An Interview with Dr. Martin Dreyling on Results from the MCL Elderly Study

At the ICML 2011 Annual Congress, New Evidence spoke with Dr. Martin Dreyling, Professor of Medicine and Head of the Lymphoma Program in the Department of Medicine III, University Hospital Grosshadern, Ludwig Maximilians-University, Munich, Germany about results from the MCL Elderly study, which examined the use of maintenance rituximab in elderly patients with mantle cell lymphoma.
**New Evidence:** Please describe the patients that were included in the MCL Elderly study.

**Dr. Dreyling:** The participants in our study were elderly patients, with a median age of 70 years in the R-maintenance group and 71 years in the interferon group. Although most patients had a good performance status, about 90% had intermediate/high-risk disease according to the mantle cell international prognostic index (MIPI). In addition, around 35% of patients had elevated lactate dehydrogenase (LDH) levels, with the majority of patients in advanced-stage disease. This study population is therefore a good reflection of patients we tend to see in clinical practice.

**New Evidence:** Please describe the design of your study.

**Dr. Dreyling:** Our study was designed with two sequential randomizations. Given the success of FCR in treating chronic lymphocytic leukemia (CLL), we were interested to explore its potential role in MCL. The first randomization therefore allocated patients to R-CHOP or FCR induction treatment.

More than 80% of patients responded to induction and went on to the second phase of the study. We know that maintenance treatment works best when patients respond to induction with a high quality remission. Patients not responding to induction were therefore excluded from the second randomization and were treated with a salvage treatment according to physician discretion.

In the second randomization, patients responding to induction received either interferon using conventional (three million, three times per week) or pegylated interferon (100 μg once weekly) dosing, or R-maintenance (375 mg/m² every two months). Because the goal in elderly patients with MCL was to maintain remission as long as possible, we gave maintenance treatment until progression.

**New Evidence:** What was your rationale for using eight cycles of R-CHOP and six cycles of FCR as induction treatment?

**Dr. Dreyling:** Since MCL is a more aggressive disease than FL, we felt it was important to use eight cycles instead of the typical six cycles of R-CHOP used in FL. In addition, to compare the two induction treatments, it is important to use the same duration of treatment. By using eight cycles of R-CHOP and six cycles of FCR, we were able to ensure induction treatment with the same duration in both induction arms. Although we cannot exclude the possibility that giving eight cycles vs. six cycles of R-CHOP affected study results, I would suspect that the impact would be minimal, if any.

**New Evidence:** What was the rationale for using a two-month maintenance interval of rituximab?

**Dr. Dreyling:** In FL, studies have shown that R-maintenance is effective when given every two months in the first-line setting and every three months in the relapsed setting. In addition, data has shown that R-maintenance given every two months maintains serum levels at around 25 μg/mL, which is the level that has been associated with response to rituximab. Since MCL is a more aggressive disease than FL, we picked the shorter interval of two months for R-maintenance. Although we do not have any meaningful data on serum levels of rituximab in MCL, we can assume they would be similar to what has been shown in FL.

**New Evidence:** Why do you think the benefit of maintenance treatment was greater in the R-CHOP than the FCR induction arm?

**Dr. Dreyling:** Results of our study showed response to maintenance treatment was significantly lower in the FCR than the R-CHOP induction arm. Patients treated with R-CHOP showed an overall survival (OS) advantage over those treated with FCR (three-year OS was 85% vs. 70% after interferon; \( p = 0.037 \)). In addition, FCR followed by R-maintenance resulted in a higher infection rate than in any other treatment group. Targeting T-cells with purine analogues such as fludarabine followed by eliminating B-cells with rituximab maintenance may be the reason for the higher number of infections and lower efficacy seen in this group. Given the lower efficacy and higher toxicity of FCR followed by R-maintenance, we do not recommend this induction regimen in the first-line treatment of MCL.
**New Evidence:** Please describe the efficacy results of the maintenance portion of the study.

**Dr. Dreyling:** When we started the MCL Elderly study, we hypothesized that there would be a benefit of R-maintenance, but that the benefit would be minor compared with what has been shown in FL, based on results from the Ghielmini study. It was therefore surprising that R-maintenance showed a highly clinically significant benefit in these MCL patients. The difference in progression-free survival (PFS) was more than four years between the R-maintenance and interferon groups (77 months vs. 24 months). In addition, we have already seen a benefit in OS of R-maintenance vs. interferon in the R-CHOP subgroup ($p = 0.006$). These results are not only clinically meaningful, but also support a new standard in the treatment of MCL.

**New Evidence:** Please describe the safety results of the study.

**Dr. Dreyling:** With the exception of the FCR subgroup, in which infectious complications were observed in the R-maintenance arm, there was a higher rate of side effects in the interferon arm. Patients in the interferon arm experienced greater hematological toxicity and a higher number of flu-like symptoms, fatigue, and depression. Accordingly, fewer patients stopped maintenance due to side effects in the R-maintenance arm than in the interferon arm.

**New Evidence:** How should clinical practice change based on the results of this study?

**Dr. Dreyling:** Based on the large prolongation of remission seen with R-maintenance in our study, there is a consensus in our group that R-maintenance should be the standard treatment following induction in patients with MCL. We have also changed our institution guidelines to reflect this consensus. The use of R-maintenance after induction is, however, an off-label recommendation. We are now hoping that the indication for rituximab maintenance will be extended to MCL based on our convincing study results.

Investigators who are aware of our study have also adapted their MCL trials to use R-maintenance as a standard treatment arm. In addition, ongoing studies are examining the role of rituximab after autologous stem cell transplant (AuSCT) in younger patients.

Based on the results of the induction portion of our study, I would discourage the use of fludarabine-containing treatments in MCL. However, whether R-CHOP is always the optimal induction treatment is unclear. Rituximab plus bendamustine (BR) is a promising alternative to R-CHOP. Bendamustine has some alkylator and purine analogue properties, suggesting that it may be favourable in patients with MCL. However, I would strongly discourage a dose of bendamustine above 90 mg/m$^2$ on days 1 and 2 every four weeks due to the toxicities we have seen with purine analogues such as fludarabine. Given our available treatment options, I would still prefer R-CHOP in fit patients with aggressive disease, as indicated by elevated LDH levels. In contrast, in elderly patients with a more indolent MCL, BR may be the treatment of choice.

**References:**
A Spotlight on Bendamustine

Bendamustine: Shaping its Use in Lymphoproliferative Disorders

Bendamustine is a water-soluble, bifunctional chemotherapeutic agent that combines the properties of an alkylating agent with those of a purine analogue that only has partial cross-resistance with other alkylators.1,2 Its unique mechanism of action, decreased susceptibility to drug resistance, clinical activity in non-Hodgkin lymphomas (NHL) and chronic lymphocytic leukemia (CLL), and favourable side-effect profile render this agent a promising option in the management of lymphoproliferative disorders.1

The incurability of indolent B-cell lymphomas with the current treatment, combined with the long-term survival of some patients with indolent lymphomas identifies an unmet need for highly effective therapeutics with favourable side effect profiles and minimal long-term risks.1 Bendamustine has the potential to fill this need.

Further studies to clarify the role of bendamustine are ongoing. Some of these were presented at ASCO 2011, EHA 2011 and ICML 2011:

- A phase I/II study of bendamustine with bortezomib for the treatment of multiple myeloma demonstrating that this combination was well tolerated was presented at ASCO 2011.
- At EHA 2011, preliminary results of a study combining bendamustine with rituximab for the treatment of indolent, non-follicular NHL in elderly previously untreated patients indicated that this combination is effective and safe with tolerable toxicities.
- A systematic review and meta-analysis of randomized controlled trials of bendamustine in patients with indolent lymphoma and CLL presented at EHA 2011 demonstrated for the first time that bendamustine improves overall survival (OS) and progression-free survival (PFS) compared with other chemotherapy regimens.
- In an attempt to improve outcomes for patients undergoing allogeneic stem cell transplantation, bendamustine was substituted for cyclophosphamide in the conditioning treatment for nonmyeloablative allogeneic stem cell transplantation that also contained fludarabine and rituximab. The results, presented at ICML 2011, suggest for the first time that this conditioning treatment was well tolerated and effective.


Berenson JR, et al. ASCO 2011: Abstract 8070

Efficacy and safety of bendamustine plus bortezomib in relapsed/refractory multiple myeloma: A phase I/II trial

Background

Novel and effective treatment combinations are needed for patients with relapsed/refractory multiple myeloma (MM). Bendamustine is a unique alkylating agent, which is active in MM. Bortezomib is approved for the treatment of MM and has previously been shown to be effective in combination with other alkylators such as melphalan and cyclophosphamide.

Berenson and colleagues presented the results of an open-label, phase I/II study that assessed the efficacy and safety of bendamustine plus bortezomib in relapsed/refractory MM at ASCO 2011.1
Study design

- Patients older than 18 years, with measurable, relapsed/refractory MM were enrolled in this study.
- Treatment included escalating doses of intravenous bendamustine at 50, 70, or 90 mg/m² (on days 1 and 4 of each cycle) plus bortezomib 1.0 mg/m² (on days 1, 4, 8, and 11 of each cycle) for up to eight 28-day cycles.
- Dose-limiting toxicities (DLTs) were assessed after cycle 1.
- A standard three-plus-three approach was used to determine the maximum tolerated dose (MTD), and the MTD cohort was expanded to 40 patients.
- Endpoints included response, duration of response, time to progression (TTP), and safety.

Key findings

- 38 patients with a median age of 67 years (range: 43–89 years) received treatment with this experimental study drug combination and were included in the analysis.
- The patients had received a median of 3.5 prior therapies (range: 1–21), including bortezomib in 71% and alkylators in 68% of cases.
- A median of three treatment cycles (range: 1–9 cycles) were administered, and study treatment is ongoing in 14 patients (median cycles administered to date is four [range: 1–7 cycles] in these patients).
- No DLTs were observed, and bendamustine at a dose of 90 mg/m² plus bortezomib 1.0 mg/m² was designated the MTD.
- Grade 3–4 adverse events (AEs) that occurred in ≥10% of patients included neutropenia (13 patients [34%]), thrombocytopenia (seven patients [21%]), and anemia (four patients [11%]).
- Grade 3–4 infection occurred in three patients (8%), and grade 3 renal failure was observed in two patients (5%).
- No grade 3–4 peripheral neuropathy (PN) was observed but grade 1–2 PN was reported in 10 patients (26%), with eight of these patients having baseline PN at the time of study enrollment.
- In 36 evaluable patients, the objective response rate (ORR) was 47%, including one very good partial response, six partial responses, and 10 minimal responses.
- In subgroups of patients, the observed ORR was:
  - 52% in the 90 mg/m² cohort (n = 27);
  - 37% in patients with prior bortezomib exposure;
  - 40% in patients with prior alkylator exposure.
- An additional 17 patients had stable disease.
- Taking all of these results together, the clinical benefit rate (ORR plus stable disease) was 94%.
- The median duration of response and TTP have not been reached.

### Table 1. Grade 3–4 adverse events

<table>
<thead>
<tr>
<th>Grade 3–4 adverse event that occurred in ≥10% of patients</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>13 (34)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

Key conclusions

- **Bendamustine 90 mg/m² plus bortezomib 1.0 mg/m² is well tolerated.**
- **Bendamustine plus bortezomib demonstrates promising efficacy in this heavily pretreated population of MM patients.**

Rituximab plus bendamustine regimen in elderly previously untreated patients with indolent, non-follicular NHL: Preliminary data of a single centre study

Background
Bendamustine has shown considerable activity for solid and lymphoid malignancies. It has recently become available for clinical use as a first-line treatment for chronic lymphocytic leukemia (CLL) and as salvage therapy after rituximab or rituximab-based regimens for early relapsed or refractory indolent B-cell non-Hodgkin lymphoma (NHL). Recent clinical trials have demonstrated the safety and efficacy of bendamustine in these settings.

Pennesse and Di Renzo assessed the efficacy and safety of bendamustine in combination with rituximab in elderly previously untreated patients with indolent, non-follicular NHL. The results of this study were presented at EHA 2011.1

Study design
- Elderly patients with previously untreated indolent, non-follicular NHL were enrolled in this single centre study.
- The study treatment consisted of six to eight 21- to 28-day cycles of rituximab at a dose of 375 mg/m² given intravenously on day 1 of each cycle, and bendamustine 80 mg/m² given intravenously on days 1 and 2.
- Response assessment was planned after the first three cycles were administered and at the end of treatment.
- Supportive therapy with granulocyte colony-stimulating factor (G-CSF) and erythropoietin-stimulating agents (ESA) were provided as needed.

Key findings
- Between October 2008 to May 2010, 20 patients (15 males and five females) with previously untreated indolent, non-follicular NHL were enrolled in the study.
  - The median age was 74 years (range: 64–85 years) with 17 patients (85%) being older than 70 years.
  - 11 patients (55%) had B-cell CLL or small lymphoblastic lymphoma (B-CLL/SLL), eight patients (40%) had lymphoplasmacytoid lymphoma or Waldenström’s macroglobulinemia (LPL/WM), and one patient (5%) had splenic marginal zone lymphoma (SMZL).
  - Extranodal site involvement was present in one patient (5%) and all patients had bone marrow involvement.
  - 14 patients (70%) had comorbid conditions and 30% had two or more diseases.
  - A median of five cycles was delivered (range: 3–8 cycles) and 14 patients (70%) completed the planned treatment.
  - Dose reduction occurred in four patients (20%); Nine patients (45%) received G-CSF as primary (10%) and secondary (25%) prophylaxis; ESA support was required in four patients (22%).
  - Complete response (CR) was achieved in 11 patients (55%) and partial response (PR) in nine patients (45%), resulting in an overall response rate (ORR) of 100%.
  - 10 of the 11 (91%) patients with B-CLL/SLL achieved CR, while all patients with LPL/WM had a PR.
  - No relapses were observed.
  - The median follow-up was 16 months (range: 4–23 months).
  - The regimen of rituximab and bendamustine was safe and well tolerated.
  - The main adverse event (AE) was neutropenia, which occurred in 39% of patients.
  - Severe neutropenia (grade 3–4) was observed in four patients (20%).
  - No non-hematological AEs were observed and there were no deaths related to the study medication.

Key conclusions
- Rituximab and bendamustine is an effective regimen for elderly patients with previously untreated indolent non-follicular NHL including CLL/SLL.
- The treatment is safe, with tolerable toxicities consisting of myelosuppression.
- A longer follow-up period is needed to define response duration and long-term safety.

Bendamustine for patients with indolent lymphoma – a systematic review and meta-analysis of RCTs

Background
Outcomes of patients with indolent lymphoma have improved in recent decades. While it is clear that the addition of rituximab to induction chemotherapy improves survival of these patients, it is unclear what the best chemotherapy partner for rituximab is. None of the chemotherapy regimens that have been compared in randomized controlled trials (RCTs) were superior in terms of overall survival (OS). A number of RCTs have examined the effect of bendamustine in patients with indolent lymphoma including follicular lymphoma (FL). Progression-free survival (PFS) was similar or prolonged with bendamustine compared with other chemotherapy, but an OS benefit has not yet been shown.

At EHA 2011, Vidal, et al., presented the results of their systematic review and meta-analysis in which they evaluated the effect of bendamustine on the OS of patients with indolent lymphoma.1

Study design
• RCTs that compared bendamustine to other chemotherapy regimens for patients with indolent lymphoma were included in this meta-analysis.
• The Cochrane Library, MEDLINE, LILACS, references and personal correspondence, conference proceedings from ASH, ASCO, and EHA (2000–2010), and databases of ongoing trials were searched in December 2010.
• Methodological quality assessment was performed using the individual component approach.

Key findings
• Four trials were identified for inclusion in this meta-analysis.
  ◦ They were conducted between the years 1994 and 2010 and published between 2006 and 2010.
  ◦ The studies randomized a total of 1,251 adult patients with a mean or median age of 58 to 68 years.
• The rate of patients with FL ranged between 40% to 52%, and mantle cell lymphoma 20% to 21% in the three trials that included patients with those types of lymphomas.
• One trial included only patients with chronic lymphocytic leukemia (CLL).
• The comparisons were between:
  ◦ Bendamustine, vincristine, prednisone to cyclophosphamide, vincristine, prednisone (COP);
  ◦ Bendamustine-rituximab to rituximab, cyclophosphamide, adriamycin, vincristine, prednisone (R-CHOP);
  ◦ Bendamustine-rituximab to fludarabine-rituximab;
  ◦ Bendamustine to chlorambucil.

Table 1. Characteristics of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Mean/median age (years)</th>
<th>Lymphoma</th>
<th>Bendamustine regimen</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herold 2006</td>
<td>164</td>
<td>58</td>
<td>FL (40%), MCL (21%), other</td>
<td>Bendamustine, vincristine, prednisone</td>
<td>COP</td>
</tr>
<tr>
<td>Rummel 2009</td>
<td>549</td>
<td>64</td>
<td>FL (52%), MCL (20%), other</td>
<td>Rituximab, bendamustine</td>
<td>R-CHOP</td>
</tr>
<tr>
<td>Rummel 2010</td>
<td>219</td>
<td>68</td>
<td>FL (46%), MCL (20%), other</td>
<td>Rituximab, bendamustine</td>
<td>R-fludarabine</td>
</tr>
<tr>
<td>Knauf 2009</td>
<td>319</td>
<td>63</td>
<td>CLL</td>
<td>Bendamustine</td>
<td>Chlorambucil</td>
</tr>
</tbody>
</table>

CLL = Chronic lymphocytic lymphoma; COP = cyclophosphamide, vincristine, prednisone; FL = follicular lymphoma; MCL = mantle cell lymphoma; R-CHOP = rituximab, cyclophosphamide, adriamycin, vincristine, prednisone
Patients treated with bendamustine had an improved OS compared with controls and the RR for death was 0.80 (95% CI: 0.67–0.97, I² = 0). (Figure 1)

After excluding the trial with only CLL patients, the RR for death became 0.82 (95% CI: 0.67 –1.01).

PFS was improved with bendamustine, with an hazard ratio (HR) of 0.47 (95% CI: 0.39–0.57).

Complete remission rates improved with bendamustine compared with controls, with an RR of 2.31 (95% CI: 1.07–4.96, random effects model, I² = 88%).

The rate of grade 3–4 adverse events was unaffected, with an RR of 1.21 (95% CI: 0.99–1.48).

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**Figure 1. All cause mortality in patients with indolent lymphoma treated with bendamustine compared to other chemotherapy**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bendamustine</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent lymphomas (FL, MCL, others)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herold 2006</td>
<td>32/82/43</td>
<td>80/43</td>
<td>29.5%</td>
<td>0.73 (0.52–1.02)</td>
</tr>
<tr>
<td>Rummel 2009</td>
<td>34/260/33</td>
<td>253/33</td>
<td>17.0%</td>
<td>1.00 (0.64–1.57)</td>
</tr>
<tr>
<td>Rummel 2010</td>
<td>42/109/46</td>
<td>99/46</td>
<td>33.5%</td>
<td>0.83 (0.60–1.14)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>451/432</td>
<td>80.0%</td>
<td></td>
<td>0.82 (0.67–1.01)</td>
</tr>
<tr>
<td>Total events</td>
<td>108/122</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau* = 0.00; Chi² = 1.32, df = 2 (p = 0.52); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.87 (p = 0.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| CLL patients only                 |              |         |            |            |
| Knauf 2009                        | 31/162/41    | 157/41  | 20.0%      | 0.73 (0.49–1.11) |
| Subtotal (95% CI)                 | 162/157      | 20.0%   |            | 0.73 (0.49–1.11) |
| Total events                      | 108/41       |         |            |             |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.48 (p = 0.14) |

| Total (95% CI)                    | 613/589      | 100%    | 0.80 (0.67–0.97) |
| Total events                      | 139/163      |         |             |
| Heterogeneity: Tau* = 0.00; Chi² = 1.54, df = 3 (p = 0.67); I² = 0% |
| Test for overall effect: Z = 2.33 (p = 0.02) |
| Test for subgroup differences: Chi² = 0.24, df = 1 (p = 0.62), I² = 0% |

95% CI = 95% confidence interval; CLL = Chronic lymphocytic lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma

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**Key conclusions**

- This meta-analysis shows for the first time that bendamustine improves OS and PFS in patients with indolent lymphoma and CLL compared with other chemotherapy regimens.

- These results should be interpreted cautiously due to the wide clinical heterogeneity of patients and treatments.

- Further trials of a more homogenous group should be performed to explore the role of bendamustine in various lymphoproliferative neoplasms.

Background
It has previously been reported that fludarabine, rituximab, and cyclophosphamide have been used as nonmyeloablative conditioning therapy. Based on bendamustine’s efficacy in a number of different types of lymphoma, it is hypothesized that in the setting of nonmyeloablative allogeneic allografting, it can induce remission and stabilize disease with low toxicity. In order to improve outcomes in allogeneic stem cell transplantation, Khouri and colleagues studied the impact of substituting cyclophosphamide with bendamustine in conditioning. The results of this study were presented at ICML 2011.

Study design
• Patients with relapsed CD20-positive non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL) were included in this study.
• Bendamustine was given intravenously in an escalated dose of 70, 90, 110, and 130 mg/m² daily three and five days prior to transplantation.
• Fludarabine at a dose of 30 mg/m² was given on the same days.
• Rituximab was given at a dose of 375 mg/m² 13 days prior to transplant and at a dose of 1,000 mg/m² on six days prior, and one and eight days after transplant.
• Tacrolimus and methotrexate were used for graft versus host disease (GVHD) prophylaxis.
• Thymoglobulin 1 mg/kg was given one and two days prior to transplant to patients who were being transplanted from an unrelated donor.
• The primary endpoints were engraftment and dose-limiting toxicities (DLTs).
• The secondary endpoints were response rates and occurrence of GVHD.

Key findings
• The study included 23 patients: nine with mantle cell lymphoma (MCL), four with follicular lymphoma (FL), six with CLL (two of whom had del 17p and one Richter), and four with diffuse large B-cell lymphoma (DLBCL).
• Median age was 60 years (range: 30–70 years).
• Median prior treatments was two (range: 1–5) and three patients (13%) had prior transplant.
• At the time of transplant, 18 patients (78%) were relapsed and sensitive to induction while four (22%) were refractory or had primary induction failure.
• 15 patients received their transplants from related donors and eight from matched unrelated donors.
• The number of patients who received the 70, 90, 110, and 130 mg/m² daily doses of bendamustine were two, three, three, and 15, respectively.
• One patient had a secondary rejection of stem cells from an unrelated donor (low stem cell dose).
• 14 patients (61%) did not nadir to an absolute neutrophil count (ANC) <500 and 19 (83%) did not experience a platelet count <20,000/mm³.
• The median donor T-cell chimerism at day 30 was 93%.
• One patient developed acute GVHD (grade 3) and one of 21 evaluable patients developed chronic GVHD.
• With a median follow-up time of eight months (range: 3–25 months), the overall survival (OS) and progression-free survival (PFS) rates were 92% and 79%, respectively. (Figure 1)
• Complete remission was observed in 18 patients (78%) and partial remission in three (13%) patients. (Figure 2)
• Fungal infection was the cause of the only death observed and that patient also experienced grade 4 gastrointestinal and neurologic adverse events (AEs).
• The maximal grade of other observed toxicities was 3 and these included 11 grade 3 infections and two grade 3 cardiovascular AEs.
• No DLT was observed.

Bendamustine in combination with fludarabine and rituximab: A phase I-II novel non-myeloablative conditioning for AST in patients with lymphoid malignancies

Khouri IF, et al. ICML 2011: Abstract 042
Figure 1. Bendamustine-based allogeneic nonmyeloablative conditioning survival

![Cumulative Proportion Surviving](image)

OS, 92%
PFS, 79%

Months Post Transplant

OS = overall survival; PFS = progression-free survival

Figure 2. Bendamustine-based allogeneic nonmyeloablative conditioning response

![Response](image)

CR = complete response; PR = partial response; SD = stable disease

Key conclusions

- This study is the first report to suggest that combining bendamustine at a dose of up to 130 mg/m² daily for three days with fludarabine and rituximab is safe and constitutes a well-tolerated conditioning treatment for nonmyeloablative allogeneic stem cell transplantation.

- Immunosuppression without myelosuppression was achievable and the toxicities were minimal, with no DLT and low rates of acute GVHD.

- Currently, patients are being treated with this regimen in an outpatient setting and the study is ongoing to verify the safety and efficacy of bendamustine, fludarabine, and rituximab.

References:
Bendamustine is a unique cytotoxic agent with structural similarities to both alkylating agents and purine analogs. It is a well-tolerated drug with a favourable toxicity profile and has demonstrated a high level of efficacy in both indolent non-Hodgkin lymphoma (iNHL) and chronic lymphocytic leukemia (CLL). It is anticipated to be available for clinical use in Canada in the near future. Available data provides ample evidence to support the use of bendamustine in both untreated and relapsed/refractory patients, and once approved, will provide an important additional therapeutic option for patients with lymphoproliferative disorders.

Berenson and colleagues examined the safety and efficacy of bendamustine combined with bortezomib in relapsed/refractory multiple myeloma using a phase I/II dose escalation study design. Bortezomib is a standard treatment option for multiple myeloma and this trial demonstrated that adding bendamustine to bortezomib up to a dose of 90 mg/m² is feasible and safe, with no dose-limiting toxicities (DLTs) or unexpected safety signals. While this combination appears to have promising efficacy in this heavily pretreated population, further studies will be necessary to assess the clinical benefit over other approaches, including bortezomib monotherapy.

In the study by Pennesse and Di Renzo, the combination of rituximab plus bendamustine was evaluated in elderly patients (median age 74 years; range: 64–85 years) with previously untreated non-follicular iNHL. Patients with multiple histologies were included in this study: 55% had B-cell CLL or small lymphocytic lymphoma, 40% had lymphoplasmacytic lymphoma or Waldenström’s macroglobulinemia, and 5% had splenic marginal zone lymphoma. This single-arm phase II study demonstrated that this combination was very well tolerated by this elderly patient cohort with multiple comorbid conditions.

Planned treatment was completed by 70% of the patients. The most commonly observed hematological toxicity was myelosuppression, which was manageable with a low rate of infection; no non-hematological adverse events were seen.

Rituximab plus bendamustine demonstrated an impressive level of efficacy, with an overall response (ORR) rate of 100% (55% complete responses and 45% partial responses). While longer follow-up is required to assess long-term safety and response duration, further studies comparing this treatment combination against the current standard of care would seem warranted. This trial by Pennesse and Di Renzo adds to the growing number of trials that support the utility of bendamustine plus rituximab for iNHL.

Vidal, et al. conducted a meta-analysis of four trials that compared bendamustine to other chemotherapy regimens in patients with indolent lymphomas. A limitation of this meta-analysis is the small number of studies identified, the inclusion of studies covering multiple histologies and a variety of treatment regimens, which make it difficult to interpret findings. However, the individual studies demonstrate that bendamustine is highly effective in CLL and iNHL in the upfront and relapsed settings, with superior response rates and progression-free survival (PFS) rates. Longer follow-up will be required to fully assess the potential benefit in terms of overall survival (OS).

In the study by Khouri, et al. the combination of bendamustine, fludarabine, and rituximab was evaluated in a phase I/II setting as a conditioning regimen for patients with iNHL undergoing allogeneic stem cell transplantation. Studies that attempt to improve the efficacy and safety of conditioning regimens prior to transplant are warranted to achieve better disease control. Incorporating bendamustine into this conditioning regimen appears to have a high level of efficacy, is safe with minimal toxicities, no DLTs, and low rates of acute graft versus host disease. Further studies are therefore warranted to evaluate the role of bendamustine in the pre-transplant setting.

Once approved by Health Canada, bendamustine will provide an additional treatment option for patients with CLL and iNHL, particularly for those who are not candidates for more aggressive chemotherapy. Current evidence suggests that bendamustine is safe and effective, with demonstrated activity in both the upfront and relapsed settings. There will likely be a strong desire by both physicians and patients to have it funded in a timely fashion. It is expected that this agent will be highly utilized and play a major role in the management NHL and CLL.
New Evidence: Please describe the results of studies using bendamustine in CLL.

Dr. Vidal: A trial conducted by Knauf, et al. randomized 319 patients with advanced chronic lymphocytic leukemia (CLL) to receive bendamustine (n = 162) or chlorambucil (n = 157) as first-line therapy. Although bendamustine did not significantly improve overall survival (OS), overall response rates (ORR) and progression-free survival (PFS) were statistically superior in the bendamustine vs. the chlorambucil arm (ORR: 68% vs. 31%; PFS: 21.6 months vs. 3 months; \( p < 0.001 \)). Bendamustine also improved the median duration of remission, compared with chlorambucil (21.8 months vs. 8.0 months). The rate of grade 3/4 adverse events (AEs), including hematologic AEs and infections, was higher with bendamustine compared with chlorambucil. Based on the results of this trial, bendamustine was approved by the FDA for patients with CLL.

A number of ongoing phase I/II studies are examining the effect of bendamustine in combination with other agents such as rituximab, ofatumumab, lenalidomide, and fludarabine. In addition, a phase III study is comparing bendamustine plus rituximab (BR) with chlorambucil plus rituximab in previously treated and untreated patients with CLL.

New Evidence: Please describe the results of studies using bendamustine in indolent lymphomas.

Dr. Vidal: The first randomized trial examining bendamustine in indolent lymphoma was a phase III study conducted by Herold, et al. that compared bendamustine, vincristine, and prednisone (BOP) to cyclophosphamide, vincristine, and prednisone (COP) in untreated patients with indolent non-Hodgkin lymphoma (iNHL) or mantle cell lymphoma (MCL). Efficacy of BOP and COP were comparable, with complete response (CR) rates of 22% vs. 20%, and projected five-year OS rates of 61% vs. 46%, respectively. Safety outcomes were comparable in both groups, although alopecia and leukopenia were more severe with COP.
Following the study by Herold, *et al.*, a study by Rummel, *et al.* compared BR to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line therapy in 549 patients with follicular lymphoma (FL) and MCL. Although ORR was similar across groups, PFS, event-free survival (EFS), and time to next treatment (TTNT) were significantly longer after BR vs. R-CHOP (PFS: 54.8 months vs. 34.8 months; EFS: 54 months vs. 31 months; TTNT: median not reached vs. 40.7 months; *p* <0.001). In addition, R-CHOP was more frequently associated with AEs than BR, such as hematological toxicities, infectious complications, and peripheral neuropathy (*p* <0.05), as well as alopecia (15% vs. 62% of patients). However, a greater number of skin reactions were reported in the BR group (*p* = 0.01).

A second study by Rummel, *et al.* compared BR to rituximab plus fludarabine (FR) in 208 relapsed patients with FL, MCL, or indolent lymphoma. ORR and median PFS were statistically superior with BR compared with FR (ORR: 83.5% vs. 52.5%; PFS: 30 months vs. 11 months; *p* <0.0001). In addition, safety outcomes were comparable between groups. The full reports of both Rummel studies are pending.

Bendamustine is currently approved by the FDA for indolent lymphoma patients with early relapse following rituximab-containing therapy. In Israel, bendamustine is approved as second-line therapy for patients with indolent lymphomas.

A number of ongoing studies are examining the role of bendamustine in combination with other agents such as rituximab, bortezomib, and GA-101. The efficacy of bendamustine is also being examined in elderly patients with FL. Finally, first-line treatment with BR is being compared with rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP), and R-CHOP in a randomized trial of patients with indolent lymphoma or MCL.

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**New Evidence:** Please describe the methodology used in your meta-analysis.

**Dr. Vidal:** Our study was a collaboration between myself, Dr. Anat Gafter-Gvili, and Dr. Ofer Shpilberg from Israel, as well as Dr. Martin Dreyling from Germany. The methodology included a systematic review and meta-analysis of randomized trials comparing bendamustine with other chemotherapies for patients with indolent lymphomas including FL, MCL, lymphoplasmacytic lymphoma, marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and CLL. In December 2010, we searched The Cochrane Library, MEDLINE, LILACS, conference proceedings, and databases of ongoing trials. Two reviewers independently assessed the quality of the studies and extracted relevant data. Authors of all included trials were contacted for complementary information.

The primary outcome of our study was all-cause mortality. Relative risk (RR) for dichotomous data and hazard ratio (HR) for time-to-event data were estimated and pooled using a random-effects model, which is a conservative method used for meta-analyses.

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**New Evidence:** Please describe the efficacy results of your meta-analysis.

**Dr. Vidal:** We identified a total of four eligible trials, which were conducted from 1994–2010 and included a total of 1,251 patients. Patients treated with bendamustine had improved OS compared with pooled controls, with a RR of death of 0.80 (95% CI: 0.67–0.97). After excluding the trial with only CLL patients (Knauf, *et al.* 2009), the RR was 0.82 (95% CI: 0.67–1.01). PFS was also improved with bendamustine, with a HR of 0.47 (95% CI: 0.39–0.57). In addition, the CR rate improved with bendamustine compared with controls, with a RR of 2.31 (95% CI: 1.07–4.96).

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**New Evidence:** Please describe the safety results of your study.

**Dr. Vidal:** In general, the safety profile of bendamustine is comparable to that of the standard of care in iNHL. This was reflected in our study, which showed the rate of grade 3/4 AEs was not affected by the allocated treatment arm (RR 1.21; 95% CI: 0.99–1.48).
**New Evidence:** What are the limitations of your study?

**Dr. Vidal:** In our meta-analysis, there was great degree of heterogeneity between trials. Studies varied in patient populations, with differences in included disease types such as CLL, FL, and MCL. In addition, there was a wide variation in the regimen of bendamustine that was used, as well as comparator treatments. Studies also varied in the length of follow-up, and two of the included trials were published only as abstracts and were not yet available as published papers (Rummel, et al. 2009; Rummel, et al. 2010).

**New Evidence:** In your opinion, how should bendamustine be used in CLL and iNHL?

**Dr. Vidal:** For patients with CLL, bendamustine can be considered in patients who are not candidates for fludarabine-containing therapy. In patients with iNHL, current data supporting the use of BR as first-line treatment are based on one randomized trial. Therefore, based on current data, both BR and R-CHOP are reasonable options for first- and second-line treatment of patients with indolent lymphomas. In the relapsed setting, BR may be used in patients who did not previously receive it as first-line therapy.

**New Evidence:** How should potential hematologic toxicity and infections be effectively managed with the use of bendamustine?

**Dr. Vidal:** Physicians should be aware of the hazards of bendamustine especially when used as second-line therapy or earlier, as well as in patients with advanced CLL. For these patients, bendamustine should be prescribed with granulocyte colony stimulating factor (G-CSF) prophylaxis, along with careful monitoring of blood counts.

**References:**
Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

Data from one single publication suggest that ant partum thromboprophylaxis is warranted in pregnant women with idiopathic thrombosis or symptomatic thrombophilia.

Teratogenic Effects: As with other low molecular weight heparins (LMWH), FRAGMIN should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received LMWHs during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

Non-teratogenic Effects: There have been postmarketing reports of fetal death when pregnant women received low molecular weight heparins. Causality for these cases has not been established. Pregnant women receiving anticoagulants, including FRAGMIN, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving FRAGMIN should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if FRAGMIN is administered during pregnancy.

Nursing Women:
It is not known whether FRAGMIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to nursing women.

Pediatrics:
The safety and effectiveness of FRAGMIN in children have not been established.

Geriatrics:
Elderly patients receiving low molecular weight heparins are at increased risk of bleeding. Careful attention to dosing intervals and concomitant medications, especially anti-platelet preparations, is advised. Close monitoring of elderly patients with low body weight (e.g., <45 kg) and those predisposed to decreased renal function is recommended.

Patients with Extreme Body Weight:
Safety and efficacy of low molecular weight heparins in high weight (e.g., >120 kg) and low weight (e.g., <46 kg) patients have not been fully determined. Individualized clinical and laboratory monitoring are recommended in these patients.

Data from one single publication suggest that in the thrombosis treatment setting, a weight-adjusted dose beyond the recommended maximum dose of 18,000 IU per day (the largest patient weighed 190 kg and received a daily dose of 38,000 IU) results in mean peak anti-Xa levels that are within the therapeutically acceptable range.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

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Data from one single publication suggest that ant partum thromboprophylaxis is warranted in pregnant women with idiopathic thrombosis or symptomatic thrombophilia.

Teratogenic Effects: As with other low molecular weight heparins (LMWH), FRAGMIN should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received LMWHs during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

Non-teratogenic Effects: There have been postmarketing reports of fetal death when pregnant women received low molecular weight heparins. Causality for these cases has not been established. Pregnant women receiving anticoagulants, including FRAGMIN, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving FRAGMIN should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if FRAGMIN is administered during pregnancy.

Nursing Women:
It is not known whether FRAGMIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to nursing women.

Pediatrics:
The safety and effectiveness of FRAGMIN in children have not been established.

Geriatrics:
Elderly patients receiving low molecular weight heparins are at increased risk of bleeding. Careful attention to dosing intervals and concomitant medications, especially anti-platelet preparations, is advised. Close monitoring of elderly patients with low body weight (e.g., <45 kg) and those predisposed to decreased renal function is recommended.

Patients with Extreme Body Weight:
Safety and efficacy of low molecular weight heparins in high weight (e.g., >120 kg) and low weight (e.g., <46 kg) patients have not been fully determined. Individualized clinical and laboratory monitoring are recommended in these patients.

Data from one single publication suggest that in the thrombosis treatment setting, a weight-adjusted dose beyond the recommended maximum dose of 18,000 IU per day (the largest patient weighed 190 kg and received a daily dose of 38,000 IU) results in mean peak anti-Xa levels that are within the therapeutically acceptable range.
Cardiovascular
Use in Patients with Prosthetic Heart Valves: Cases of prosthetic valve thrombosis have been reported in these patients who have received low molecular weight heparins for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and/or fetal deaths. Pregnant women are at higher risk of thromboembolism (see WARNINGS AND PRECAUTIONS, Patient Selection Criteria, SPECIAL POPULATION, Pregnant Women).

Use in Unstable Coronary Artery Disease: When thrombolytic treatment is considered appropriate in patients with unstable angina and non-Q-wave myocardial infarction, concomitant use of an anticoagulant such as FRAGMIN may increase the risk of bleeding.

Gastrointestinal
FRAGMIN should be used with caution in patients with a history of gastrointestinal ulceration.

Hematologic
Hemorrhage: Bleeding may occur in conjunction with unfractionated heparin or low molecular weight heparin use. As with other anticoagulants, FRAGMIN should be used with extreme caution in patients at increased risk of hemorrhage. Bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Platelets/Thrombocytopenia: Platelet counts should be determined prior to the start of treatment with FRAGMIN and, subsequently, twice weekly for the duration of treatment. Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. Its incidence is unknown at present.

Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia or platelet defects.

During FRAGMIN administration, special caution is necessary in rapidly-developing thrombocytopenia and severe thrombocytopenia (<100 000/µL). A positive or unknown result obtained from in vitro tests for antplatelet antibody in the presence of FRAGMIN or other low molecular weight heparins and/or heparins would contraindicate FRAGMIN.

Hepatic
FRAGMIN should be used with caution in patients with hepatic insufficiency, as these patients may have potentially higher risk of hemorrhage.

Hyperkalemia
Heparin and low molecular weight heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium sparing drugs. Plasma potassium should be measured in patients at risk.

Osteoporosis
Long-term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with dalteparin, the risk of osteoporosis cannot be excluded (see TOXICOLOGY, Long-term Toxicity, Human Toxicology).

Peri-Operative Considerations
Spinal/Epidural Hematomas:
When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see CONTRAINDICATIONS and ADVERSE REACTIONS).

When a higher dose (5000 IU s.c.) of FRAGMIN is administered for thromboprophylaxis in conjunction with surgery, no spinal/epidural invasion should be performed for at least 12 hours following the last dose of FRAGMIN and the next dose should be held until at least 12 hours after the anesthetic procedure. Alternatively, when a lower dose (2500 IU s.c.) of FRAGMIN is administered, the dose can be initiated 1-2 hours prior to surgery. FRAGMIN injection should be given after spinal/epidural anesthesia and only if the anesthesiologist considers the spinal/epidural puncture as uncomplicated. Indwelling catheters should not be removed or manipulated for at least 10-12 hours following the last dose of FRAGMIN.

Use in Knee Surgery: The risk of bleeding in knee surgery patients receiving low molecular weight heparins may be greater than in other orthopedic surgical procedures. It should be noted that hemarthrosis is a serious complication of knee surgery. The frequency of bleeding events observed with FRAGMIN in orthopedic surgery patients is derived from clinical trials in hip replacement surgery patients. The physician should weigh the potential risks with the potential benefits to the patient in determining whether to administer a low molecular weight heparin in this patient population.

Selection of General Surgery Patients: Risk factors associated with postoperative venous thromboembolism following general surgery include history of venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone fracture of a lower limb, bed rest for more than 5 days prior to surgery, predicted duration of surgery of more than 30 minutes, and age 60 years or above.

Renal
FRAGMIN should be used with caution in patients with renal insufficiency.

Patients with impaired renal function should be carefully monitored because the half-life for anti-Xa activity after administration of low molecular weight heparin may be prolonged in this patient population. Dose reduction should be considered in patients with severe renal impairment.

Emerging data from one single publication suggest that in critically ill patients with severe renal insufficiency, thromboprophylaxis with FRAGMIN at 5,000 IU once daily does not appear to be associated with an excessive anticoagulant effect due to drug bioaccumulation and is unlikely to contribute to bleeding.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Clinically significant adverse reactions observed with use of FRAGMIN and other low molecular weight heparins include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions.

Post-Marketing Adverse Reactions
In post-marketing experience, the following undesirable effects have been reported:

- **Bleeding:** Intracranial hemorrhage, gastrointestinal hemorrhage, retroperitoneal hemorrhage or hemorrhage (bleeding at any site) have been reported, occasionally leading to fatality

- **Blood and Lymphatic System:** thrombocytopenia, thrombocythemia

- **Skin and Subcutaneous Tissue Disorders:** skin necrosis, alopecia, rash

- **Immune System Disorders:** immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications), anaphylactic reactions

- **Injury, Poisoning and Procedural Complications:** spinal or epidural hematoma

DRUG INTERACTIONS

Drug-Drug Interactions
FRAGMIN should be used with caution in patients receiving oral anticoagulants, platelet inhibitors, non-steroidal anti-inflammatory agents, thrombolytic agents and dextran because of increased risk of bleeding. Acetylsalicylic acid (ASA), unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarctions.

Because NSAIDs and ASA analgesic/anti-inflammatory doses reduce production of vasodilatatory prostaglandins, and thereby renal blood flow and the renal excretion, particular care should be taken when administering dalteparin concomitantly with NSAIDs or high-dose ASA in patients with renal failure.

Drug-Food Interactions
Interactions with food have not been established.

Drug-herb Interactions
Interactions with herbs have not been established.

Drug-lab tests Interactions
Interactions with lab tests have not been established.

Drug-lifestyle Interactions
Interactions with lifestyle have not been established.
To report an adverse event, please contact: your physician, pharmacist or Pfizer Medical Information: 1-800-463-6001.

**DOSAGE AND ADMINISTRATION**

FRAGMIN may be given by subcutaneous (s.c.) injection or by intermittent or continuous intravenous (i.v.) infusion, depending upon the circumstances. **FRAGMIN must NOT be administered intramuscularly.** Clinical trials conducted in support of clinical uses outlined below generally used subcutaneous dosing.

**Dosing**

*Thrombophrophaxis in Conjunction with Surgery*

The dose of FRAGMIN required for adequate prophylaxis without substantially increasing bleeding risk varies depending on patient risk factors.

**General surgery with associated risk of thromboembolic complications:**

2500 IU s.c. administered 1-2 hours before the operation, and thereafter 2500 IU s.c. each morning until the patient is mobilized, in general 5-7 days or longer.

**General surgery associated with other risk factors:** 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative, 2500 IU s.c. is given 1-2 hours before the operation, with 2500 IU s.c. given again no sooner than 4 hours after surgery, but at least 8 hours after the previous dose, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

**Elective hip surgery:** 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative 2500 IU s.c. is given 1-2 hours before the operation and 2500 IU s.c. given again no sooner than 4 hours after surgery, but at least 8 hours after the previous dose, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

The pre-operative dose may be omitted and an initial dose of 2500 IU s.c. administered 4-8 hours after the operation, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

Treatment of Acute Deep Vein Thrombosis

The following dosage is recommended: 200 IU/kg body weight given s.c. once daily. The expected plasma anti-Xa X level during subcutaneous treatment would be <0.3 IU anti-Xa/mL. After injection and <1.7 IU anti-Xa/mL 3-4 hours after injection. In order to individualize the dose, a functional anti-Xa assay should be performed 3-4 hours post-injection. The single daily dose should not exceed 18,000 IU. The following weight intervals are recommended to be adapted to the single-dose prefilled syringes as in the table below.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dosage (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤56</td>
<td>7500</td>
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<tr>
<td>57-68</td>
<td>10000</td>
</tr>
<tr>
<td>69-82</td>
<td>12500</td>
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<tr>
<td>83-98</td>
<td>15000</td>
</tr>
<tr>
<td>≥99</td>
<td>18000</td>
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</tbody>
</table>

*For patients weighing 83 kg and above, data from one single publication suggest that in the thrombosis treatment setting, a weight-adjusted dose beyond the recommended maximum dose of 18,000 IU per day (the largest patient weighed 190 kg and received a daily dose of 38,000 IU) results in mean peak anti-Xa levels that are within the therapeutically acceptable range.*

**Extended Treatment of Symptomatic Venous Thromboembolism (VTE) to Prevent Recurrence of VTE in Patients with Cancer**

**Month 1:** 200 IU/kg body weight given s.c. once daily for the first 30 days of treatment. The total daily dose should not exceed 18,000 IU daily.

**Months 2-6:** Approximately 150 IU/kg given s.c. once daily using the table shown below.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dosage (IU)</th>
<th>Reduced Dose (IU)</th>
<th>Mean Dose Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤56</td>
<td>7500</td>
<td>5000</td>
<td>33</td>
</tr>
<tr>
<td>57-68</td>
<td>10000</td>
<td>7500</td>
<td>25</td>
</tr>
<tr>
<td>69-82</td>
<td>12500</td>
<td>10000</td>
<td>20</td>
</tr>
<tr>
<td>83-98</td>
<td>15000</td>
<td>12500</td>
<td>17</td>
</tr>
<tr>
<td>≥99</td>
<td>18000</td>
<td>15000</td>
<td>17</td>
</tr>
</tbody>
</table>

**Unstable Coronary Artery Disease (Unstable Angina and Non-Q-Wave Myocardial Infarction)**

120 IU/kg body weight given s.c. twice daily with a maximum dose of 10,000 IU/12 hours.

The expected plasma anti-Xa X level during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and <1.6 IU anti-Xa/mL 3-4 hours after injection. These levels were obtained from another patient population. Treatment should be continued for up to 6 days. Concomitant therapy with ASA is recommended.

**Deep Vein Thrombosis in Hospitalized Patients with Severely-Restricted Mobility**

In hospitalized patients with severely-restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

**Use in Patients with Renal Impairment**

All patients with renal impairment treated with low molecular weight heparins should be monitored carefully.

Administration of low molecular weight heparins to patients with renal impairment has been shown to result in prolongation of anti-Xa activity, especially in those with severe renal impairment (creatinine clearance <30 mL/min), which may lead to an increased risk of bleeding. This effect has not yet been determined for FRAGMIN. Consideration of dosage adjustment in patients with severe renal impairment should be undertaken.

Emerging data from one single publication suggest that in critically ill patients with severe renal insufficiency, thrombophrophaxis with FRAGMIN at 5,000 IU once daily does not appear to be associated with an excessive anticoagulant effect due to drug bioaccumulation and is unlikely to contribute to bleeding.

**Anticoagulation for Hemodialysis and Hemofiltration**

**Chronic renal failure, patients with no other known bleeding risk:** Hemodialysis and hemofiltration for a maximum of 4 hours: dose as below, or only i.v. bolus injection of 5000 IU. Hemodialysis and hemofiltration for more than 4 hours: I.v. bolus injection of 30-40 IU/kg body weight followed by I.v. infusion of 10-15 IU/kg body weight per hour. This dose normally produces plasma levels lying within the range of 0.5-1.0 IU anti-Xa/mL.
Acute renal failure, patients with high bleeding risk: i.v. bolus injection of 5-10 IU/kg body weight, followed by i.v. infusion of 4-5 IU/kg body weight per hour. Plasma level should lie within the range of 0.2-0.4 IU anti-Xa/mL.

Dilution
FRAGMIN solution for injection may be mixed with isotonic sodium chloride or isotonic glucose infusion solutions in glass infusion bottles and plastic containers. Post-dilution concentration: 20 IU/mL.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration, whenever solution and container permit.

1 mL 10 000 IU

<table>
<thead>
<tr>
<th>Isotonic NaCl Infusion (9 mg/mL)</th>
<th>500 mL</th>
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</thead>
<tbody>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Isotonic Glucose Infusion (50 mg/mL)</td>
<td>500 mL</td>
</tr>
</tbody>
</table>

The infusion rate is 10 mL/hour. The solution should be used within 24 hours.

Study References

Cancer-associated thrombosis

† Multi-centre, randomized, open-label, parallel group clinical trial. N= 672 cancer patients with acute symptomatic VTE comparing FRAGMIN to oral anticoagulants. FRAGMIN at a dose of 200 IU/kg of body weight sc once daily for 5 to 7 days followed by a coumarin derivative for 6 months (target INR 2.5) was compared to FRAGMIN alone for 6 months (200 IU/kg once daily for 1 month, followed by a daily dose of approximately 150 IU/kg for 5 months). The primary efficacy outcome was the first episode of objectively documented, symptomatic, recurrent deep-vein thrombosis, pulmonary embolism, or both during the 6-month study period. Secondary outcome events included clinically overt bleeding (both major bleeding and any bleeding) and death.

SUPPLEMENTAL PRODUCT INFORMATION

Overdosage
Accidental overdose following administration of FRAGMIN may lead to hemorrhagic complications. FRAGMIN should be immediately discontinued, at least temporarily, in cases of significant excess dosage. In more serious cases, protamine should be administered.

The anticoagulant effect of FRAGMIN is inhibited by protamine. This effect may be largely neutralized by slow intravenous injection of protamine sulphate. The dose of protamine to be given should be 1 mg protamine per 100 anti-Xa IU of FRAGMIN administered. A second infusion of 0.5 mg protamine per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain prolonged to a greater extent than usually seen with unfractionated heparin. Anti-Xa activity is never completely neutralized (maximum about 60%).

Particular care should be taken to avoid overdosage with protamine sulphate. Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulphate, it should be given only when resuscitation equipment and treatment of anaphylactic shock are readily available. Refer to the protamine sulphate Product Monograph for further directions for use.

Product Monograph available on request.

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INSIDE THIS ISSUE

CHRONIC LYMPHOCYTIC LEUKEMIA
Improving tolerability of treatment with new agents and treatment combinations

NON-HODGKIN LYMPHOMA
New management strategies

SPOTLIGHT ON BENDAMUSTINE
Exploring its use in hematological malignancies

INVESTIGATOR INTERVIEWS
Interviews with Dr. Martin Dreyling on results from the MCL elderly study and with Dr. Liat Vidal on a meta-analysis of bendamustine studies

Moving Toward Improved Patient Care
EHA/ICML 2011

Managing hematological toxicities with FCR in chronic lymphocytic leukemia