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**New Evidence in Oncology** is pleased to announce that our first issue of 2008 is a green publication. Since we began, we’ve made progressive changes in publishing the latest clinical research data and practices for Canadian oncology professionals. Now we feel it is time to make a commitment to the environment. Our green issue presents coverage of the American Society of Hematology Annual Meeting held in December, 2007.

Our website has also improved. The look and feel of the website has changed to meet the needs of our visitors and match the vision of our publication — this has resulted in much more activity over the last year. For recent oncology research, downloadable as presentations, visit our new website at www.newevidence.com.

The idea of going green is not a new thing, but we as a company are very excited to have taken the step. We hope you enjoy reading this issue, knowing that we have saved 4.37 mature trees in its production. Please join us in embracing our commitment to the environment.

**Our Mission:** New Evidence in Oncology is a publication for Canadian healthcare professionals. Our concentrated effort provides busy oncology specialists with concise, timely, credible, and objective scientific data, focusing on prominent issues from international oncology conferences and select Canadian conferences. In every issue, key opinion leaders provide a distinctive Canadian perspective in response to the conference coverage. They comment on the ways the latest international developments may shape how oncology patients are treated and managed in Canada.
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Behind the Scene
The Conundrum of Venous Thromboembolism in Hematological Malignancies
Ronan Foley, MD

Director of the Stem Cell Laboratory and Chair of the Clinical Trials Network of the Canadian Bone Marrow Transplant Group (CBMTG)
Associate Professor of Pathology and Molecular Medicine, McMaster University

Dr. Foley, a clinical hematologist, completed a Terry Fox Fellowship in the Centre of Gene Therapeutics, McMaster University. During this time, he became interested in the evaluation of cellular gene transfer in the context of cancer immunotherapy, which led to his current research focus: the development of therapeutic cancer vaccines.
Among the large number of presentations at the 49th Annual Meeting of the American Society of Hematology, held December 8–11, 2007, in Atlanta, Georgia, several papers on non-Hodgkin’s lymphoma (NHL) and on chronic lymphocytic leukemia (CLL) offered interesting insights into possibilities in these areas. This issue of New Evidence in Oncology reports on highlights of some of these presentations.
Background
Transformation of indolent lymphoma into diffuse large B-cell lymphoma (DLBCL) is usually associated with poor survival. Median overall survival (OS) post-transformation has been reported in various studies to range from 0.5 to 1.8 years. Rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) (R-CHOP) has been shown to significantly improve the outcome of patients with de novo DLBCL. However, the impact of R-CHOP therapy on the survival of patients with transformed DLBCL remains unclear. Investigators at the B.C. Cancer Agency investigated this issue in a retrospective analysis of the long-term natural history of patients initially diagnosed with indolent lymphoma in British Columbia.

Non-Hodgkin’s Lymphoma Update

Advances in chemoimmunotherapy have altered the natural history of indolent and aggressive lymphomas. The addition of rituximab to CHOP chemotherapy is the new standard of care for diffuse large B-cell lymphoma (DLBCL). Although outcomes have markedly improved, elderly patients, patients with transformed DLBCL, and patients with relapsed disease continue to pose a therapeutic challenge for the treating physician. Managing patients with indolent non-Hodgkin’s lymphoma is another area that is drawing a lot of attention from oncologists. This section contains highlights of some notable presentations on treatment strategies for DLBCL and follicular lymphoma (FL) that were presented at the 49th Annual Meeting of the American Society of Hematology.

Diffuse Large B-cell Lymphoma

Meenakshi Kashyap

The addition of rituximab to CHOP chemotherapy significantly improves overall survival of patients with transformed lymphoma

Excluded cases

Received rituximab any time pre-transformation (n = 51)

Too frail to receive multi-agent chemotherapy (n = 40)
Burkitt-like lymphoma (n = 8)
Received high-dose CT and stem cell transplant (n = 9)
**Study design**

- The objectives of the analysis were to evaluate the impact of the addition of rituximab to CHOP chemotherapy on the outcome of patients with transformed DLBCL.

- A large (n = 690) retrospective analysis of the long-term outcome of patients with indolent lymphoma in British Columbia is ongoing. A cohort of patients who developed transformation (n = 165) were identified from the British Columbia Cancer Agency Lymphoid Cancer Database.

- Before 2001, CHOP-like chemotherapy was used to treat transformed DLBCL. Since then, rituximab has been added to CHOP for the management of both de novo and transformed DLBCL. The retrospective analysis of the two cohorts of patients with transformed DLBCL included patients treated before 2001 with CHOP and patients treated after 2001 with R-CHOP.

- Diagnosis of transformation was confirmed by pathologic confirmation or the presence of one or more clinical features defined, such as rapid discordant nodal or extranodal growth; sudden rise in lactic dehydrogenase (LDH) to >2 times previous baseline; involvement of unusual extranodal sites, or hypercalcemia.

- The extent of disease at transformation was considered limited in patients with single nodal region involvement, no B symptoms, non-bulky disease (<10 cm) and, at most, limited extranodal involvement. Patients with disease involving multiple nodal sites, B symptoms, bulky disease, or extensive extranodal involvement were considered to have advanced transformation.

**Key findings**

- The median age of patients at time of transformation was 55 years (22–70) in the CHOP cohort and 58 (44–65) in the R-CHOP cohort.

- One hundred and eight patients were identified from the B.C. Lymphoid Cancer Database. Transformation was histologically confirmed in 74 patients. A majority of patients in both cohorts had an IPI status of 0–3 (87% in the CHOP group and 82% in the R-CHOP group).

- Median follow-up for all living patients was 7 years (3–17) in the CHOP-like cohort and 3 years (0.5–5) in the R-CHOP cohort.

- The five-year overall survival post-transformation by treatment in the CHOP versus the R-CHOP group was 33% and 61% (p = 0.01) (Figure 1). This difference in survival remained significant even when confined to patients with biopsy-confirmed transformation (p = 0.02).

- For the 78 patients with advanced disease extent treated with CHOP (n = 59) or R-CHOP (n = 19), there was a significant difference in five-year OS post-transformation in patients treated with R-CHOP (21% versus 57%, respectively; p = 0.005).

- Patients with limited disease extent CHOP (n = 26) or R-CHOP (n = 4) showed no significant difference in the five-year OS post-transformation (p = 0.2).

**Figure 1: Post-transformation overall survival**

![Graph showing post-transformation survival](image)

**Key conclusions**

- The addition of rituximab to CHOP chemotherapy significantly improves survival after transformation to diffuse large B-cell lymphoma in rituximab-naïve patients with indolent lymphoma.

- Patients with advanced disease have significantly better outcomes than patients with limited disease.

Densification of rituximab plus six cycles of CHOP-14 achieves higher rituximab serum levels, and higher complete response and event-free survival in elderly patients with poor-prognosis DLBCL

**Background**

Age is an important issue in the treatment of diffuse large B-cell lymphoma (DLBCL). In the landmark GELA trial, superior progression-free survival (PFS) and overall survival (OS) were reported with R-CHOP-21 in previously untreated elderly patients with DLBCL. In the RICOVER-60 trial, Pfreundschuh and colleagues demonstrated that biweekly rituximab has a greater impact on high-risk DLBCL than rituximab administered every three weeks. Pharmacokinetic studies show that even with biweekly rituximab treatment, serum levels build up rather slowly. Pfreundschuh and colleagues therefore initiated a phase II trial to investigate if dose-dense rituximab administration in conjunction with CHOP therapy could result in an earlier plateau of serum rituximab levels and further improve outcomes in elderly patients with poor-prognosis DLBCL.

**Study design**

- One hundred elderly patients with aggressive CD20+ B-cell lymphoma received six cycles of biweekly CHOP-14 combined with twelve infusions of rituximab (375 mg/m²) on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 99.
- Radiotherapy was planned to sites of initial bulk and/or extranodal involvement.
- Three hundred and six patients treated within the RICOVER-60 trial with six cycles of CHOP-14 and eight infusions of rituximab served as control.
- Patient demographics were similar by age in both experimental and control groups. However, there were significantly more patients with IPI status 3, 4, and 5 in the experimental group (p = 0.013).

**Key findings**

- Ninety-seven of the 100 patients were evaluable for response.
- Dose-dense rituximab resulted in plateau trough serum levels of rituximab as early as day one of the first chemotherapy cycle, and higher rituximab levels were maintained throughout the treatment as compared to eight biweekly applications in the control population (Figure 1).
- Because three therapy-associated deaths were observed among the first 20 patients treated, prophylaxis with acyclovir for cytomegalovirus (CMV) and cotrimoxazole for *Pneumocystis carinii* became mandatory for the patients who continued to receive therapy.
- Despite a less favorable study population, DENSE-R-CHOP-14 resulted in a somewhat higher complete remission (83% versus 78%) rates in all patients (Figure 2).
- Event-free and overall survival were not different compared to the eight biweekly applications of rituximab in the control group (Figure 3). However, a subgroup analysis of patients according to IPI risk group showed that DENSE-R-CHOP-14 resulted in a higher complete response rate of patients with poor-prognosis (IPI 3–5) disease (81% versus 68%). This advantage translated into a better one-year event-free survival rate (74% versus 65%) of these patients.
Figure 1: Trough serum levels

[Graph showing trough serum levels over time for DENSE-R-CHOP-14 and R-CHOP-14 treatments.]

Figure 2: Complete remission rates

[Bar chart showing complete remission rates for RICOVER-60 (control study) and DENSE-R-CHOP-14 (study) across different categories. The chart indicates that the remission rates are 78%, 83%, 84%, and 84% for different groups.]

*IPI = International Prognostic Index*
Key conclusions

- Densification of rituximab in combination with six cycles of CHOP-14 achieves earlier and higher rituximab serum levels, and higher complete response and event-free survival rates in elderly patients with poor-prognosis DLBCL.

- The increased toxicity (grade 3/4 infections) can be controlled by specific prophylaxis (Figure 4).

- These observations from a phase II trial need to be further confirmed in a randomized study.

Rituximab maintenance following high-dose therapy (HDT) and autologous stem cell rescue improves event-free survival and overall survival in patients receiving rituximab as part of pre-HDT cytoreduction

**Background**

Previous studies by Kewalramani and colleagues support the addition of rituximab to ICE (ifosfamide, carboplatin, and etoposide) as second-line therapy before autologous stem cell transplantation (ASCT) for patients with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL). Furthermore, a small phase II study performed at Stanford University also suggests that improvement in event-free survival (EFS) and overall survival (OS) can be obtained with the addition of rituximab maintenance therapy following high-dose therapy and autologous stem cell rescue (HDT/ASCR) in rituximab-naïve patients. However, it is not known whether patients receiving rituximab as part of pre-HDT cytoreduction could also benefit from rituximab maintenance. A retrospective study conducted by Rice and colleagues evaluated patients with the objective of answering the above question.

**Study design**

- Patients with relapsed and refractory DLBCL who underwent uniform pre-HDT/ASCR cytoreduction with rituximab in combination with ICE (RICE) between 1999 and 2006 were retrospectively identified.
- Patients proceeded to HDT/ASCR if they achieved an objective response to RICE chemotherapy.
- There were two treatment cohorts
  - No maintenance cohort (n = 37)
  - Maintenance rituximab cohort (n = 43)

- In the maintenance cohort
  - Twenty-six patients received rituximab in two blocks of four-weekly doses starting on day 42 and again on day 180.
  - Seventeen patients received rituximab every eight weeks times six starting on day 29.

**Key findings**

- Median follow-up for surviving patients was four years in the no maintenance group, and two years in the rituximab maintenance group.
- A Cox regression model was constructed to include disease status (relapsed versus refractory), maintenance rituximab status, and second-line IPI (low/low-intermediate versus high-intermediate/high risk) for both event-free and overall survival. Only rituximab maintenance was significant for EFS ($p < 0.0001$) and OS ($p = 0.008$).
- For the no maintenance and rituximab maintenance groups respectively, the three-year EFS was 42% and 84% ($p < 0.0001$), and OS was 58% and 86% ($p = 0.008$) (Figures 1 and 2).
- Maintenance rituximab resulted in improved EFS in each second-line IPI (sIPI) risk group. OS was improved in patients with sIPI high-intermediate risk–high-risk scores (Figure 3).
- Toxicities associated with maintenance therapy were tolerable. Grade 3/4 asymptomatic febrile neutropenia was observed in 16 patients. No serious adverse events were observed.
Key conclusions

- Maintenance rituximab therapy post HDT/ASCR in DLBCL patients who had received prior rituximab is significantly associated with improvement in EFS and OS and was well tolerated by patients.

- The prospective CORAL study is currently underway to fully evaluate the issue of maintenance therapy with rituximab versus observation.

Salvage chemotherapy incorporating rituximab provides a high response rate in rituximab-naïve patients

Background
Salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) is the standard of treatment for chemosensitive relapses in diffuse large B-cell lymphoma (DLBCL). The effectiveness of adding rituximab to second-line therapy for patients previously treated with rituximab remains unclear. The addition of rituximab to salvage chemotherapy regimens may improve the overall response rate with ICE (ifosfamide, carboplatin, and etoposide) and DHAP (dexamethasone, high-dose cytarabine, and cisplatin). The ongoing CORAL trial was designed to answer questions about the optimal chemotherapy regimen in relapsed/refractory DLBCL patients.

Study design
- Included in the study were DLBCL CD20+ patients in first relapse or partial response to first-line treatment, ≤65 years old, eligible for transplant, previously treated with a chemotherapy regimen containing anthracyclines with or without rituximab, and a PS ≤2.
- The first randomization was between R-ICE and R-DHAP, and the second randomization was between rituximab and no further therapy.
- Stratification for the subgroup analysis was by centre, group, prior treatment with rituximab during first-line treatment, relapse <12 months, and refractory (non-achieving complete response during first-line treatment).
- Responding patients received HDT (BEAM) and ASCT and were randomized between observation and maintenance with rituximab for one injection every two months for one year.
- Over 400 patients have been randomized in 11 countries since 2003.
- The planned interim analysis was performed on the first 200 patients with a minimum follow-up of one year.
- Six patients did not receive any treatment. Intent-to-treat analysis was therefore conducted on 194 patients (100 in the R-ICE arm and 94 in the R-DHAP arm). For the second randomization, there were 52 patients in the rituximab arm and 52 patients in the observation arm.
- The two arms were well balanced. In the prior rituximab cohort exposure, more patients had refractory disease and adverse prognostic factors. However, at inclusion, patient characteristics were not significantly different in the stratified subgroups.
- The median age of patients in the R-ICE and R-DHAP groups was 55 years. Of the 194 patients, 97 patients had had prior treatment with rituximab, and 97 patients had not.
- Primary objectives were:
  - For induction therapy: Overall response rate (ORR) adjusted with successful mobilization
  - For maintenance therapy: Event-free survival (EFS) at two years post-transplantation
- Secondary objectives of the study were to evaluate eligibility for transplant, toxicities with R-ICE and R-DHAP, toxicity with post-transplant rituximab treatment, time to progression or relapse, disease-free survival for complete responders, and overall survival.

\[DLBCL = \text{diffuse large B-cell lymphoma}\]
Figure 1: Efficacy analysis: overall survival and event-free survival

* Median follow-up 20 months
EFS = event-free survival; OS = overall survival

Figure 2: Overall survival and event-free survival of ITT transplanted patients

* Median follow-up 17 months
EFS = event-free survival; ITT = intent to treat; OS = overall survival
Table 1: Toxicity

<table>
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<tr>
<th>(Median + range)</th>
<th>R-ICE</th>
<th>R-DHAP</th>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td></td>
<td></td>
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<tr>
<td>Day 10</td>
<td>10.6 (15–6)</td>
<td>11.1 (16–7)</td>
</tr>
<tr>
<td>Day 14</td>
<td>10.3 (15–5)</td>
<td>10.1 (15–7)</td>
</tr>
<tr>
<td>White blood cells (/mcL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 10</td>
<td>3.8 (30–0)</td>
<td>6 (86–0)</td>
</tr>
<tr>
<td>Day 14</td>
<td>6.3 (71–0)</td>
<td>6 (68–0)</td>
</tr>
<tr>
<td>Platelets (/mcL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 10</td>
<td>190 (1,088–9)</td>
<td>101 (2,940–2)</td>
</tr>
<tr>
<td>Day 14</td>
<td>58 (616–2)</td>
<td>47 (2,360–1)</td>
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<tr>
<td>Transfusion (% patients)</td>
<td>18</td>
<td>38</td>
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<tr>
<td>Nb patients with 3 cycles</td>
<td>90 (90%)</td>
<td>82 (87%)</td>
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<td>Infection with neutropenia</td>
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<tr>
<td>Grade 3–4 Yes</td>
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<td>18 (21%)</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
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<td></td>
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<td>Grade 3–4 Yes</td>
<td>6 (7%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Renal Grade 3–4 Yes</td>
<td>0</td>
<td>6 (7%)</td>
</tr>
</tbody>
</table>

Key findings

- First randomization: overall EFS and OS rates in the ITT population (n = 194) 20 months from the time of first randomization was 50% and 69% (Figure 1 and Figure 2).
  - EFS in rituximab-naïve patients (n = 97) and in patients with prior exposure to rituximab (n = 97) was 66% and 34% (p <0.0001) respectively.
  - EFS in the failure from diagnosis at <12 (n = 108) and ≥12 (n = 86) months was 36% and 68% (p <0.0001) respectively.
  - EFS in the age-adjusted IPI 0–1 (n = 112) and IPI 2–3 (n = 74) groups was 56% and 39% (p = 0.0084) respectively.
- Second randomization: EFS and OS in the ITT population (rituximab n = 52, observation n = 52) after transplantation and a median follow-up of 17 months was 75% and 89% respectively.
- Toxicity was similar to what is expected with intensive therapy. There were 72 SAEs reported, with 12 deaths during the initial salvage regimens (Table 1).
- No unexpected toxicity was seen in the 17% events that occurred. This precludes subgroup analysis.

Key conclusions

- Initial results from this study show that both rituximab-containing salvage regimens appear to be equally effective in this hard-to-treat population.
- In patients who are refractory to upfront rituximab-associated chemotherapy within 12 months, results of salvage therapy with rituximab chemotherapy remain poor.
- Up to now, the number of events (17%) after transplantation is still limited and precludes subgroup analysis.
- The data from the maintenance part of this trial were not mature enough to allow any reliable interpretation of the results during this interim analysis. Results from the maintenance part are expected next year.

Diffuse large B-cell lymphoma (DLBCL), or aggressive histology lymphoma, is a serious form of cancer. Typically patients with de novo disease are divided by age (above or below 60 years) and assigned a prognostic score called the International Prognostic Index (IPI). Our current treatment practice has been guided by three studies, GELA, U.S. Intergroup, and MiNT. Findings from the GELA and U.S. Intergroup studies have indicated that the addition of rituximab to conventional chemotherapy results in a survival advantage for both low and high IPI elderly patients. A study led by Sehn and colleagues in Vancouver has confirmed the GELA and U.S. Intergroup as well as the MiNT study overall survival observations in a population of Canadian patients (age 15/80). The MiNT study, which evaluated younger patients (<60 years) with low or favourable IPI, found that the addition of rituximab to conventional chemotherapy improved the overall survival to as high as 93%. In Canada, by using current immunochemotherapy protocols that incorporate rituximab as part of standard chemotherapy, we have succeeded in increasing cure rates to 60%. However, there is still room for improvement, specifically in the treatment of young patients with unfavourable prognostic features and, of course, in the treatment of elderly patients where the presence of comorbid medical illnesses and low tolerance to chemotherapy remains a challenge.

Against this background, three studies presented at ASH, Atlanta 2007, suggest that we may further improve the rates of durable remission in this aggressive malignancy.

The first study by Pfreundschuh et al. evaluates the benefit of an increased dose-density of rituximab. In current practice, we conveniently administer rituximab at the same time as chemotherapy, i.e., every three weeks. Pfreundschuh et al. have conducted a comprehensive evaluation of the pharmacokinetics and have devised a schedule that facilitates higher serum peak levels (12 doses) of rituximab earlier during the course of chemotherapy. The concept of looking at pharmacokinetics with novel immunotherapeutic drugs is relatively new and likely to be very important. It offers the potential to further improve upon current practices for treating this disease with the potential to influence downstream outcome measures in a significant manner.

The second study by J.Connors et al. (Vancouver, B.C.) retrospectively assessed a large cohort of patients to determine if R-CHOP has improved the outcome for patients with transformed aggressive histology lymphoma. Lymphoma transformation is obviously a serious, life-threatening situation that can pose unique therapeutic challenges. Results from this study indicate an enhanced efficacy in combining rituximab with chemotherapy in patients with transformed lymphoma who previously have not been treated with rituximab.

The third study by Rice et al., also a retrospective study, evaluated the benefit of continuing rituximab treatment in patients who have completed autologous stem cell transplant for relapsed DLBCL. At present, relapsed patients are treated with salvage therapy followed by autologous stem cell transplant. The Rice study, albeit limited by retrospective analysis, is one of the first to suggest a significant clinical benefit for rituximab maintenance following autologous bone marrow transplant. Although the results from this study may not change practice today, it does provide a glimpse into what may be achieved with rituximab maintenance post-transplant. The fact that we can prevent further relapse following autologous stem cell transplant may improve overall cure rates in patients with relapse. Important, large prospective randomized trials, including the CORAL and Canadian NCIC LY.12 trials, are currently addressing this important issue.

De novo large B-cell lymphoma has the potential to be cured, and the choice of an optimal therapeutic strategy is critical. Incorporation of immune-based treatment to standard cytotoxic agents has had a dramatic effect on overall patient survival. The ability to schedule rituximab administration based on accurate pharmacokinetics may further enhance therapeutic benefit. Moreover, demonstration of improved outcomes for transplant patients and patients demonstrating large cell transformation further our optimism for future success in this disease.
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- A cancer-specific regimen that was manageable for patients
  - Once-daily, weight-adjusted monotherapy for 6 months
  - Month 1: 200 IU/kg sc once daily (maximal daily dose, 18,000 IU)
  - Months 2-6: ≈150 IU/kg sc once daily

- With subcutaneously-injected FRAGMIN, gastrointestinal absorption is not a concern

- Comparable risk of any bleeding shown with FRAGMIN and OAC (14% vs. 19%; p=0.09)³

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³ (coumarin derivative) n=336, FRAGMIN n=336; randomized 6-month trial; patients with cancer who had acute venous thromboembolism.

² Incidence of major bleeding according to the FRAGMIN Product Monograph: FRAGMIN 5.6%; OAC 3.6%; p=0.27.
Follicular Lymphoma

Meenakshi Kashyap

In vivo purging of B cells with rituximab followed by HDT/ASCT and rituximab maintenance with or without interferon is feasible and well tolerated in high-risk patients with relapsed follicular lymphoma

Background
High-dose therapy with autologous stem cell transplantation (HDT/ASCT) may prolong remission and survival after first progression in patients with follicular lymphoma.\(^1\) In vivo purging of circulating and marrow B cells with rituximab followed by high-dose therapy;\(^2\) maintenance rituximab, and maintenance interferon-alpha have individually demonstrated a potential beneficial role in extending remissions.\(^3,4,5\) In this study, Cheung and colleagues have incorporated post-transplant maintenance immunotherapy with a combination of rituximab and interferon-alpha along with rituximab-driven in vivo pre-purging of B cells to assess feasibility and potential to improve remission duration post–HDT/ASCT.\(^6\)

Study design
- Thirty patients aged ≤65 years with one to two relapses of follicular lymphoma and ECOG PS 0–2 were included in this phase II study.
- Patients received salvage chemotherapy with:
  - CHOP: cyclophosphamide (750 mg/m\(^2\)), doxorubicin (50 mg/m\(^2\)), vincristine (2 mg), and prednisone (100 mg x 5 days), or
  - DHAP: dexamethasone (40 mg x 4 days), cytarabine (2,000 mg/m\(^2\) x 2 doses), and cisplatin (100 mg/m\(^2\)).
- Salvage chemotherapy was followed by in vivo purge of B cells with 375 mg/m\(^2\) rituximab given every three weeks prior to stem collection.
- Patients who demonstrated >75% response and <15% bone marrow involvement proceeded with stem cell mobilization and HDT/ASCT.
- HDT was initiated with cyclophosphamide (1.8 g/m\(^2\) x 4 days), carmustine (450 mg/m\(^2\)), and etoposide (2.4 g/m\(^2\) [CBV]).
- Maintenance immunotherapy with interferon-alpha (3 million u/m\(^2\) twice a week) at week 10 post-ASCT (for 2 years) and rituximab (375 mg/m\(^2\) x 6 weekly doses) at week 12 was initiated post-ASCT.
- Samples for real-time PCR (sensitivity 0.01%) of detectable chromosome translocation t(14;18) or patient-specific clonal V(D)J rearrangements were taken from blood or bone marrow to assess for molecular remission (MR).
- Results from results obtained in this study were compared to results from the Hicks et al. study.\(^7\)

ASCT = autologous stem cell transplant; CHOP = cyclophosphamide/doxorubicin/vincristine/prednisone; DHAP = dexamethasone/cytarabine/cisplatin; HDT = high-dose therapy; IFN= interferon
Table 1: Patient characteristics*

<table>
<thead>
<tr>
<th></th>
<th>HDT/ASCT + rituximab/IFN maintenance</th>
<th>HDT/ASCT + rituximab alone†</th>
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</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td><strong>Median age (range)</strong></td>
<td>46 (30–65)</td>
<td>50 (32–57)</td>
</tr>
<tr>
<td><strong>Gender, male (%)</strong></td>
<td>15 (52)</td>
<td>12 (52)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II (%)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>III (%)</td>
<td>4 (15)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>IV (%)</td>
<td>23 (85)</td>
<td>15 (65)</td>
</tr>
<tr>
<td><strong>BM + (%)</strong></td>
<td>20 (69)</td>
<td>15 (65)</td>
</tr>
<tr>
<td><strong>LDH, normal (%)</strong></td>
<td>18 (64)</td>
<td>10 (43)</td>
</tr>
<tr>
<td><strong>Bulk &gt;5 cm (%)</strong></td>
<td>17 (63)</td>
<td>14 (61)</td>
</tr>
<tr>
<td><strong>FLIPI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low (%)</td>
<td>8 (29)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>intermediate (%)</td>
<td>10 (36)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>high (%)</td>
<td>10 (36)</td>
<td>4 (17)</td>
</tr>
<tr>
<td><strong>ECOG, 0–1 (%)</strong></td>
<td>23 (88)</td>
<td>unknown</td>
</tr>
<tr>
<td><strong>Prior therapies, median (range)</strong></td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td><strong>Time from diagnosis, median (range)</strong></td>
<td>29 months (9–181)</td>
<td>21 months (9–98)</td>
</tr>
</tbody>
</table>

*Comparison to 23 patients from a previous HDT/ASCT study by Hicks et al.*
7 that incorporated rituximab in vivo purge and maintenance therapy (without IFN-α)

ASCT = autologous stem cell transplant; BM = bone marrow; ECOG = Eastern Cooperative Oncology Group; FLIPI = Follicular Lymphoma International Prognostic Index; HDT = high-dose therapy; IFN = interferon; LDH = lactic dehydrogenase

Table 2: Toxicity

<table>
<thead>
<tr>
<th>Grade 3/4 adverse events</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Depression</td>
<td>5 (24)</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Key findings

- Twenty-nine patients with a median follow-up of 3.1 years were assessed.
- Median patient age was 46 years (30–65) and patients had undergone a median number of two prior regimens (Table 1).
- Median response duration to prior therapy was 0.6 years, and patients were enrolled for 2.3 years (median) following diagnosis.
- Pre-ASCT:
  - The overall response rate to salvage therapy was 93% (95% CI 84%–100%).
  - Twenty-three of 29 patients proceeded to ASCT.
  - Six patients did not undergo ASCT due to inadequate response (n = 2), failed mobilization (n = 2), cardiomyopathy (n = 1), and patient withdrawal (n = 1).
- Post-ASCT:
  - Interferon-alpha maintenance was initiated in 21 of 23 patients.
  - Thirteen of the 21 patients completed two years of interferon-alpha maintenance therapy.
  - The median dose interferon-alpha at two years was 3 x 10^6 units/m² twice a week.
  - Eight patients discontinued interferon-alpha therapy due to depression (n = 5), weight loss (n = 1), progression (n = 1), and secondary malignancies (n = 1).
- Significant non-hematologic ASCT toxicities (grade 3/4) included five episodes of interstitial pneumonitis and thrombotic thrombocytopenic purpura (n = 1). Significant hematological toxicities are summarized in Table 2.
- There was no transplant-related mortality.
Follow-up
- Twelve patients have relapsed/progressed.
- Three patients developed progressive lymphoma and have died.
- One patient with chromosome 11q23 inversion developed acute lymphoblastic leukemia 30 months after HDT/ASCT.
- When compared to the preceding study of HDT/ASCT with rituximab in vivo purging and maintenance, the addition of interferon-alpha to rituximab did not further improve progression-free survival (Figure 1).
- At baseline, 19 patients had detectable markers by PCR. Stem cell graft PCR positivity did not affect subsequent molecular remission ($p = \text{non-significant}$).
- Of 16 assessable patients post-ASCT, eleven patients achieved molecular remission prior to immunotherapy, and all of them achieved molecular remission during maintenance.
- In 3/3 patients, molecular relapse preceded clinical relapse.
- Median progression-free survival for all patients is 50 months, and median overall survival has not been reached.

**Key conclusions**

- In vivo B-cell purging with rituximab followed by HDT/ASCT and maintenance immunotherapy with rituximab ± interferon-alpha is feasible, well tolerated, and may improve long-term disease control in this high-risk population who have had relapsed follicular lymphoma.
- Addition of interferon-alpha to rituximab maintenance therapy does not further improve three-year progression-free survival in this patient cohort.
- Molecular detection of lymphoma in the auto-graft does not preclude post-transplant extended molecular remission and clinical remissions.
- Maintenance immunotherapy post-ASCT possibly results in enhanced clearance of minimal residual disease.
- Further research to clarify the relative role of HDT/ASCT and immunotherapy in the care of patients with relapsed follicular lymphoma is needed.

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**Canadian perspective by Dr. Foley**

There are several interesting points that are illustrated by this work. Firstly, the overall survival and PFS data is impressive when monitored over time. Moreover, although many patients respond favourably to current first- or second-line immunochemothterapeutic approaches, there remain some patients with relatively short remission duration. This approach may eventually be suitable for specific patients where durable disease control is problematic. The benefit of rituximab post-transplant as well as the timing of molecular responses is interesting. This study highlights the benefit of incorporating monoclonal antibody therapy into an autologous transplant procedure.

**References:**

Rituximab plus CHVP+I provides superior disease control in follicular lymphoma

Background
The GELA-GOELAMS FL2000 study was initiated to evaluate the combination of rituximab with chemotherapy and α-interferon as a first-line treatment in patients with a high tumour burden follicular lymphoma. Previous analyses were presented at ASH 2004 (after 31 months), and at ASCO 2006 (after 43 months). At ASH 2007, the authors presented the final results from this phase III trial.3

Study design
- Untreated follicular lymphoma patients (n = 358) presenting with a high tumor burden were randomly assigned to receive
  - Arm A: twelve courses of the chemotherapy regimen CHVP+I (cyclophosphamide, doxorubicin, etoposide, and prednisone) plus α-interferon-2b (CHVP+I arm, n = 156) over 18 months, or
  - Arm B: six courses of the same chemotherapy regimen combined with six infusions of 375 mg/m² of rituximab and interferon for the same time period (R-CHVP+I arm, n = 175).

Key findings
- Patients with histologically proven, previously untreated follicular lymphoma and needing treatment for at least one of the following criteria were included in the study:
  - high lactic dehydrogenase (LDH) (above normal) or β2-microglobulin (≥3 mg/L);
  - presence of B symptoms or ECOG performance status >1;
  - tumour bulk with largest nodal diameter >7 cm or three nodes >3 cm in three distinct areas or symptomatic spleen enlargement or compression or effusion.
- The primary endpoint of the study was event-free survival.
- Final analysis was based on the intent-to-treat population.

Cyclophosphamide  Day 1  600 mg/m²
Doxorubicin  Day 1  25 mg/m²
Etoposide  Day 1  100 mg/m²
Prednisone  Days 1–5  40 mg/m²
Every month for 6 months in arms A and b, then every 2 months in arm A

Interferon-α2β  tiw  4.5 MU (3 MU if aged ≥ 70)
For 18 months in arms A and B

Rituximab  375 mg/m²
Six infusions of rituximab for the same time period

*tiw = three times weekly*
• Response duration in complete remission (CR), unconfirmed complete remission (CRu) (50% and 67%) or partial response (PR) patients after treatment was also improved in the R-CHVP+I arm ($p = 0.034$).

• The five-year overall survival (OS) estimates were not statistically different in the CHVP+I (79%, 95% CI 72–84) and R-CHVP+I (84%, 95% CI 78–84) arms.

• The Follicular Lymphoma International Prognostic Index (FLIPI) score allowed separation of the whole study population into three different risk categories. Each group had a significantly different outcome, both for five-year EFS ($p < 0.0001$) and OS ($p < 0.0001$).

• In a multivariate regression analysis, event-free survival was significantly influenced by both the FLIPI score (HR = 2.08, 95% CI 1.6–2.8) and the treatment arm (HR = 0.59, 95% CI 0.44–0.78).

• In an exploratory analysis considering the 187 patients with a low to intermediate (<3) FLIPI score, the outcome according to each treatment arm was not statistically different.

• The benefit of the rituximab combination was highly significant in terms of EFS ($p = 0.0002$) and OS ($p = 0.025$) in the 162 patients with a high ($\geq 3$) FLIPI score.

Key conclusions

- These results confirm the benefit observed in the R-CHVP-I arm for the primary endpoint of event-free survival.
- This benefit is sustained over a prolonged period of time.
- The absence of significant difference for overall survival is likely due to the efficacy of salvage treatments.
- Cox analysis confirmed the strong prognostic impact of FLIPI ($p < 0.0001$) and treatment arm ($p < 0.0003$) for EFS and of FLIPI ($p < 0.0001$) for OS.
- In an exploratory analysis, the benefits observed in the experimental arm appear to be restricted to the high risk ($\geq 3$ factors) FLIPI group. However, the addition of rituximab for the low and intermediate risk patients was associated with a less intensive treatment (6 courses of CHVP+I instead of 12).

Oral fludarabine plus rituximab is highly effective in relapsed/refractory indolent B-cell non-Hodgkin’s lymphoma

Background
Intravenous fludarabine in combination with rituximab has been reported to be effective against indolent B-cell non-Hodgkin’s lymphoma (B-NHL). However, intravenous administration of fludarabine for three to five consecutive days is inconvenient in an outpatient setting. Ishizawa and colleagues conducted an open-label, multicenter, phase II trial to investigate the efficacy and safety of oral fludarabine in combination with rituximab for relapsed or refractory indolent B-NHL.

Study design
- Eligible patients (n = 41) ranging in ages from 20 to 74 years, with CD20⁺ indolent B-NHL and measurable lesions (the greatest transverse diameter >1.5 cm by CT), performance status 0 or 1, and no major organ dysfunctions were included in the study. Prior chemotherapies were limited to ≤ 2 regimens, and prior rituximab treatments up to 16 times were allowed.
- Thirty-eight patients (93%) had follicular lymphoma, two patients had mucosa-associated lymphoid tissue (MALT) lymphoma, and one patient had small lymphocytic lymphoma. Patients with mantle cell lymphoma, patients who received nucleoside analogs or stem cell transplants, and patients with progressive disease within six months of receiving rituximab therapy were excluded.
- Thirty-four patients (83%) had received rituximab with or without chemotherapy prior to enrollment.
- Based on the results of the preceding phase II study, oral fludarabine 40 mg/m² was administered on days 1 to 5, with rituximab 375 mg/m² on day 1, repeated every four weeks, for up to six cycles.
- The primary endpoint was the best overall response rate (ORR). Secondary endpoints were CR, PFS, and OS.

Key findings
- The overall response rate was 76% (95% CI, 60%–88%), CR rate was 68% (95% CI, 52%–82%) (Table 1).
- Median PFS for all patients was 10.8 months (95% CI, 8.6 months to not defined), and median PFS for 31 responders was not reached.
- The CR rate and median PFS correlated well with the risk of groups according to the FLIPI (Table 1 and Figure 1).

<table>
<thead>
<tr>
<th>Table 1: Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>WHO</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>MALT</td>
</tr>
<tr>
<td>SLL</td>
</tr>
<tr>
<td>Previous rituximab</td>
</tr>
<tr>
<td>R (+)</td>
</tr>
<tr>
<td>R (-)</td>
</tr>
<tr>
<td>FLIPI</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>High</td>
</tr>
</tbody>
</table>

*Included CRu

CRu = unconfirmed complete response; MALT = mucosa-associated lymphoid tissue; FLIPI = Follicular Lymphoma International Prognostic Index; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; SLL = small lymphocytic lymphoma; WHO = World Health Organization
Figure 1: Progression-free survival (FLIPI risk group)

![FLIPI risk group graph]

*FLIPI = Follicular Lymphoma International Prognostic Index*

Figure 2: Progression-free survival (previous rituximab)

![Previous rituximab graph]
Table 2: Hematologic adverse events (AEs)

<table>
<thead>
<tr>
<th></th>
<th>All grades, n (%)</th>
<th>Grade 3, n (%)</th>
<th>Grade 4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>41 (100)</td>
<td>21 (51)</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41 (100)</td>
<td>11 (27)</td>
<td>28 (68)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41 (100)</td>
<td>1 (2)</td>
<td>40 (98)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28 (68)</td>
<td>6 (15)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>27 (66)</td>
<td>5 (12)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

- The median PFS for patients with prior rituximab therapy was 10.8 months (95% CI, 8.6 months to not defined) and not reached in patients with no prior rituximab (Figure 2).
- The median OS was not reached.
- Toxicity was primarily hematologic, transient, and manageable (Table 2).
- The most common grade 4 hematologic toxicities included lymphopenia (98%), neutropenia (68%), and leukopenia (41%). Non-hematological toxicities ≥ grade 3 were observed in 29% of patients. Grade 4 toxicities included one each of stomatitis and hyperuricemia, and a decrease in immunoglobulins IgA, IgG, and IgM.
- Dose reductions of oral fludarabine (from 40 to 30 mg/m²) was necessary in 44% of patients.
- Eleven non-fatal serious adverse events (AEs) were observed in nine patients (22%) during the study.
- No deaths were reported during the study period. Three patients died at the end of the study, two from disease progression and one from *P. jiroveci*.

**Key conclusions**

- **Oral fludarabine combined with rituximab was highly effective in patients with relapsed or refractory indolent B-NHL who were mostly pretreated with rituximab.**
- **Oral fludarabine and rituximab combination has an acceptable toxicity profile and is more convenient than the combination of iv fludarabine and rituximab.**
- **Prolonged prophylactic therapy against *Pneumocystis jiroveci* pneumonia is recommended.**

Chronic Lymphocytic Leukemia Update

Meenakshi Kashyap

Combination chemoimmunotherapy regimens using monoclonal antibodies, such as rituximab and alemtuzumab, and other novel therapies have changed the therapeutic landscape of chronic lymphocytic leukemia (CLL). The resulting paradigm shift has led to an active exploration of these regimens in front-line, refractory, and relapsed CLL treatment. Highlights of some interesting studies from the 49th Annual Meeting of the American Society of Hematology are presented in this section.

FCR-lite is as effective as conventional FCR in the treatment of primary chronic lymphocytic leukemia

Background

A complete response (CR) rate of 70% has previously been reported by Keating et al. in a single arm trial with fludarabine, cyclophosphamide and rituximab (FCR) as initial therapy for chronic lymphocytic leukemia (CLL).1 The addition of rituximab to FC was associated with significantly greater reductions in residual CLL cells in the marrow than the reductions seen with FC alone. This CR rate is the highest rate reported for initial therapy for CLL, and supports the concept of additive or synergistic interactions of these three agents. In the Keating et al. study, grade 3/4 neutropenia was seen in 52% of 927 evaluable treatment courses. Tarhini et al.3 reduced the doses of fludarabine and cyclophosphamide and increased the dose of rituximab to investigate if it was possible to reduce levels of neutropenia without compromising efficacy in the FCR-lite regimen.

Study design

• A Simon two-stage design was used to recruit a total of 50 patients into the phase II study.
• Fifteen patients with previously untreated advanced CLL were accrued in the first stage of the study.
• Following acceptable toxicity and relative risks, an additional 35 patients were treated in the second stage of the study.

Key findings

• Of the 42 evaluable patients, CR rates of 86% and 80% were observed in patients with Rai Stages I/II, and III/IV respectively.
• Patients ≥70 years had lower CR rates (57%) as compared to younger patients (≥90–93%).
• Complete response rates of 100% were observed in patients with chromosome 12 trisomy and 11q abnormalities, while patients with 13q abnormalities had CR rates of 88%. No patients with 17p abnormalities achieved CR.
• An overall response rate of 100% was observed in 42 evaluable patients regardless of the Rai Stage, age, or chromosomal abnormalities.
• Of the 36 patients in complete response, CD5/CD19 positivity in bone marrow of 35 patients was tested by flow cytometry. No positive cells were detected in 33 (94%) patients (Table 1).
• Minimal residual disease was evaluated in 18 of the 36 patients in complete response. No minimal residual disease was seen in 14 (78%) patients (Table 2).
• Grade 3/4 neutropenia, thrombocytopenia, and anemia were the major hematological toxicities observed with the FCR-lite regimen (Table 3).

Dosage

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Chemotherapy</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 20 mg/m²</td>
<td>Days 1–3</td>
<td></td>
</tr>
<tr>
<td>C 150 mg/m²</td>
<td>Days 1–3</td>
<td></td>
</tr>
<tr>
<td>R 375 mg/m²</td>
<td>Day 1, cycle 1</td>
<td></td>
</tr>
<tr>
<td>R 500 mg/m²</td>
<td>Day 1 and 14, Q4W X 6 cycles</td>
<td>D1 Q3M X1</td>
</tr>
</tbody>
</table>

F = fludarabine; C = cyclophosphamide; R = rituximab; Q3M = every three months; Q4W = every four weeks
Key conclusions

- FCR-lite is a highly effective regimen and is associated with considerably less grade 3/4 neutropenia than standard FCR.

CFAR therapy is highly effective in front-line therapy of high-risk chronic lymphocytic leukemia

Background

Serum β2-microglobulin greater than or equal to 4 mg/L has been previously identified by Keating et al. to be a prognostic factor for lower complete response (CR) rates and shorter progression-free survival (PFS) in chronic lymphocytic leukemia (CLL) following first-line chemotherapy.1 For patients <70 years old with serum β2-microglobulin ≥4 treated with FCR, the CR rate and estimated median PFS were observed to be 59% and 60 months, compared to 81% and 80 months for similar aged patients with serum β2-microglobulin ≤4. Alemtuzumab, a humanized monoclonal antibody that targets CD52 when combined with FCR (CFAR), has previously been demonstrated by Wierda and colleagues to be active in relapsed or refractory disease with CR, PR, and OR rates of 27%, 38% and 65% respectively.2 Wierda and colleagues evaluated the activity of this regimen in high-risk CLL patients with an NCI indication for front-line therapy.3

Study design

- The CFAR regimen was administered to 40 high-risk CLL patients. The regimen was compared with the historical FCR control.
- Baseline parameters of patients in the CFAR group were similar to the historical control group.
- The median duration from diagnosis to treatment in the CFAR group was 35 months (range: 2–117).
- Patients were prophylactically treated with allopurinol for tumour lysis, valacyclovir/valganciclovir for herpes virus, pegfilgrastim for neutropenia, and antibiotics (trimethoprim-sulfamethoxazole) for infection.

Key findings

- Twenty-six patients were evaluable for response. An objective response rate of 96% was seen in the CFAR regimen.
- Complete remission (CR) was higher for patients in the CFAR cohort (69%) as compared with FCR (60%).
- Mutation status, ZAP70 expression, and CD38 expression did not correlate with CR or OR.
- Incidences of grade 3/4 neutropenia and anemia were lower with CFAR (62% and 8%) than with FCR (86% and 21%). Grade 3/4 thrombocytopenia was found to be higher with CFAR (34%) versus FCR (26%). (Table 1)
- CMV reactivation was observed in two of seven patients receiving valacyclovir. It was not observed in any patient receiving valganciclovir.
- Infection rates were similar in both the CFAR and the FCR groups.
- Fever of unknown origin was observed in 35% of the CFAR group and 26% of the FCR group.
- Major and minor infection rates in the CFAR and FCR groups were 8% and 23% versus 15% and 18%. Herpes simplex viral infection rates were 4% and 3% respectively.

<table>
<thead>
<tr>
<th>Table 1: Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicities (%)</td>
</tr>
<tr>
<td>Grade 3 or 4 neutropenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Major infections</td>
</tr>
<tr>
<td>Minor infections</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
</tr>
</tbody>
</table>

Key conclusions

- **CFAR is a highly active and well-tolerated regimen in the front-line treatment of high-risk CLL patients with β2-microglobulin ≥4 mg/L.**
- **Accrual and treatment are continuing on this clinical trial.**

FCM-R is active in primary chronic lymphocytic leukemia but does not further improve overall survival as compared with FCR.

Background
The development of chemoimmunotherapy in chronic lymphocytic leukemia (CLL) is changing the natural history of this disease. Various combinations of chemoimmunotherapies are being explored for the treatment of front-line CLL. Bosch and colleagues have recently demonstrated that mitoxantrone in combination with fludarabine and cyclophosphamide (FCM) induces a high response rate, including minimal residual disease (MRD)–negative complete responses (CRs) in untreated patients with active CLL.1 The objective of the study by Faderl and colleagues was to determine the role in CLL of mitoxantrone in combination with FCR (FCM-R) and compare this regimen to the FCR historical control.2

Study design
- Untreated, symptomatic CLL patients (n = 31) aged <70 year, with a beta-2 microglobulin (β2M) <4 mg/dL and ECOG PS ≤ 2 were included in the study.
- The median age of patients was 57 years (range 38–69). Four patients (13%) had Rai Stage ≥ 3.
- Sixty-two percent of patients had unmutated IgVH status. The median β2M of patients was 2.7 mg/dL (1.4–3.8). Other prognostic markers that were characterized in these patients were CD38 >20% status (47%), ZAP-70 positivity (44%), and FISH analysis of 17p deletions (8%), 11q deletions (8%), gains of chromosome 12 (23%), and 13q deletions (38%).
- The FCM-R regimen was compared to the FCR historical controls.

Key findings
- Thirty patients were evaluable for response.
- Response rates at completion of therapy were 80% complete response (CR), 10% nodular partial response (nPR) and 7% partial response (PR) for an overall response (OS) rate of 97% (Table 1).
- Of 23 patients with CR, 65% patients were found to have <1% CD19+/CD5 cells by flow cytometry analysis.
- MRD negativity, assessed by polymerase chain reaction (PCR), was observed in 59% of the 17 patients with CR.
- Complete response plus nodular partial response rates (CR+nPR) in FCM-R versus FCR were 80+10 and 85+7 respectively.
- Grade 3 neutropenia was the most common adverse event seen in both regimens (Table 2).

Key conclusions
- While FCM-R is active in front-line CLL, the addition of mitoxantrone to FCR does not provide additional benefit.
- There was no difference in outcome and adverse events as compared to FCR.

Clinical trial with FCM-R followed by rituximab maintenance initiated in untreated, active chronic lymphocytic leukemia

**Background**

Rituximab maintenance therapy has been demonstrated to provide a clear clinical benefit after induction with rituximab plus chemotherapy, chemotherapy alone, or rituximab monotherapy in previously untreated and relapsed/refractory follicular lymphoma. There is some evidence to show that rituximab maintenance therapy in chronic lymphocytic leukemia (CLL) could provide a similar benefit as well. Bosch and colleagues presented data from their prospective clinical trial in which patients with untreated CLL received R-FCM as induction therapy followed by maintenance with rituximab.

**Study design**

- Patients (n = 69) younger than 70 years with untreated, active disease (NCI-WG criteria) and adequate performance status were included in the study.
- At study entry, 83% of the patients were in advanced (B and C) Binet’s clinical stage, and 64% had increased (>20%) ZAP-70 expression.
- Primary endpoints were to assess the response rate and toxicities of FCM-R followed by maintenance rituximab therapy in untreated CLL patients.
- Other objectives were to analyze the impact of biological prognostic factors in response and to evaluate the clinical significance of minimal residual disease (MRD) in patients achieving complete response (CR).
- Response was assessed three months after FCM-R treatment and included MRD evaluation by four-colour flow cytometry.

**Key findings**

- Thirty-eight patients were evaluable for response to the first part of the treatment (FCM-R induction therapy).
- Ninety percent of the patients received the entire planned treatment.
- An overall response (OR) rate of 92%, CR rate of 77%, nodal partial response (nPR) rate of 7%, and partial response (PR) rate of 8% were observed.
- Of the 77% CR, 36% of patients were MRD-negative and 41% of patients were MRD-positive. Two out of four PR cases were MRD-negative.
- Toxicity was manageable, with grade 3/4 neutropenia being observed in 8% of the cases.
- Six serious adverse events were documented [four infections, one coronary disease, one cytomegalovirus (CMV) reactivation], two of them unrelated to the treatment.

**Key conclusions**

- These extremely promising interim results have effectively set the stage for assessing if rituximab maintenance therapy can further prolong the response duration in primary CLL patients.
- The study to date confirms that FCM-R induction is a well-tolerated regimen with a high CR rate that includes an important proportion of MRD-negative CRs.

FCR/FR induction therapy followed by rituximab maintenance results in almost 100% complete response in patients with B-cell chronic lymphocytic leukemia

**Background**
Achievement of durable complete response is a new goal of clinical research in chronic lymphocytic leukemia (CLL). With this objective in mind, Egle and colleagues designed a study which incorporated a two-part induction strategy with rituximab maintenance therapy in previously untreated CLL patients.1

**Study design**
- The study was a phase II trial with 40 patients. Patients with an ECOG performance status 0–2 and previously untreated B-cell CLL as determined by CD23, CD5, CD19, or CD20 positivity were included in the study.
- During induction therapy, FCR was administered for three cycles as per the Keating protocol2 followed by FR for three cycles as per the Byrd protocol.3
- Maintenance therapy with rituximab was administered every three months for two years.
- Patients were followed up for three years, with staging visits every six months inside the study schedule after the end of maintenance.

**Key findings**
- Objectives were to attain a 65% complete response (CR) rate, and to assess response rate, minimal residual disease (MRD), toxicity, serious adverse events, relapse-free survival, and treatment-free survival.
- A CR and CR tox rate of 83% following FCR as first induction therapy was observed at week 12 (Figure 1).
- A CR and CR tox rate of 94% following FR as second induction therapy was observed at week 24 (Figure 2).
- CR and CR tox rate at first-stage maintenance therapy was 100% (Figure 3).
- At weeks 12 and 24, 42% (13/31) and 59% (10/17) patients respectively were negative for MRD.
- Forty-two serious adverse events were reported in 25 patients.
- There were 19 treatment-related serious adverse events; most were fever or infection, and the patients experienced complete recovery (Table 1).
Figure 1: Response at week 12 following FCR as first induction therapy

- CR: complete response
- CR tox*: no evidence of disease but has persisting cytopenia
- PR: partial response
- PR tox†: evidence of PR but has persisting cytopenia
- SD: stable disease
- PD: progressive disease

* No evidence of disease but has persisting cytopenia
† Evidence of PR but has persisting cytopenia
CR = complete response; FCR = fludarabine/cyclophosphamide/rituximab; PD = progressive disease; PR = partial response; SD = stable disease

Figure 2: Response at week 12 following FCR as second induction therapy

- CR: complete response
- CRu: unconfirmed complete response
- CR tox*: no evidence of disease but has persisting cytopenia
- PR: partial response
- PR tox†: evidence of PR but has persisting cytopenia

* No evidence of disease but has persisting cytopenia
† Evidence of PR but has persisting cytopenia
CR = complete response; CRu = unconfirmed complete response; FCR = fludarabine/cyclophosphamide; PD = progressive disease; PR = partial response; SD = stable disease
Table 1: Interim analysis toxicity*

<table>
<thead>
<tr>
<th></th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretherapy  (n = 43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and bone marrow</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Induction Therapy† (n = 39)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and bone marrow</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*According to National Cancer Institute Common Toxicity Criteria
†Maximal grade

Key conclusions

- Induction therapy with FCR and FR at the first stage of rituximab maintenance therapy demonstrates an almost 100% complete response rate.

- The long-term myelosuppression rates for this regimen warrants monitoring throughout therapy.

Lenalidomide is effective in fludarabine-refractory chronic lymphocytic leukemia

Background
Fludarabine either as monotherapy or as part of combination chemotherapy is effective in the treatment of chronic lymphocytic leukemia (CLL). However, most CLL patients eventually become refractory to fludarabine, and survival for this group of patients is relatively short, ranging from 9 to 13 months.1 Phase II studies have demonstrated the clinical efficacy of lenalidomide in patients with relapsed or refractory CLL.2,3 Chanan-Khan and colleagues conducted a subset analysis in patients who were refractory to fludarabine.4

Study design
- Twenty-nine patients with fludarabine-refractory disease who were enrolled in the Chanan-Khan et al. (n = 17) and the Ferrajoli et al. (n = 12) phase II lenalidomide monotherapy trials were included in this analysis.
- In both studies, the median number of prior therapies was four and the median beta-2 microglobulin level was 5 mg/dL.
- Lenalidomide was administered as follows:
  - Chanan-Khan et al.: 25 mg po on days 1–21 of each 28 day cycle
  - Ferrajoli et al.: 10 mg po on days 1–28 followed by 5 mg increments every 28 days, to a maximum dose of 25 mg

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ferrajoli et al. (n = 12)</th>
<th>Chanan-Khan et al. (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission (CR)</td>
<td>0 (0)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>3 (25)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (33)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Overall response (CR + PR)</td>
<td>3 (25)</td>
<td>7 (41)</td>
</tr>
</tbody>
</table>

Figure 1: Progression-free survival following lenalidomide monotherapy
A

FCM-R is more effective than FCM in relapsed chronic lymphocytic leukemia

Adding rituximab or mitoxantrone to the standard FC regimen improves outcome in untreated chronic lymphocytic leukemia (CLL) patients.1,2 At ASH 2007 Hillmen and colleagues presented results from a randomized, phase II trial, which compared FCM with FCM-R in relapsed CLL.3

Study design
- Fifty-two patients were entered into this randomized, phase II trial. Each arm had 26 patients. The median age was 65 years (32–79), and 79% were men.
- Forty-two percent of the patients had a beta-2 microglobulin (β2m) >4.
- The median number of prior therapies was two (1–6); 31 patients had prior fludarabine exposure; and six patients (12%) were refractory to or had relapsed <6 months after fludarabine.
- Unmutated IgV_H genes were found in 26/44 (59%) patients (15/22 in the FCM-R arm and 11/22 in the FCM arm). Eleven patients had deletion of 11q (five in the FCM-R arm and six in the FCM arm) and one patient in the FCM-R arm had >20% 17p deleted cells.
- Sixty-nine percent of the patients had received four or more cycles of therapy. There was no difference with regard to the number of cycles of therapy between the FCM and FCM-R arms.
- Patients were prophylactically treated with aciclovir and cotrimoxazole.
- The primary endpoint was response by NCI criteria two months after therapy.

Key conclusions
- Lenalidomide, a novel agent with immunomodulating properties, has clinical efficacy in patients with relapsed or refractory CLL.
- Clinical response to lenalidomide monotherapy was also noted in 35% of fludarabine-refractory patients (a subset of CLL patients with poor survival and limited therapeutic options).
- The observed clinical benefit of treatment with lenalidomide, independent of responsiveness to prior fludarabine, is encouraging and warrants further evaluation.

Key findings

- Adding rituximab to FCM resulted in a higher complete response rate (43% CR + CRi (complete remission with incomplete marrow recovery) for FCM-R and 13% CR + CRi for FCM) (Table 1).
- More patients in the FCM-R arm (five after FCM-R and two after FCM) achieved minimal residual disease (MRD) negativity as compared with FCR.
- Thirty-five serious adverse events (SAEs) were reported in 23 patients.
- There was no difference in the number of patients with SAEs between the arms (11 in the FCM arm and 12 in the FCM-R arm).
- Eighty-six percent of patients (6/7) who had four or more prior therapies reported an SAE, compared to 38% of patients (17/45) who had less than four prior therapies. Sixteen and ten SAEs were suspected to be related to FCM-R and FCM respectively.

Key conclusions

- **Adding rituximab to FCM appears to be more effective than FCM alone in the treatment of relapsed CLL.**
- **The results of this randomized phase II trial warrant that FC with mitoxantrone and/or rituximab be studied in larger, randomized phase III trials.**

ABRAXANE®
Now Approved in Ontario

When fighting metastatic breast cancer... little things count

Compared to standard paclitaxel injection – ABRAXANE demonstrated:

Superior Efficacy in Primary Endpoint of target Lesion Response Rate\(^1\,^2\)

- 33% vs 19%
- \(p=0.001\)

- 73%

Significantly Longer Median Time to Tumour Progression

- 23.0 vs 16.6 weeks
- \(p=0.002\)

- 1.6 months

Significantly Less Grade 4 Neutropenia

- 9% vs 22%
- \(p<0.001\)

- 59%

Proprietary, nanoparticle albumin-bound (nab\(^{TM}\)) technology

- Solvent-free ABRAXANE at a starting dose of 260mg/m\(^2\)
- No premedication to prevent hypersensitivity reactions
- Convenient 30-minute infusion only once every 3 weeks

ABRAXANETM for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel) is indicated for: the treatment of metastatic breast cancer.

Common Adverse Events\(^*\)

The most common adverse events (>10% of patients) included neutropenia (<2.0 x 10\(^9\)/L = 80%; <0.5 x 10\(^9\)/L = 9%), leukopenia (<4.0 x 10\(^9\)/L = 72%; <1.0 x 10\(^9\)/L = 0%), infections (24%), abnormal ECG (all patients 60%; with normal baseline 35%), dyspnea (12%), sensory neuropathy (any symptoms 71%; severe 10%), myalgia/arthritis (any symptoms 44%; severe 8%), fluid retention/edema (any symptoms 10%; severe 0%), nausea (30%); vomiting (18%), diarrhea (27%), alopecia (90%), asthenia (any symptoms 47%; severe 8%), alkaline phosphatase elevation (36%), AST elevation (39%).\(^*\)

Severe sensory neuropathy occurred more frequently in the ABRAXANE arm (10% vs. 2%; \(p<0.001\)). However, the sensory neuropathy seen with ABRAXANE improved from grade 3 to lower grades in a median of 22 days after interrupting ABRAXANE therapy.\(^1\) No episodes of grade 4 sensory neuropathy were reported.\(^2\)

\(^*\) In a multi-centre, international open-label, randomized phase III trial, 460 patients were randomized to receive either ABRAXANE at 260 mg/m\(^2\) q3w (n=229) or solvent-based paclitaxel at 175 mg/m\(^2\) q3w (n=225). Solvent-based paclitaxel was administered over 3 hours along with standard premedication for hypersensitivity reactions. ABRAXANE was administered over 30 minutes and no premedication for hypersensitivity reactions was given.\(^1\) The primary endpoint of the study was overall target lesion response rate (RR) including a pre-planned analysis in 1st line treated patients. Secondary endpoints included time to tumour progression (TTP) and overall survival.\(^1,^2\)


Abraxis Oncology
45 Vogel Road, Suite 210
Richmond Hill ON L4B 3P6

Abraxane®
for Injectable Suspension
(paclitaxel powder for injectable suspension)
nanoparticle, albumin-bound (nab) paclitaxel

Abraxis Bioscience Inc

See prescribing summary on page 41
The Conundrum of Venous Thromboembolism in Hematological Malignancies

Suzanne Simoni

Although an estimated 45,000 Canadians are diagnosed with venous thromboembolism (VTE) each year, many individuals remain undiagnosed.\(^1\) At the 49th Annual Meeting of the American Society of Hematology, held in Atlanta, Georgia, VTE took center stage. The significance and magnitude of the problem was discussed at various special interest and educational sessions.

Venous thromboembolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Thrombosis can develop in any vein, but most thrombi occur in the veins of the leg. Deep vein thrombosis in the leg can embolize and eventually reach the lungs, causing pulmonary embolism.\(^2\) In the general population, VTE is mostly a disease of the elderly, except for women during their childbearing years and individuals who have been immobile, had surgery, or have a history of thrombosis. VTE can occur concomitantly with many disease states, but the particular nature of hematological malignancies and the associated risk of VTE pose a unique therapeutic challenge for the treating physician.

**Venous thromboembolism risk in individuals with cancer**

As far back as 1000 BC, the Indian surgeon Sushruta made reference to the relationship between malignancy and VTE.\(^3\) Today VTE is the second-leading cause of death after cancer in hospitalized cancer patients; this statistic includes patients who were responding well to cancer therapy.\(^4,5\) Almost one-fifth of all new VTE events are related to active cancer.\(^4\) The risk of VTE varies according to the type of cancer and other factors (Tables 1 and 2).

Consequences of thrombosis in patients with cancer include chemotherapy interruption, hospitalization, morbidity, and even mortality.\(^6\) In spite of the existence of guidelines for VTE in patients with cancer, oncologists in North America report that they routinely administer thromboprophylaxis to less than 5% of their patients.\(^6\)

<table>
<thead>
<tr>
<th>Table 1: Venous thromboembolism risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease condition</td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Active cancer(^4)</td>
</tr>
<tr>
<td>Factor V Leiden mutation(^7)</td>
</tr>
<tr>
<td>Prothrombin 20210A(^7)</td>
</tr>
<tr>
<td>Type and stage of cancer(^4,7)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Initial 3–6 months after cancer diagnosis(^7)</td>
</tr>
<tr>
<td>Chemotherapy(^4)</td>
</tr>
<tr>
<td>Surgery/trauma(^8)</td>
</tr>
<tr>
<td>Recurrent VTE(^4)</td>
</tr>
</tbody>
</table>

*As compared to individuals without cancer
\(^1\) For patients with cancer (three-fold increased risk of fatal PE)
\(^2\) Five-fold increased risk of VTE in patients with advanced malignancies
Venous thromboembolism in patients with hematological malignancies

Traditionally perceived as low-risk for VTE, patients with hematological malignancies, which include lymphoma, leukemia, and myeloma, are at as high a risk or even higher risk of developing VTE than patients with solid tumors. According to Blom et al, the highest risk of VTE, after adjusting for age and sex, is for patients with hematological malignancies, followed by lung and GI cancers. Of all VTE events observed in over 66,000 patients, Khorana et al. found that one-third of VTE events occurred in patients with non-Hodgkin’s lymphoma or leukemia. Pathogenic risk factors for VTE in conjunction with an increased risk of bleeding complications (Tables 3 and 4) present a double-edged challenge to oncologists. The propensity to bleed from the disease and therapy-related thrombocytopenia may overshadow the hypercoagulable state in patients such as those with acute leukemia.

<table>
<thead>
<tr>
<th>Type of malignancy</th>
<th>Risk of VTE by malignancy* (95% CI)</th>
<th>Site of cancer and associated rate of VTE in hospitalized patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hematological malignancies</td>
<td>28.0</td>
<td>n/a</td>
</tr>
<tr>
<td>Myeloma</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>10.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>n/a</td>
<td>4.6</td>
</tr>
<tr>
<td>Leukemia</td>
<td>n/a</td>
<td>4.2</td>
</tr>
<tr>
<td>Lung</td>
<td>22.2</td>
<td>5.1</td>
</tr>
<tr>
<td>All gastrointestinal malignancies</td>
<td>20.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Pancreas</td>
<td>n/a</td>
<td>8.1</td>
</tr>
<tr>
<td>Colon</td>
<td>n/a</td>
<td>4.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>n/a</td>
<td>4.9</td>
</tr>
<tr>
<td>Brain</td>
<td>6.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Kidney</td>
<td>6.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Breast†</td>
<td>4.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Ovarium</td>
<td>3.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Endometrium and cervix</td>
<td>2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.2</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* In patients with a diagnosis of cancer within five years before diagnosis of VTE. Adjusted for age and sex, when applicable
† A total of 12 patients and 0 control participants used hormone therapy
n/a: not analyzed

Table 3: Risk of venous thromboembolism in hematological malignancies

Determinants for clotting activation and higher risk in hematological malignancies include:
- Prothrombotic factors such as tissue factor (TF) and cancer procoagulant (CP) produced in leukemic cells
- Increased blood viscosity from hyperleukocytosis
- Comorbid conditions including hereditary thrombophilia, infection, endothelial cell activation by cytokines, antiphospholipid syndrome, and acquired activated protein C (APC) resistance
- Treatment with anti-angiogenesis drugs such as thalidomide or lenalidomide, especially in combination with chemotherapy and steroids in patients with multiple myeloma

Table 4: Risk of bleeding in hematological malignancies

For patients with hematological malignancies, the risk of bleeding complications poses a challenge. Some of the risks include:
- Thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Development of Factor VIII inhibitors
- Enhanced fibrinolysis by increased expression of Annexin II by leukemic cells
Venous thromboembolism prophylaxis and treatment in hematological malignancies

Clinical trials have demonstrated the efficacy of VTE prophylaxis with low-molecular-weight heparins (LMWH) and low-dose unfractionated heparin (LDUH) in patients with solid tumours after major surgery or when hospitalized for acute medical illnesses. The American College of Chest Physicians (ACCP) recommends that these patients receive prophylaxis that is appropriate for their current risk state. In addition, recent guidelines from the American Association of Clinical Oncology (ASCO) recommend LMWH for both the initial and continuing treatment of patients with cancer who have established VTE. Since clinical trials for VTE prophylaxis and treatment in patients with hematological malignancies have not been conducted, there are no guidelines that specifically address the unique nature of these diseases. In some instances, conclusions can be derived from existing guidelines for management of patients with other malignancies. ASCO, for example, states that LMWH or adjusted-dose warfarin (International Normalized Ratio [INR]~1.5) be used in myeloma patients receiving thalidomide plus chemotherapy or dexamethasone. This recommendation is based on extrapolations from studies of postoperative prophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer.

The treatment of VTE in hematological malignancies presents a unique therapeutic challenge to oncologists due to the double-edged risk of bleeding as well as thrombosis. In addition, there is a need for specific guidelines for prophylaxis and treatment of VTE in hematological malignancies. Future clinical trials will hopefully fill this gap of knowledge.

Key conclusions

- VTE is the second-leading cause of death after cancer in hospitalized cancer patients.
- In spite of the existence of guidelines, oncologists in North America report that they routinely administer thromboprophylaxis to less than 5% of their patients.
- Patients with hematological malignancies are at as high a risk for VTE as patients with solid tumours.
- The challenge for treatment of VTE in patients with hematological malignancies is the dual risks of bleeding as well as thrombosis.
- In the absence of randomized clinical trials in this patient population, prophylaxis and treatment decisions can be inferred, after careful weighing of risk factors, from existing guidelines for management of patients with other malignancies.

References:
Patient Selection Criteria

INDICATIONS AND CLINICAL USE
ABraxane® for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel) is indicated for:

- the treatment of metastatic breast cancer.

ABraxane® should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents and in the management of breast cancer. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE.

Note: An albumin form of paclitaxel may substantially affect a drug’s functional properties relative to those of drug in solution. Do not substitute with or for other paclitaxel formulations.

Geriatrics (> 65 years of age):
Evidence from clinical studies suggests that use in the geriatric population is not associated with notably more frequent toxicities among elderly patients who received ABRAXANE. A brief discussion can be found in the WARNINGS AND PRECAUTIONS section.

Pediatrics (≤ 16 years of age):
The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

CONTRAINDICATIONS
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing of ingredients see the Product Monograph.
- ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel) should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm³.

Special Populations
Pregnant Women/Teratogenic Effects: ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel powder for injectable suspension to rats on gestation days 7 to 17 at doses of 6 mg/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations was also exhibited at 3 mg/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE.

There was no exposure in pregnancy in the clinical trials.

Nursing Women: It is not known whether paclitaxel is excreted in human milk. In rats, following intravenous administration of carbon-14 labeled paclitaxel on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE therapy.

Pediatrics: The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatrics (> 65 years of age): Of the 229 patients in the randomized study who received ABRAXANE, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE.

Monitoring and Laboratory Tests
In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level > 1,500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³. In the case of severe neutropenia (< 500 cells/mm³ for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended.

Safety Information

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.
- ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.
- Note: An albumin form of paclitaxel may substantially affect a drug’s functional properties relative to those of drug in solution. Do not substitute with or for other paclitaxel formulations. In the treatment of metastatic breast cancer ABRAXANE has been evaluated as a single agent only.
Albumin (Human): ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel) contains albumin (human), a derivative of human blood and is a nanoparticle albumin-bound (nab) form of paclitaxel. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the phase III study, the adverse events which were very common were those expected for paclitaxel and included alopecia (90%), neutropenia (80%), leukopenia (72%), sensory neuropathy (71%), asthenia (47%), arthralgia/myalgia (44%), AST (SGPT) elevations (39%), alkaline phosphatase elevations (36%), abnormal ECG (all patients (60%) and patients with normal baseline (35%)), anemia in patients with normal baseline (20%), nausea (30%), vomiting (18%), infections (24%), diarrhea (27%), dyspnea (12%), and fluid retention/edema (10%).

In the phase III study, twenty-seven percent of patients receiving ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel) on a 3 weekly regimen experienced serious adverse events (SAEs). The events occurring in greater than 10 patients were grade 4 neutropenia (9%), infection (3%), and increased GGT (3%).

To report an adverse event, please contact: your physician, pharmacist, ARC of Support Medical Information at 1-866-575-5757 or Abraxis Oncology A Division of Abraxis BioScience, Inc. at: 1-877-779-7480.

DRUG INTERACTIONS

Overview

No drug interaction studies have been conducted with ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel).

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (such as ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound [nab] paclitaxel).

Recommended Dose and Dosage Adjustment

For the treatment of metastatic breast cancer, the recommended regimen for ABRAXANE is 260 mg/m² administered intravenously over 30 minutes every 3 weeks. Dose levels of mg/m² refer to mg of paclitaxel in ABRAXANE.

Dose Reduction: Patients who experience severe neutropenia (neutrophil < 500 cells/mm³ for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m² for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, an additional dose reduction should be made to 180 mg/m². For grade 3 sensory neuropathy, hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

Hepatic Impairment: The appropriate dose of ABRAXANE for patients with bilirubin greater than 1.5 mg/dL is not known.

Missed Dose

ABRAXANE is administered every three weeks. In the event that the next scheduled dose is missed, dosing should occur as soon as possible, consistent with good medical practice, after the missed dose.

Administration

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions (see WARNINGS AND PRECAUTIONS: Injection Site Reactions).

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile, intravenous infusion bag (plasticized polyvinyl chloride (PVC), PVC or non-PVC type IV bag). No further dilution is required. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Do not mix any other drugs with the ABRAXANE infusion.

Reconstitution

ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Neither freezing nor refrigeration adversely affects the stability of the product.
Stability of Reconstituted Suspension in the Vial

ABRAXANE reconstituted in the vial should be used immediately, but may be refrigerated at 2 to 8°C for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Some settling of the reconstituted suspension may occur. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile, IV bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type IV bag). No further dilution is required. The use of specialized DEHP-free solution containers or administration sets may also be used but are not required to prepare or administer ABRAXANE infusions. The use of an in line filter is not recommended.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 20 to 25°C) and ambient lighting conditions for up to 8 hours.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

ABRAXANE is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

SUPPLEMENTAL PRODUCT INFORMATION

OVERDOSAGE

There is no known antidote for ABRAXANE for Injectable Suspension (paclitaxel powder for injectable suspension) (nanoparticle, albumin-bound (nab) paclitaxel) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

Product Monograph available on request.

Abraxis Oncology
A Division of Abraxis BioScience, Inc.
45 Vogell Road, Suite 210
Richmond Hill ON L4B 3P6
Canada
INDICATIONS AND CLINICAL USE

**FRAGMIN®** (dalteparin sodium injection) is indicated for:
- Thromboprophylaxis in conjunction with surgery.
- Treatment of acute deep venous thrombosis.
- Unstable coronary artery disease (UCAD), i.e., unstable angina and non-Q-wave myocardial infarction.
- Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in connection with acute renal failure or chronic renal insufficiency.
- Extended treatment of symptomatic venous thromboembolism to prevent recurrence of venous thromboembolism in patients with cancer.
- Reduction of deep vein thrombosis (DVT) in hospitalized patients with severely restricted mobility during acute illness. Decreased mortality due to thromboembolic events and complications has not been demonstrated.

CONTRAINDICATIONS

FRAGMIN should not be used in patients who have the following:
- Hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) (see WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS, Pregnant Women, or to other low molecular weight heparins and/or heparin
- History of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an in vitro platelet-aggregation test in the presence of FRAGMIN is positive.
- Septic endocarditis (endocarditis lenta, subacute endocarditis)
- Uncontrollable active bleeding
- Major blood-clotting disorders
- Acute gastroduodenal ulcer
- Cerebral hemorrhage
- Severe uncontrolled hypertension
- Diabetic or hemorrhagic retinopathy
- Other conditions or diseases involving an increased risk of hemorrhage
- Injuries to and operations on the central nervous system, eyes and ears
- Spinal/epidural anesthesia is contraindicated where repeated high doses of FRAGMIN (100-120 IU/kg given twice daily or 200 IU/kg once daily) are required, due to an increased risk of bleeding

SPECIAL POPULATIONS

Pregnant Women:
The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal “Gasping Syndrome” in neonates. Cases of Gasping Syndrome have been reported in neonates when benzyl alcohol has been administered in amounts of 99-404 mg/kg/day. Manifestations of the disease include: metabolic acidosis, respiratory distress, gasping respirations, central nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, cardiovascular collapse and death. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

There are also postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving low molecular weight heparins for thromboprophylaxis. These events led to maternal death or surgical interventions.

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.

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.

Safety Information

**WARNINGS AND PRECAUTIONS**

**Special Warnings and Precautions**

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal “Gasping Syndrome” in neonates. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see Special Populations, Pregnant Women).

**General**

FRAGMIN should NOT be administered intra-muscularly.

FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACtIONATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWHs) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR WEIGHT DISTRIBUTION, ANTI-Xa AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

**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.

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 anaesthesia and only if the anaesthesiologist 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.

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 have been reported occasionally leading to fatality

Blood and Lymphatic System: thrombocytopenia, thrombocytopenia

Skin and Subcutaneous Tissue Disorders: skin necrosis, alopecia

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 and thrombolytic agents 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.

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.

Administration

DOSEAGE 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
Thromboprophylaxis 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. 4-8 hours after surgery, 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. Omission of the pre-operative dose may reduce risk of peri-operative bleeding, however increased risk of venous thromboembolic events is possible. This option is based on the results of the North American Fragmin Trial (NAFT), which excluded patients at high risk of bleeding, i.e., documented cerebral or gastrointestinal bleeding within 3 months prior to surgery, defective hemostasis, e.g., thrombocytopenia (<100 x 10^9/L), ongoing anticoagulant treatment.

**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 levels during subcutaneous treatment would be <0.3 IU anti-Xa/mL before 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>
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<tbody>
<tr>
<td>≤64</td>
<td>10 000</td>
</tr>
<tr>
<td>65-128</td>
<td>12 500</td>
</tr>
<tr>
<td>129-235</td>
<td>15 000</td>
</tr>
<tr>
<td>≥236</td>
<td>18 000</td>
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</table>

For patients with increased risk of bleeding, a dose of 100 IU/kg body weight given s.c. twice daily or 100 IU/kg body weight administered over a period of 12 hours as continuous i.v. infusion, can be used. The expected plasma anti-Xa levels during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and ≤1.0 IU anti-Xa/mL 3 - 4 hours after injection.

Normally concomitant treatment with vitamin-K antagonists is started immediately. Treatment with FRAGMIN should be continued until the levels of the prothrombin complex factors (II, VII, IX, X) have decreased to a therapeutic level, in general for approximately 5 days.

**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>
</tr>
</thead>
<tbody>
<tr>
<td>≤64</td>
<td>7 500</td>
</tr>
<tr>
<td>65-128</td>
<td>10 000</td>
</tr>
<tr>
<td>129-235</td>
<td>12 500</td>
</tr>
<tr>
<td>236-430</td>
<td>15 000</td>
</tr>
<tr>
<td>≥431</td>
<td>18 000</td>
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</table>

Dose reductions for chemotherapy-induced thrombocytopenia: In the case of chemotherapy-induced thrombocytopenia with platelet counts ≤50,000/mm³, FRAGMIN should be interrupted until the platelet count recovers above 50,000/mm³. For platelet counts between 50,000 and 100,000/mm³, FRAGMIN should be reduced by 17% to 33% of the initial dose (allowing for dosage adjustment using the pre-filled syringes), depending on the patient’s weight (table below). Once the platelet count recovers to ≥100,000/mm³, FRAGMIN should be re-instituted at full dose.

**Weight (kg) | Scheduled Dose (IU) | Reduced Dose (IU) | Mean Dose Reduction (%)**

| ≤64        | 7 500       | 5 000       | 33          |
| 57-68      | 10 000      | 7 500       | 25          |
| 69-82      | 12 500      | 10 000      | 20          |
| 83-98      | 15 000      | 12 500      | 17          |
| ≥99        | 18 000      | 15 000      | 17          |

**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 levels 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 by 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.

**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.

<table>
<thead>
<tr>
<th>1 mL 10 000 IU</th>
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<tbody>
<tr>
<td><strong>Isotonic NaCl Infusion (9 mg/mL)</strong></td>
</tr>
<tr>
<td><strong>Isotonic Glucose Infusion (50 mg/mL)</strong></td>
</tr>
</tbody>
</table>

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

**SUPPLEMENTAL PRODUCT INFORMATION**

**Overdose**

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 overdose with protamine sulphate. Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling
Product Monograph available on request.

NON-HODGKIN’S LYMPHOMA:
Dose densification of rituximab leads to higher serum levels and increased survival
Extending post-HDT/ASCR remission in relapsed and refractory DLBCL