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New Evidence in Oncology is a publication that provides oncology specialists with scientific data from research presented at international and Canadian oncology conferences. A special feature of the journal, the Canadian perspective, gives key opinion leaders a forum to discuss recent developments in oncology and to comment on how these advances may shape Canadian clinical practice.

Our May 2011 issue presents coverage from the 3rd Annual Meeting of the Canadian Conference on Lymphoproliferative Disorders (CCOLD), held in Banff, Alberta, from March 25–27, 2011. The issue presents discussions in follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia and multiple myeloma. We would like to thank Dr. Joseph Connors, Dr. James Johnston, Dr. Gilles Salles, and Dr. Martin Dreyling for their presentations and commentaries.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research. Slide presentations on various topics are available for download.
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Martin Dreyling, MD, PhD
Dr. Martin Dreyling is an attending physician and associate professor in the Medical Department of the University of Munich, Grosshadern, Germany. His primary interests include the molecular biology and clinical care of lymphoma. Dr. Dreyling’s research activities relate to the molecular basis of malignant transformation, cell cycle dysregulation in mantle cell lymphoma (MCL), secondary genetic alterations and biological prognostic factors in malignant lymphoma, and innovative therapeutic approaches in indolent lymphoma. He is actively involved in a number of national and European study groups, and is currently the Coordinator of the European MCL Network. Dr. Dreyling has co-authored over 300 scientific papers, book chapters and published abstracts in international peer-reviewed journals.

Gilles Salles, MD
Dr. Gilles Salles is a Professor in the Department of Hematology at the Centre Hospitalier Lyon-Sud, Lyon, France, and Head of the Research Unit Pathologie des Cellules Lymphoïdes at the University of Lyon. He served as Chairman of the Scientific Committee of GELA (Groupe d’Etude des Lymphomes de l’Adulte) until 2007 and is presently acting as vice-president of this group. He is also a member of several professional societies, including the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association. Professor Salles has been especially interested in the clinical and biological study of malignant lymphoma, and major focuses of his work include the description and validation of prognostic factors as well as clinical trials in indolent lymphomas. He has been involved as a coordinator or co-investigator in many clinical trials and studies within his field, and has published numerous articles in international peer-reviewed journals.

James Johnston, MD, FRCP
Dr. James Johnston is a professor in the Department of Internal Medicine at the University of Manitoba and a Hematologist at CancerCare Manitoba. He is primarily interested in the treatment of chronic lymphocytic leukemia (CLL) and is responsible for the CLL clinic at CancerCare Manitoba. He is also the Clinical Director of the Manitoba CLL Tumour Bank. Dr. Johnston’s research activities relate to the epidemiology of CLL and to the mechanism of action of anti-tumour agents in this disease. He is involved in a number of educational activities related to CLL and with Dr Spencer Gibson organizes the “Canadian CLL Meeting” which is held annually in Winnipeg.
Welcome to the *New Evidence* coverage of the 2011 Canadian Conference on Lymphoproliferative Disorders (CCOLD 2011) held in Banff, Alberta from March 25th to 27th.

Now in its third year, CCOLD has grown from its Western roots into a national gathering of the Canadian hematology community. This year, the emerging strength of CCOLD and its backdrop of the Canadian Rockies have attracted an impressive faculty of Canadian experts complimented by international experts from Germany, France, Greece and the United States.

In this issue, we capture key presentations and discussions from CCOLD 2011 focused on some practical issues being faced by Canadian hematologists. We also feature a spotlight article on the FCR protocol developed at The Ottawa Hospital and a Canadian recommendation paper on the use of bisphosphonates in multiple myeloma.

While CCOLD has grown in size and stature, it has maintained a unique element of family and community. Isolated in the chateaux of the Canadian Rockies it has become a true “meeting of the minds”.

See you next year at Lake Louise!
CAT can be tamed.

FRAGMIN. The only low molecular weight heparin indicated to treat Cancer-Associated Thrombosis (CAT) in Canada.

FRAGMIN is indicated for the extended treatment of symptomatic VTE to prevent recurrence of VTE in patients with cancer.

Venous thromboembolism (VTE) is a frequent medical complication in patients with cancer, occurring in 4% to 20% of cases.

FRAGMIN Achieved A Statistically Significant 52% Relative-Risk Reduction In Recurrent VTE vs. Oral Anticoagulant Therapy*,†

(27/336 vs. 53/336; p=0.002)

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

<table>
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<tr>
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<th>FRAGMIN n=336</th>
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• Evidence-based FRAGMIN dosing: 200 IU/kg sc once daily (maximum 18,000 IU daily) for the first month, followed by a maintenance dose of ~150 IU/kg sc once daily for 2–6 months sc.

• INR or APTT monitoring is not required. §

• FRAGMIN is eligible for reimbursement under many provincial formularies.

Adverse Events: Clinically significant adverse reactions with FRAGMIN and other LMWHs include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions. In clinical trials with hospitalized patients with severely restricted mobility, the incidence of thrombocytopenia was 0.54% at days 14 and 21. Injection site hematomas are a common side effect with FRAGMIN, occurring at a frequency of <5% with lower (prophylaxis) doses and <10% with higher (treatment) doses.

FRAGMIN should be used with care in patients with hepatic insufficiency, renal insufficiency or a history of gastrointestinal ulceration. Please consult the Prescribing Information for complete dosing instructions, warnings and precautions, and adverse events.

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.

FRAGMIN should NOT be administered intra-muscularly.

FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRAGMENTED 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.

Contraindications: FRAGMIN should not be used in patients who have: hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) or to other low molecular weight heparins and/or heparin or pork products; 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.

* Platelet counts should be determined prior to the start of treatment with FRAGMIN and subsequently, twice weekly for the duration of treatment. Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia, or platelet defects. Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered in patients at higher risk of bleeding and receiving FRAGMIN, such as the elderly, patients with renal impairment or the extremes of body weight, during pregnancy, or for children.

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See prescribing summary on page 57
An Update on Follicular Lymphoma: Summary of the Presentation by Dr. Gilles Salles at CCOLD

At CCOLD 2011, Dr. Gilles Salles, Professor of Hematology at the Centre Hospitalier Lyon-Sud in Lyon, France presented an update on follicular lymphoma as part of the multiple myeloma and amyloid session. The presentation covered the history of treatment, prognostic markers, current treatment, and new approaches in the management of follicular lymphoma. The article below presents a summary of the presentation by Dr. Salles.

History of treatment in FL

Until the end of the 1990s, it was thought that the natural history of follicular lymphoma (FL) could not be influenced by any therapeutic strategy. This belief was supported by a number of studies showing little improvement in overall survival (OS) until the mid- to late- nineties.\(^1\,2\) (Figure 1) Therefore, although a number of therapeutic options existed for patients with FL prior to 1990, the best treatment strategy was unclear.

In the period from 1990–1992, the five-year OS of patients with FL was around 50%, improving to around 67% in the period from 2002–2004.\(^3\) This improvement in survival was largely due to a new treatment paradigm using anti-CD20 antibodies, in particular the addition of rituximab to standard first-line chemotherapy.

Given the prognosis of patients before the 1990s, treatment strategies included palliation with repeated and prolonged treatment. With improvements in prognosis, treatment strategies have shifted, due to higher response rates and longer treatment-free intervals seen with current therapeutic agents. The current goal of treatment is therefore to extend OS, with a cure being the ultimate goal. As well as improving OS, patient preference, quality of life, and healthcare costs are taken into consideration when making treatment decisions.

Figure 1. Historical comparison of overall survival in patients with follicular lymphoma

Prognostic markers in FL

The follicular lymphoma international prognostic index (FLIPI) was validated in the year 2004 as a tool for stratifying patients based on prognostic risk. Prognostic markers included in the FLIPI score are age, hemoglobin level, serum lactose dehydrogenase (LDH) level, Ann Arbor stage, and number of nodal sites involved.

Although FLIPI is a useful measure for comparing patients across studies, it was developed in the years prior to the use of rituximab. In the year 2008, Federico, et al. developed the FLIPI-2, which was shown in one study to be highly predictive of both OS and progression-free survival (PFS). FLIPI-2 includes age, hemoglobin level, $\beta_2$ microglobulin, bone marrow involvement, and the largest diameter of the largest node as prognostic factors. We do, however, need to wait for FLIPI-2 to be validated in larger groups of patients to determine whether it is superior to the original FLIPI as a prognostic measure.

Although FLIPI scores are useful measures of prognosis, they may not be the best criteria for making treatment decisions. Currently, the Groupe d’ Étude des Lymphomes de l’ Adulte (GELA) and the British National Lymphoma Investigation (BNLI) have identified clinical criteria that can be used to initiate cytotoxic treatment. A number of new prognostic criteria are also being explored in FL. These include cytogenetic markers, new targets identified on $\mu$-arrays, and host genetic factors.

Therapeutic options at diagnosis

At diagnosis, patients may be grouped into those who should undergo observation only before starting treatment (watch and wait) and those who should begin cytotoxic treatment combined with rituximab at diagnosis. The RWW study by Ardesinha, et al. compared rituximab induction and maintenance versus a watch and wait strategy in asymptomatic patients with FL. Results showed a delay in time to treatment with chemotherapy, prolongation of PFS, and very high response rates (RRs) after treatment with rituximab. However, longer follow-up of the RWW study and results from other studies are needed to determine whether early treatment is beneficial in all asymptomatic patients with FL.

During his presentation, Dr. Salles stated that he prefers to use tumour burden rather than FLIPI score as the criterion for grouping patients into watch and wait versus cytotoxic treatment. In low tumour burden patients, a number of treatment strategies are being examined in clinical trials. Ongoing studies are modifying rituximab treatment using prolonged treatment, maintenance, or higher doses of rituximab. Radio-immunotherapies, such as tositumomab and ibritumomab, are another option in these patients. Short-term immunochemotherapies, such as R-CVP and rituximab plus bendamustine (R-bendamustine), are also being examined in ongoing clinical trials. Finally, the addition of rituximab to other antibodies or immunomodulatory agents may provide further treatment options in these patients.

Figure 2. Progression-free survival after treatment with R-bendamustine versus R-CHOP

The standard treatment for patients with high tumour burden includes six to eight courses of R-CHOP or R-CVP. However, other chemotherapeutic agents, such as bendamustine and fludarabine, are being examined in clinical trials. A study by Rummel, et al. compared treatment with R-bendamustine versus R-CHOP as first-line therapy for patients with FL, indolent, and mantle cell lymphoma (MCL). Results of the study showed improved PFS and RRs with R-bendamustine compared to R-CHOP, as well as an improved safety profile in patients given R-bendamustine. However, it is important to consider that bendamustine may impair DNA and DNA reparation, potentially resulting in long-term hematopoietic effects.

In patients with a high tumour burden, consolidation with autologous stem cell transplant (ASCT) or radio-immunotherapy; combination with targeted therapies, such as bortezomib; new anti-CD20 antibodies, such as ofatumumab and GA101; and combination with immunomodulatory agents, such as GM-CSF and lenalidomide, are additional treatment options being examined in clinical trials.

**Maintenance treatment in FL**

Maintenance treatment is not a new concept in hematology and has been used for many years in patients with acute lymphoblastic leukemia (ALL). Some data suggest that rituximab’s mechanism of action is dependent on the mobilization of the patient’s immune system. We may therefore hypothesize that using rituximab maintenance in patients who have recovered from the side effects of chemotherapy may better mobilize the antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism.

A European Organization for Research and Treatment of Cancer (EORTC) study by van Oers, et al. examined the use of rituximab maintenance in relapsed patients with FL. Patients in complete remission (CR) or partial remission (PR) after induction treatment were randomly assigned to maintenance treatment with rituximab (375 mg/m²) every three months or observation. An improvement in PFS was observed in the rituximab maintenance group, compared to patients in the observation alone group ($p < 0.001$).

A second study, the Swiss Group for Clinical Cancer Research (SAKK) study by Martinelli, et al., presented important data comparing observation alone and four additional doses of rituximab given at two-month intervals (prolonged exposure) after rituximab monotherapy. Results of the SAKK study showed a long-term favourable effect of prolonged rituximab treatment on event-free survival (EFS) in these patients ($p < 0.001$).

Based on results of previous studies, the GELA group designed the PRIMA study comparing first-line rituximab maintenance versus observation following induction treatment in patients with FL. The choice of induction treatment was left to the discretion of each study centre. Patients who failed to respond to induction treatment were not included in the study.
Baseline characteristics were similar across all induction treatment groups and maintenance versus observation groups. However, initial response rates following induction treatment with R-CHOP were slightly higher than those seen for R-CVP (92.8% versus 84.7%, respectively).

After a median follow-up of 36 months, PFS was 75% in the rituximab maintenance versus 58% in the observation group (p <0.0001). (Figure 5) Of note, the shape of the curve after 24 months remained similar in both groups, despite having stopped rituximab maintenance at this point. This suggests that patients who were given maintenance rituximab continue to do well even after stopping treatment.

When examining PFS by age, sex, FLIPI score, induction treatment, and response to induction treatment, a benefit remained across all subgroups. However, the benefit of rituximab maintenance was borderline significant in the R-CVP subgroup (HR 0.68; CI: 0.45–1.02) and not significant in the R-FCM subgroup (HR 0.54; CI: 0.13–2.24). A Cox multivariate analysis was performed to determine which factors influenced PFS. Factors associated with a higher risk of relapse included age ≥60 years, male sex, induction treatment with R-CVP versus R-CHOP/R-FCM, and a higher FLIPI score. The benefit of rituximab maintenance on PFS was found to be highly significant, independent of the above associated factors (p <0.0001).

A notable result of the PRIMA study is that 75% of patients in the rituximab maintenance arm achieved a CR or unconfirmed CR (CRu), compared to 55% of patients in the observation arm. In addition, more patients in the rituximab maintenance arm converted from a PR to a CR/CRu (52%) versus patients in the observation arm (30%). A previous study by Bachy, et al. (GELF-86 study) found that patients achieving a CR with the first line of treatment had significantly longer OS than those achieving only a PR. Therefore, using rituximab maintenance to achieve higher rates of CR may translate into an improvement in OS in FL patients.

A higher rate of adverse events (AEs) occurred with rituximab maintenance versus observation (52% vs. 35%, respectively). (Figure 6) Most of the AEs included neutropenia and infections; however, the majority of them were easily managed. Only 4% of patients in the rituximab maintenance group withdrew from the study due to AEs.

Results of PET scans are being examined from patients in the PRIMA study with interesting results. All except one PET scan prior to induction treatment was positive (n = 179). Results of PET scans were highly predictive of patient outcomes, with 7/10 deaths occurring in PET-positive patients. Two of the three deaths in PET-negative patients were unrelated to lymphoma. PET scans may therefore be a useful tool in evaluating patients with FL.

In the future, the use of maintenance treatment in FL may be further improved with the use of more potent anti-CD20 antibodies, such as GA101, and by combining monoclonal antibodies with other targets, such as immunomodulatory agents. These strategies are currently under examination in ongoing clinical trials.
Figure 5. Progression-free survival in observation versus maintenance groups

![Graph showing progression-free survival](image)

**Stratified HR: 0.55**

95% CI: 0.44–0.68

$p < 0.0001$

**Patients at risk:**

<table>
<thead>
<tr>
<th>Group</th>
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<th>42</th>
<th>44</th>
<th>45</th>
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<th>55</th>
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<td>16</td>
<td>0</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>


*CI = confidence interval; HR = hazard ratio*

---

Figure 6. Safety of rituximab maintenance versus observation

![Graph showing safety](image)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Observation (n = 508)</th>
<th>Rituximab maintenance (n = 501)</th>
</tr>
</thead>
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<tr>
<td>Any adverse event</td>
<td>35%</td>
<td>52%</td>
</tr>
<tr>
<td>Grade ≥2 infections</td>
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<td>37%</td>
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<tr>
<td>Grade 3/4 adverse events</td>
<td>16%</td>
<td>23%</td>
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<tr>
<td>Grade 3/4 neutropenia</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Grade 3/4 infections</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Question #1:** Rituximab maintenance after induction with R-CVP appeared to be less effective than after R-CHOP. Can you explain this finding?

**Answer:** The hazard ratio associated with the use of rituximab maintenance following R-CHOP was 0.51, compared to 0.68 following R-CVP. The distribution of baseline characteristics between induction groups was not markedly different and therefore does not explain the observed difference between induction groups. In addition, the three-year PFS with rituximab maintenance was 62% with R-CVP, compared to 78% with R-CHOP. Thus, rituximab maintenance may be more effective in patients who achieve a better response to induction treatment.

**Question #2:** What is the appropriate dosing interval for upfront maintenance treatment with rituximab?

**Answer:** Dr. Berinstein published data showing that after four infusions of rituximab the serum level of rituximab in patients who respond is around 25 μg/mL, but is much lower in patients who do not respond. Based on pharmacological data, we will achieve a serum concentration of 25 μg/mL in 85%–90% of patients if we give rituximab every two months and in only 50% of patients if we give it every three months. In first-line patients, I tend to give rituximab maintenance according to the evidence from current clinical studies. Therefore, I give rituximab maintenance every two months in the upfront setting and every three months in relapsed patients.

**Question #3:** What is the appropriate duration of maintenance treatment?

**Answer:** Several studies are investigating the benefits of long-term maintenance. However, results of these studies are not conclusive at this time. With two years of maintenance, we achieve an optimal risk:benefit ratio for our patients. I therefore will continue to give two years of rituximab maintenance.

**Question #4:** Are you examining the risk of transformation according to the different treatments used in the PRIMA study?

**Answer:** About 40% of patients who progressed in the PRIMA study had histological documentation. The proportion of patients from this subset who transformed was identical in the observation and rituximab maintenance arm. We have not yet analysed this data according to induction treatment, but we hope to do so in the future.
Time to Abandon Watchful Waiting in FL: Summary of the Presentation by Dr. Joseph Connors at CCOLD

Intervention with rituximab plus chemotherapy improves overall survival

A number of studies have shown that the addition of rituximab to chemotherapy (R-chemo) improves overall survival (OS) in symptomatic patients with follicular lymphoma (FL).

A study by Marcus, et al. randomized patients with symptomatic FL to first-line R-CVP or CVP every three weeks for eight cycles. Results of this study demonstrated a significant OS benefit after four years for patients given R-CVP versus CVP (p = 0.03). A study by Hiddemann, et al. also supports the benefit of R-chemo, showing a substantial survival advantage for first-line R-CHOP versus CHOP in elderly patients with FL (p = 0.039). Finally, a study by Forstpointner, et al. found a survival advantage of R-FCM versus FCM in patients with relapsed disease (p = 0.003). (Figure 1)

OS is often influenced by the use of subsequent treatments, which tend to reduce the observed difference in OS between study arms. Nevertheless, results from the studies previously discussed suggest that patients who are given R-chemo early in their disease have better outcomes than those receiving chemotherapy alone, even after receiving subsequent treatments for FL.

As part of the lymphoma session at CCOLD 2011, Dr. Joseph Connors, Clinical Professor at the University of British Columbia and Medical Oncologist at the British Columbia Cancer Agency, presented a synopsis of issues related to watchful waiting versus early treatment in asymptomatic patients with follicular lymphoma.

Figure 1. Overall survival after treatment with R-FCM versus FCM


FCM = fludarabine, cyclophosphamide, mitoxantrone; R = rituximab
Rituximab maintenance in FL

A number of studies have also shown a survival advantage for rituximab maintenance (R-maintenance) versus observation alone in FL.

A study by Hochster, et al. randomly assigned advanced-stage indolent lymphoma patients to R-maintenance or observation alone after treatment with CVP. OS at three years for FL patients was 91% in the R-maintenance group versus 86% in the observation group (HR 0.6; log-rank one-sided \( p = 0.08 \)). A trend favouring R-maintenance was also observed among patients with high tumour burden (log-rank one-sided \( p = 0.03 \)).

First-line treatment in the study by Hochster, et al. did not include rituximab and is therefore not generalizable to the current treatment protocol for FL. To examine the effect of R-maintenance after R-chemo, van Oers, et al. randomized relapsed patients with FL to R-maintenance or observation after treatment with R-CHOP or CHOP. Results at three years showed an OS benefit of R-maintenance (85%) versus observation (77%) (HR 0.52; \( p = 0.011 \)). A trend in OS advantage of R-maintenance was also seen when data from the R-CHOP induction subgroup was examined (HR 0.49; \( p = 0.059 \)).

The PRIMA study by Salles, et al. randomized patients with FL to two years of R-maintenance or observation after first-line treatment with R-CVP, R-CHOP, or R-FCM. After a median follow-up of 36 months, three-year progression-free survival (PFS) was 60.3% in the observation arm and 78.6% in the R-maintenance arm (HR 0.55; \( p <0.0001 \)). Although no OS advantage of R-maintenance has been seen to date, such a finding would be unlikely until we have data from at least five years of follow-up.

A meta-analysis performed by Vidal, et al. included studies comparing OS with R-maintenance versus observation in patients with FL. Overall, a significant survival benefit was found for R-maintenance versus observation (HR 0.76; 95% CI 0.62–0.92). (Figure 2)

As a result of the improvements in the treatment of FL, physicians in British Columbia have seen an overall decrease of about 30% in ten-year mortality between 1980 and 2006.

**Figure 2. Meta-analysis of studies comparing R-maintenance versus observation in follicular lymphoma**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hazard Ratio</th>
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<td>Hochster 2007</td>
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<tr>
<td>Heterogeneity: CHi(^2) = 2.60, df = 4 (p = 0.47); I(^2) = 0%</td>
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<tr>
<td>Test for overall effect: Z = 2.80 (p = 0.005)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<tr>
<td>Heterogeneity: CHi(^2) = 6.85, df = 9 (p = 0.65); I(^2) = 0%</td>
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<tr>
<td>Test for overall effect: Z = 2.78 (p = 0.005)</td>
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<tr>
<td>Test for subgroup differences: CHi(^2) = 0.69, df = 1 (p = 0.41); I(^2) = 0%</td>
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</table>

CI = confidence interval; R-M = rituximab maintenance
Rate of progression in FL over time

Studies have shown that the rate of progression decreases over time in patients with FL, whether or not treatment is given.

A study by Ardeshna, et al. compared immediate treatment with chlorambucil to observation until progression in asymptomatic patients with non-Hodgkin's lymphoma (NHL). The study showed that the rate of progression in the observation arm decreased from 20% per year at the beginning of the study to 2% per year after approximately 12 years. (Figure 3)

The observed deceleration in progression shown in the study by Ardeshna, et al. can be easily explained. Some patients started the study with a high tumour burden and a high rate of proliferation; these patients had the highest rate of relapse. Other patients who started the study with either a high tumour burden or a high rate of proliferation had a moderate level of progression. Finally, those patients who had a low tumour burden and low rate of proliferation had the lowest rate of relapse. This is a universal principle and can be seen by examining the results from a number of studies showing that progression rates decelerate over time.6,8

Early treatment in asymptomatic patients with FL

In a recent study by Ardeshna, et al. (RWW study), asymptomatic patients with FL were randomized to rituximab induction, rituximab induction plus maintenance, or observation alone for two years. (Figure 4) The endpoint of the study was time to initiation of new therapy (TTINT) — a useful endpoint, as it establishes the length of time patients are able to wait before requiring aggressive chemotherapies.

The study's definition of progression that warrants initiation of new therapy included criteria used in standard clinical practice, such as development of a symptomatic enlarged spleen, B symptoms or severe pruritus, >3 nodal sites with nodes >5 cm, or histological transformation. Patients included in the study had good performance status and advanced, aggressive disease.

Toxicities with rituximab were minimal; as expected, however, more adverse events (AEs) were seen in the rituximab induction plus maintenance arm than in the rituximab induction arm. After a median follow-up of 32 months, the greatest overall response rates (ORRs) were seen with the rituximab induction plus maintenance arm (85%), followed by the rituximab induction (54%), and observation alone (12%) arms ($p<0.0001$).
Currently, no OS difference has been observed between arms in the RWW study, but the OS is impressive, with a total of 90% of patients surviving after 5 years. These OS results are far superior to those seen in the earlier study by Ardeshna, et al., which showed a five-year OS of 60% in the observation and chlorambucil arms combined.8 We therefore cannot compare the RWW study with older studies, since patients with FL now live longer than they previously did.

The median TTINT in the RWW study was 2.5 years in the observation arm, which is similar to that of the FL population in British Columbia, where the median TTINT is 3.1 years. Therefore, by around five years, most patients without treatment will require treatment with chemotherapy. The proportion of patients not requiring treatment at three years was 91% in the rituximab induction plus maintenance arm, 80% in the rituximab induction arm, and 48% in the observation arm. (Figure 5)

By extrapolating the curves for TTINT, we can hypothesize what might happen in the future. In the worst case scenario, TTINT will accelerate to meet the observation arm, with a median TTINT of around 6.5 years in the rituximab arms. However, the worst case scenario is unlikely, since we have shown that the rate of progression tends to decelerate rather than accelerate over time. A second possibility is that the rate of progression will remain stable, with a median TTINT of around 10 years in the rituximab arms. The third and most likely possibility is that the rate of progression will decrease over time. In that case, the median TTINT could end up being more than 12 years in the rituximab arms, extending the period before systemic treatment of R-CVP and R-maintenance would be required.

In British Columbia, we encounter about 25 asymptomatic patients with FL each year. From years one to ten, we would therefore spend around three million dollars on rituximab treatment. During this ten-year period, only half of the patients will progress, saving the cost of R-CVP for these patients ($6.25 million). The net savings from early intervention with rituximab would be approximately $3.5 million. In addition, only 125 patients will have relapsed using this strategy, instead of the 200 patients you would expect to relapse without early intervention. Each asymptomatic patient treated with four doses of rituximab induction will save around $38,000.

If we were to perform a similar calculation for the worst case scenario, where the median TTINT is 6.5 years, there would still be a net savings of $2.15 million, and only 82 patients would have relapsed with early intervention, compared to 103 patients with observation alone. Therefore, until we have further data, we should choose the cheapest effective intervention, namely four doses of rituximab induction. For the moment, this strategy makes the most sense in terms of reducing treatment cost and toxicity.

With early rituximab induction treatment, at least 40% of patients will not need treatment for a period of approximately ten years. Many elderly patients or those with co-morbidities may never live to require more aggressive and toxic treatments. Younger, healthier patients may hold off aggressive treatments until the time when more effective, potentially curative, treatments become available. The time has therefore come to make a change from watchful waiting to early intervention with rituximab in asymptomatic patients with FL.
Figure 5. Time to initiation of new therapy in the RWW study

- **W&W (n = 187)** 83 events
- **R x 4 (n = 84)** 19 events
- **R x 4 + R-M (n = 192)** 19 events


**R = rituximab; R-M = rituximab maintenance; W&W = watch and wait; TTINT = time to initiation of new therapy**

**Questions from the Audience**

**Question #1:** Response rates (RRs) reported in the RWW study were greater in the rituximab induction plus maintenance arm than in the rituximab induction arm. If we use RRs to predict outcomes, we might assume that the rituximab induction arm was not effective. What can we say about these results?

**Answer:** In this case, RRs were erroneous in terms of predicting what would happen. Results showed that TTINT was 80% in the rituximab induction arm, a figure not greatly different from the TTINT of 91% seen in the rituximab induction plus maintenance arm.

**Question #2:** The TTINT endpoint is subject to bias, since investigators were not blinded to the treatment that was given. Therefore, investigators could have been biased in terms of subsequent treatment given to these patients, based on initial therapy. Please comment on this.

**Answer:** The TTINT is going to be a minimum of four years after the end of treatment with rituximab. Therefore, there is no reason for us to be concerned about giving our standard treatment of R-CVP after such a long interval without treatment. Unless we have a better treatment option by that time, it makes sense to give R-chemo followed by R-maintenance, because these therapies have shown a survival benefit in patients with FL.

**Question #3:** Is there any concern about subsequent resistance to rituximab after initial treatment?

**Answer:** If you have a patient who is receiving a treatment and the disease starts to progress quickly, it does not make sense to repeat the same treatment. However, if you have a treatment that works effectively for four to ten years before another treatment is needed, most clinicians would feel comfortable using the same treatment again. Therefore, I do not see a reason to be concerned about resistance to rituximab.

**Question #4:** Is the follow-up of the RWW study long enough to feel confident about the results?

**Answer:** The median follow-up in the RWW study was 3.6 years. It is always wise to be cautious about extrapolating results over time. However, when we look at data from studies with longer follow-up periods, we do not see large departures from the original curves. I therefore feel confident that the five-year projection will not be far off from what we end up seeing in this study after longer follow-up.

**Question #5:** In the trial by Ardeshna, et al. that compared chlorambucil to observation, around 50% of patients never required therapy. If you were to treat all of these patients, you would be treating some who may never have required
treatment. In addition, some patients who were given rituximab in the RWW study had already progressed. It may therefore be important to identify those patients who are rapid or spontaneous progressors using a brief period of observation. Would you give rituximab to all asymptomatic patients or should some patients be observed only?

**Answer:** In practice, if we encounter patients who have a number of co-morbidities, it does not make sense to treat them if they are unlikely to survive. Giving early treatment with rituximab is only applicable to those patients who are likely to survive for five to ten years. I would also identify patients who are likely to progress using biomarkers and clinical factors. I might observe those patients who appear to have a good chance of progressing before giving rituximab. In patients who seem to be rapid progressors, it may make sense to wait and then give standard treatment with R-CVP followed by R-maintenance. Despite these considerations, giving rituximab early would still apply to a substantial number of the asymptomatic patients that I see in my practice.

**Question #6:** Is it better to give rituximab induction plus maintenance rather than just giving rituximab induction?

**Answer:** We need to wait for the evidence from this study to show whether giving the longer duration of rituximab is superior to giving rituximab induction alone. The investigators closed the rituximab induction arm prematurely, as they thought that the evidence for R-maintenance was strong, based on results from other studies. This decision was unfortunate, but the study still does have an adequate sample size of 80 patients in the rituximab induction arm. In general, if I have a choice to give less treatment, I would want to see strong evidence to show that giving more treatment is going to benefit the patient.

**Question #7:** Does the economic analysis take into consideration a discount rate related to the time-value of the money (3%–5%), as well as the 15%–20% of patients who would theoretically never require treatment?

**Answer:** I have not done a detailed pharmaco-economic study that includes all of these factors. However, even with substantial reductions, using early rituximab treatment still results in a considerable cost saving. Even if you do not save any money, the benefit of early treatment is worthwhile, considering the number of patients who can avoid aggressive treatment. For patients who would not have needed treatment, giving rituximab would only further extend their time without aggressive treatment.

**Question #8:** Why do you think the observation curves for OS have improved over the years?

**Answer:** The five-year OS in the 2003 study by Ardeshna, et al. was around 60%, while current studies achieve 80%–90%. One reason for the improvement in OS is that we have removed the nodular mantle cell lymphoma patients. We also have other treatment strategies that improve OS. Therefore, we are now better at both diagnosing and treating patients with FL.

**References:**
An Interview with Dr. Gilles Salles on Follicular Lymphoma

At the CCOLD 2011 meeting, New Evidence spoke with Dr. Gilles Salles, Professor of Hematology at the Centre Hospitalier Lyon-Sud in Lyon, France, about his presentation on recent advances in follicular lymphoma.

New Evidence: What are the greatest milestones in follicular lymphoma that have been achieved in recent years?

Dr. Salles: In the year 2010, some important results were presented in the area of follicular lymphoma (FL). A number of studies examined the role of maintenance treatment, including the Swiss Group for Clinical Cancer Research (SAKK) study, which presented updated data showing the long-term favourable effect of prolonged rituximab treatment on event-free survival (EFS). A second key study, the RWW study by Ardeshna, et al., compared rituximab induction and maintenance versus a watch and wait strategy in asymptomatic patients. Finally, our group presented final results of the PRIMA study, which examined the benefit of two years of rituximab maintenance following induction treatment. The development of newer molecular antibodies, such as GA101, and small molecules, such as CAL101 and Bruton tyrosine kinase (BTK) inhibitors, have also shown promising results.

New Evidence: Has your practice changed based on the results of these studies?

Dr. Salles: Changes to the practice of treating patients with FL are mostly based on the results of the PRIMA study. Given the strength of the PRIMA results, most centres in Europe now use first-line rituximab maintenance, as recommended by European agencies and health authorities.

New Evidence: In asymptomatic patients, what is the previous justification for the watch and wait strategy?

Dr. Salles: Asymptomatic patients with FL experience a quiet life without symptoms related to their disease. According to previous studies, around 20% of these patients can remain treatment free for a period of up to ten years. A number of randomized studies have shown that there is no benefit to giving alkylating agents alone versus observation until patients become symptomatic. For this reason, observation alone became the standard of care in asymptomatic patients with FL.

New Evidence: Please describe the strength of the results from the rituximab watch and wait study.

Dr. Salles: The RWW study randomized patients between a watch and wait arm, a rituximab induction only arm, and a rituximab induction plus maintenance arm. The eligibility criteria were well described and included patients with low tumour burden. The results showed a delay in time to treatment with chemotherapy, prolongation of progression-free survival (PFS), and very high response rates (RRs) after treatment with rituximab. It would have been interesting to know whether the rituximab induction arm responded as well as the extended treatment arm; however, the investigators prematurely closed this arm of the study. RWW was, however, a good study and does provide very important results. The study provides evidence of a prolongation of the treatment-free interval, improved disease control, and high remission rates with early rituximab treatment.
**New Evidence:** Are you concerned about resistance to rituximab if given to asymptomatic patients?

**Dr. Salles:** Based on all the data that have been collected in this area, it is very likely that the use of rituximab will change the natural history of FL. However, the RWW study does raise two important questions. First, there is some concern that early use of rituximab will result in resistance. However, relapsed patients may respond to rituximab when it is added to chemotherapy (R-chemo) or used with a different treatment schedule. Second, delaying treatment may not be beneficial for all patients. In our experience and in previous trials in asymptomatic patients, we have found that within a period of one to two years, a group of about 20%–30% of patients develop disease justifying the use of chemotherapy plus rituximab. Delaying treatment in these patients may not be necessary, since we know R-chemo does provide an overall survival (OS) benefit. Thus, although the RWW study is very important, we need further data to determine how these results should influence clinical practice.

**New Evidence:** How might results of the rituximab watch and wait study impact clinical practice?

**Dr. Salles:** Although the RWW study does demonstrate that using rituximab confers a disease control benefit, it is not clear whether we should adopt this strategy in all asymptomatic patients with FL. Two other studies that address the use of rituximab maintenance in patients with FL may give us further insight into this issue. The SAKK study has shown improved event-free survival (EFS) with prolonged rituximab treatment and is now assessing long-term maintenance (5 years). The rituximab extended treatment versus re-treatment (RESORT) study is examining the time until rituximab resistance as well as the duration of the effect of second-line treatment.

I do continue to observe patients with low tumour burden for three to six months and then decide whether to treat these patients or not. In patients who are happy to wait for treatment, I tend to observe until they require immunochemotherapy, because no current evidence suggests that early treatment will extend survival. In other patients I do give rituximab, followed by maintenance using the extended protocol described in the SAKK study.

**New Evidence:** Based on the results of the rituximab watch and wait study, would you use rituximab induction only or induction plus maintenance?

**Dr. Salles:** In asymptomatic patients, induction treatment is needed to reduce tumour burden. I also think it is important to give extended treatment in addition to induction, although the optimal maintenance scheme is unclear. In the PRIMA study, we gave one infusion of rituximab every two months for two years, but PRIMA was in a very different group of patients. I would tend to use one infusion every two months for a total of four infusions, as was used in the SAKK study. The optimal treatment schedule may change when long-term results from the RWW study and results from the RESORT study become available.

**New Evidence:** Were there any demographic differences between the R-CHOP and R-CVP groups in the PRIMA study? Which treatment regimen do you use in follicular lymphoma?

**Dr. Salles:** The choice of induction treatment in the PRIMA study was left to the discretion of the investigator. The majority of study centres used R-CHOP, but around 25% of the centres used R-CVP. We found no differences in demographic variables between the induction groups, with the exception of a 1.5 year difference in median age between the R-CHOP and R-CVP groups. It is therefore unlikely that demographic differences between the induction groups would have influenced the results. In our practice, when a patient requires cytotoxic treatment, I tend to use R-CHOP.

**New Evidence:** Were there higher rates of adverse events with R-CHOP versus R-CVP in the PRIMA study?

**Dr. Salles:** The incidence of adverse events (AEs) was not dramatically different between the R-CHOP and R-CVP groups, except for a higher incidence of hematological toxicity with R-CHOP. However, R-CHOP is well tolerated by FL patients, and few patients present with febrile neutropenia, as compared to other disease states, such as diffuse large B-cell lymphoma.
**New Evidence:** How openly do you discuss the potential risk of progressive multifocal leukoencephalopathy with your patients given rituximab?

**Dr. Salles:** There have been a few cases of progressive multifocal leukoencephalopathy (PML) with the use of rituximab. However, I do not talk about PML with patients prior to giving rituximab, since the main risk for these patients is dying from their disease and the risk of PML is very low. I may discuss the risk of PML with patients who have non-malignant disease or with those being given rituximab as re-treatment. The data on PML are very limited, and there are other treatments that may increase the risk of developing this condition, such as purine analogues and transplant. Given the large numbers of patients treated with rituximab, the risk of PML appears to be very low.

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**New Evidence:** With more cycles of rituximab, do you find higher rates of bowel perforation or secondary malignancies?

**Dr. Salles:** The PRIMA study was a randomized trial, so we are able to use it to look at the risk of AEs with prolonged exposure to rituximab. Thus far, we have not seen any increased risk of secondary malignancies between the observation and maintenance arms of the study. In addition, we did not observe any bowel perforation during treatment with rituximab maintenance. In a long-term survey of our patients, we observed two cases of PML. These patients had relapsed, with one receiving autologous transplant and both receiving some experimental treatments. One of these patients was in the observation arm and one was in the rituximab maintenance arm. Therefore, it is not possible to say that the risk of these secondary effects increases in patients given prolonged treatment with rituximab.

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**New Evidence:** In which patients do you re-treat with rituximab after relapse?

**Dr. Salles:** In patients who relapse, I use R-chemo in younger patients prior to autologous stem cell transplant (SCT). Even when a patient relapses early or during maintenance, I tend to give R-chemo to patients where I plan to intensify treatment. For elderly patients or those not eligible for transplant, I tend to give chemotherapy alone for early relapse and to administer rituximab again (alone or in combination with chemotherapy, depending on patient and disease features) when progression occurs more than one year after the last rituximab infusion.

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**New Evidence:** If patients do not respond well to prior rituximab, are there any cases where you would re-treat with rituximab?

**Dr. Salles:** If patients do not respond well to rituximab alone, no real evidence indicates that they will respond well to R-chemo. However, since we know that rituximab plus chemotherapy is better than chemotherapy alone, there may be a synergy between these agents. I would therefore still add rituximab to chemotherapy in patients who were initially given rituximab alone. However, if a patient fails R-chemo, it is not necessarily beneficial to give rituximab again.

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**New Evidence:** Do you think the PRIMA trial will show an overall survival benefit with further follow up?

**Dr. Salles:** We do hope to see an OS benefit in the PRIMA study, and some indices suggest this may occur. First, a meta-analysis of studies performed in relapsed patients demonstrated that there is a significant OS benefit of rituximab maintenance. Second, the very high response rates shown with rituximab maintenance in the PRIMA study may translate into an OS benefit after greater follow-up.

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**New Evidence:** Do you think we should use R-maintenance every two or three months?

**Dr. Salles:** Regarding the use of rituximab maintenance, we need to adopt schemes that have been validated in clinical studies. In first-line treatment, the PRIMA study tested the infusion of rituximab every two months. On the other hand, evidence for relapsing patients came from the European Organization for Research and Treatment of Cancer (EORTC) study that used rituximab every three months. I therefore use rituximab maintenance every two months for first-line treatment and every three months in relapsing patients.
**New Evidence:** In the PRIMA study, it appears that the R-CVP induction group fared worse than the R-CHOP subgroup after rituximab maintenance. Please discuss this result.

**Dr. Salles:** We do need to be careful in interpreting this data from the PRIMA study, since PRIMA is not a randomized study comparing R-CHOP and R-CVP. Overall the benefit of maintenance appears to be highly significant in the R-CHOP subgroup and borderline significant in the R-CVP subgroup. We were surprised to see that the benefit of R-maintenance was slightly better in patients given R-CHOP than in those given R-CVP. This finding indicates that maintenance is not just completing a treatment but may also be controlling the disease to prevent relapse. We need to look further at this data with longer follow-up to determine whether the difference in PFS between these induction groups does eventually result in a survival advantage.

**New Evidence:** In the PRIMA study, did you look at the positron emission tomography (PET) scan results by induction subgroup?

**Dr. Salles:** We had the opportunity to look at more than 120 PET scans performed at the end of induction treatment. Around 26% of these patients had positive PET scans, as measured using a visual scale. The proportion of positive PET scans was somewhat higher in patients receiving R-CVP than in those receiving R-CHOP. We observed that a positive PET scan was highly predictive of an increased risk of disease progression in patients receiving either R-CVP or R-CHOP. Therefore, while the type of induction treatment is important, achieving an optimal response that results in a negative PET scan is more critical.

**New Evidence:** Do you use a second round of rituximab maintenance? When do you stop using rituximab maintenance?

**Dr. Salles:** When a patient shows a benefit of first-line maintenance with rituximab, I may use it again a second time. I would define a benefit as a prolongation in the time without disease that is expected by the trial. If a patient benefits from at least one year of disease-free interval following maintenance, I am more likely to offer this treatment again. Also, in light of the results of PET scans, I may consider giving a more intensive treatment if a patient relapses early to bring them into a true complete response and then give maintenance.

**New Evidence:** For relapsed patients, was CD20 expression different between the observation and rituximab groups?

**Dr. Salles:** Unfortunately, we do not have data on CD20 expression at the time of relapse, but we are collecting this data and hope to discuss these results in the future.

**New Evidence:** Do you use rituximab maintenance in other indolent lymphomas?

**Dr. Salles:** I do think rituximab maintenance has a role to play in mantle cell lymphoma (MCL), as MCL has some features that resemble indolent disease. Some data indicate that rituximab maintenance may be of benefit for these patients. For other patients with indolent malignancies, I tend to give induction treatment that includes four infusions of rituximab and then extend treatment by giving an additional four infusions of rituximab, similar to maintenance treatment. I do not tend to use rituximab maintenance in marginal cell or MALT lymphoma, as there is no evidence for its benefit in these diseases.

**New Evidence:** What are the most exciting new treatments being examined in follicular lymphoma?

**Dr. Salles:** Some small molecules have been developed, many of which are generating a great deal of interest. Given the favourable results seen with anti-CD20 antibodies in the last decade, any treatment that will optimize the use of anti-CD20 antibodies is interesting. Several antibodies have been engineered to increase the antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism. One of these new agents is GA101, which is a type II glyco-engineered anti-CD20 antibody.
**New Evidence:** What is the potential role of rituximab plus bendamustine in patients with follicular lymphoma?

**Dr. Salles:** Bendamustine is a treatment that was developed many years ago in Germany and is now being marketed in several countries. It is an interesting drug with important activity that is superior to purine analogues alone. Currently, evidence from one study indicates that rituximab plus bendamustine (R-bendamustine) achieves improved PFS compared to R-CHOP. We need to examine this study in further detail, since the PFS curve for R-CHOP is lower than we would have expected in FL patients. We know that thus far no OS difference has been observed between the two study arms. So we need to examine the data after longer follow-up before arriving at strong conclusions about the efficacy and safety of this compound.

**New Evidence:** Are there any patients where you currently give rituximab plus bendamustine?

**Dr. Salles:** In France we are able to use bendamustine in relapsing patients; we do therefore use R-bendamustine in some patients who are not undergoing transplant and have failed first-line treatment. We are currently performing a study in elderly patients with intermediate-to-high follicular lymphoma international prognostic index (FLIPI) scores, in which we are giving two courses of R-bendamustine followed by R-maintenance (BRIEF study). If R-bendamustine were currently available as first-line treatment, it would be my treatment of choice in elderly patients where I do not want to give anthracyclines.

**References:**
Canadianizing a New Standard of Care in CLL

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

The following paper is the first of a series examining some key challenges faced in the administration of FCR in Canada. Future papers will address issues such as the management of hematologic toxicities; identification of patients appropriate for treatment; use of pre-medications; and use of the oral formulations of fludarabine and cyclophosphamide. By addressing the challenges related to the administration of FCR, patients are more likely to complete all treatment cycles, thereby increasing efficacy and resulting in improved outcomes.

Developing a New Strategy for Rituximab Administration in Patients with CLL: The Ottawa Hospital Experience

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Background

Chronic lymphocytic leukemia (CLL), an indolent disease of neoplastic B cells, is the most common adult leukemia in western countries. The age-standardized incidence rate in Canada is 5.01 per 100,000, with the highest rate found in Alberta (6.82/100,000), followed by Saskatchewan (6.34/100,000), and Ontario (5.27/100,000).1,2

Although CLL still remains incurable, considerable advances have been made in the past decade. The combination of purine analogues and alkylating drugs, especially fludarabine and cyclophosphamide (FC), improved response rates and progression-free survival (PFS).3,4

More recently, chemoimmunotherapy, in particular the addition of the monoclonal antibody rituximab to standard chemotherapy, has shifted treatment goals toward overall survival (OS).1 The German CLL Study Group’s phase III, randomized CLL-8 trial, which compared fludarabine, cyclophosphamide, and rituximab (FCR) with FC in fit, treatment-naive CLL patients, demonstrated a significant OS benefit for FCR over FC at three years (FCR 87% versus FC 83%, p = 0.012).2 FCR has now become the first-line standard of care for fit patients with CLL.1

Based on results of the CLL-8 study, the FCR regimen has been approved for funding in all provinces as first-line treatment for CLL, with the exception of British Columbia, where FR is recommended first-line, and Quebec, where FCR is funded on a case-by-case basis.

CLL presents specific challenges for rituximab dosing and administration

Although the recommended dosing for rituximab in combination with chemotherapy in the treatment of non-Hodgkin’s lymphoma (NHL) is 375 mg/m² iv per cycle for a total of eight cycles,6 CLL requires higher dosages due to the low expression of the CD20 antigen on leukemic cells characteristic of the disease.5 Consequently, rituximab was administered at a dose of 375 mg/m² for the first cycle and 500 mg/m² for the second to sixth cycles in the CLL-8 trial. The rituximab product monograph recommends administering rituximab 375 mg/m² for the first cycle and 500 mg/m² for the second to sixth cycles when used in combination with chemotherapy.5,6

Infusion-related reactions

Rituximab dosing for CLL is further complicated by the fact that patients with CLL who have a high number (>25 x 10⁹/L) of circulating malignant cells, elevated white blood cell (WBC) counts, and high tumour burden may be at greater risk of developing infusion-related reactions due to severe cytokine release syndrome.4 In these patients, both the Cancer Care Ontario (CCO) drug formulary and the rituximab product monograph recommend a slow rate for the first infusion or splitting the dose of rituximab over two days with or without the addition of corticosteroids during the first cycle and any subsequent cycles if the lymphocyte count is still greater than 25 x 10⁹/L.6,7 In the CLL-8 study, at the investigators’ discretion, the rituximab dose could be split between the first and second day of the first cycle or could be omitted until the second cycle.5
Neutropenia and leukopenia

CLL patients who develop neutropenia and/or leukopenia during treatment may need to have their therapy interrupted until their blood counts improve or to have the dose of therapeutic drug reduced. As a result, these patients do not receive optimal benefit from treatment with FCR.

Current CCO guidelines do not recommend the routine use of granulocyte colony-stimulating factor (GCSF) as either a primary or secondary prophylaxis in patients with CLL. However, the authors of the guidelines do state that selected patients with recurrent infections who are experiencing some benefit from their chemotherapy may benefit from GCSF to reduce infectious morbidity. In the CLL-8 study, 45% of patients in the FCR group and 23% of patients in the FC group received GCSE. Administration of GCSE was mandated in the event of grade 3/4 neutropenia with fever >38.5 °C or hypothermia, either with or without suspected or documented infection.

Purpose of this document

At the present time, no Canadian consensus on the best approach to administering the FCR regimen in patients with CLL has been established. The lack of consensus on best practices for preventing and managing infusion-related reactions and hematological adverse events, such as neutropenia or cytopenia, has led hospitals across Canada to develop FCR treatment algorithms that can provide the optimal benefit for their patients. While dose reductions for renal toxicities appear to be standard across most hospitals, there are variations in practices for preventing and managing infusion-related reactions in CLL patients with high tumour burden and elevated WBC counts.

In order to facilitate discussion toward establishing a Canadian consensus, this paper will discuss some Canadian practices for managing infusion-related reactions, with a focus on a meeting which took place in Ottawa on November 2010 and the subsequent development at The Ottawa Hospital (TOH) of a novel treatment algorithm for the administration of the FCR regimen in CLL.

Current options used to modify the rituximab administration protocol for CLL

Various options have been tried to minimize the risk of cytokine-dependent infusion-related reactions. These options include administering rituximab at a reduced infusion rate for the first infusion, splitting the dose over two days for the first cycle, or omitting rituximab from the first cycle. However, limited data exist in the literature to guide clinicians on how to optimally administer rituximab when treating CLL.

The approach to managing patients at high risk of developing an infusion reaction differs from centre to centre within Ontario. For example, the current practice for rituximab infusions in patients with CLL at the Juravinski Hospital and Cancer Centre (JHCC) in Hamilton is to split the dose of rituximab over two days in patients who have absolute lymphocyte counts ≥25 x 10^9/L. In these patients, rituximab (50 mg/m^2) is given on day 1 and rituximab (325 mg/m^2) is given on day 2. For patients who do not exhibit a reaction with the first infusion, subsequent infusions may be given as a rapid infusion. In contrast, the preference at Princess Margaret Hospital (PMH) in Toronto is to slow down the rate of infusion in patients with high WBC counts. (Table 1)

<table>
<thead>
<tr>
<th>Table 1. Administration protocols for the FCR regimen at two Ontario hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
</tr>
<tr>
<td>Cycle 1</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Day 2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Day 3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Day 4</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Dose splitting</td>
</tr>
<tr>
<td>Rapid infusion</td>
</tr>
</tbody>
</table>

*C = cyclophosphamide; F = fludarabine; R = rituximab; WBC = white blood cell*
The Ottawa Hospital meeting

In May 2010, CCO approved funding of rituximab in Ontario for the first-line treatment of CLL when combined with a fludarabine-based regimen. CCO funding has resulted in an increased use of rituximab across Ontario, but clear guidelines for its administration in CLL are lacking.

In November 2010, a meeting of pharmacists and nurses from TOH was convened to discuss the optimal manner in which the FCR regimen could be administered in treatment-naive patients with CLL. Topics tabled for discussion at the meeting included:

- Pre-medications to prevent infusion reactions;
- Managing patients with high tumour burden;
- Managing hematological toxicities, infectious complications, and renal and hepatic impairment;
- Oral fludarabine versus intravenous fludarabine for dosing flexibility.

During the discussion, participants agreed that since patients with CLL tend to exhibit more reactions to rituximab in cycle 1 (and sometimes even in cycle 2), the team would focus their immediate efforts on refining the FCR treatment protocol to prevent infusion-related reactions.

Developing a new strategy for FCR administration at The Ottawa Hospital

Since the November meeting, TOH has developed a novel approach to administering rituximab in patients with CLL receiving FCR therapy, leading to a new TOH algorithm for FCR administration.

Initial approach to rituximab administration in patients with CLL

Initially, the protocol for rituximab administration in CLL patients during cycle 1 of treatment was adopted from the CCO drug formulary. The formulary suggests considering either a slower infusion rate or split dosing over days 1–2 (± corticosteroids) for any cycle where the tumour load is high or the WBC is >25 x 10⁹/L.²²

For all patients with CLL receiving cycle 1 of FCR treatment at TOH, rituximab (375 mg/m²) was diluted in 1 litre of NaCl 0.9%. Infusion rates started at 50 mL/hour and were increased according to the TOH protocol and a nurse’s evaluation of the patient. Pre-medication with acetaminophen and diphenhydramine, and a saline bolus were used. For patients known to have a WBC count >25 x 10⁹/L, steroids were added to the pre-medication regimen. For this patient population, the rituximab infusion rate was increased at a slower pace as per the nurse’s discretion.

Collection of data from 28 CLL patients receiving rituximab in combination with a fludarabine-based regimen

Data was collected to help assess the effectiveness of the treatment algorithm based on the CCO drug formulary. Twenty-eight (28) patients with CLL who had received a fludarabine-based regimen in combination with rituximab since May 2010 were available for review. Modifications of the algorithm occurred throughout the year to help minimize infusion-related reactions. The goal for the treatment algorithm was improved tolerability of each cycle.

Assessment of the TOH data showed that patients with CLL tended to react to rituximab more often than patients receiving rituximab for other indications. Reactions included chills, rigors, rash, hypotension, throat soreness or tightness, and heaviness in the chest.

Assessment and modification of the rituximab administration protocol for cycle 1

Sixteen (16) of the 28 patients reacted during their first infusion. Four of these patients did not exhibit signs of tumour burden and were not expected to react. The remaining 12 patients had an elevated WBC count at the time of rituximab infusion.

Based on these results, it was decided to repeat acetaminophen and diphenhydramine four hours after the initial dose for all cycle 1 patients. Intravenous steroids were also added to the pre-medication regimen for all cycle 1 patients.

This intervention was not completely successful, as the majority of patients (n = 7/13) still reacted, despite steroids and a second dose of acetaminophen and diphenhydramine. (Figure 1)

Assessment and modification of the rituximab administration protocol for cycle 2

Patients who completed cycle 1 of rituximab treatment subsequently received rituximab during cycle 2 at 500 mg/m² in 250 mL NaCl 0.9%. The rituximab infusion was initially given at 100 mL/hour for 30 minutes. If the vital signs and the patient were stable, the rate was then increased to 300 mL/hour for the remainder of the infusion. This cycle exposed the patient to a higher dose of rituximab in a more concentrated form and at a faster rate of infusion.
Three patients experienced infusion-related reactions during cycle 2. Two of these patients had been pre-medicated with steroids. In two of the three patients, the reaction occurred before the infusion rate was increased. All three patients required the rate to be capped at 100 mL/hour in order to complete the infusion.

Following assessment of patients receiving cycle 2 of rituximab treatment, the protocol was modified to cap the rate at 100 mL/hour for all cycle 2 infusions. If cycle 2 proceeded without incident, rituximab was then administered according to the TOH lymphoma-based rapid infusion protocol for cycle 3 onward.

Interestingly, two of the three patients who experienced infusion-related reactions during cycle 2 had not had a reaction during cycle 1. Consequently, steroids were included in the protocol as a pre-medication for cycle 2. Most patients had already been scheduled to receive steroids as a pre-medication for cycle 2, because they had reacted during cycle 1. However, this change resulted in one extra patient receiving steroids prior to cycle 2. No infusion-related reaction was observed in this patient.

Assessment of other protocol modifications

Of the 28 TOH patients with CLL included in the review, those who had elevated WBC counts experienced the greatest number of infusion-related reactions during cycle 1 of rituximab therapy, despite steroid pre-medication and a slow rate of dose escalation. Two other strategies to minimize infusion-related reactions were therefore tried with eight of the patients: dividing the rituximab dose over two days for cycle 1 or omitting rituximab from cycle 1.
In both groups, 50% of patients still experienced infusion-related reactions. Also, the split-dose regimen required a twelve-hour bed to be available for two consecutive days. If this option were to be chosen, initiating treatment could be delayed. Finding a twelve-hour appointment on two consecutive days is extremely difficult, due to limited capacity and other scheduled treatments.

**Arriving at a new TOH rituximab administration protocol for patients with CLL**

While searching for ways to minimize patient reactions during rituximab infusions, TOH decided to administer rituximab on day 3 of cycle 1 for patients with high WBC counts. This approach, however, did not capture patients with low WBC counts who had reacted to treatment with rituximab. Additionally, some patients who did not have elevated WBC counts at the time of evaluation in the clinic did have high WBC counts on the day of treatment. Therefore, in February 2011, the TOH rituximab treatment protocol was modified to administer rituximab on day 3 rather than day 1 for all cycle 1 patients. Rituximab would then be given on day 1 for subsequent cycles. (Figure 2)

None of the three patients who received rituximab on day 3 experienced infusion-related reactions. Of note, all three patients had an elevated WBC count $>25 \times 10^9/L$.

**Figure 2. The Ottawa Hospital FCR administration protocol**

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycles 3–6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab cycle 1</strong></td>
<td><strong>Rituximab cycle 2</strong></td>
<td><strong>Rituximab cycles 3–6</strong></td>
</tr>
<tr>
<td>Allopurinol to start 1 week prior to chemo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 – FC</td>
<td>Day 1 – FCR (500 mg/m²)</td>
<td>Day 1 – FCR (500 mg/m²)</td>
</tr>
<tr>
<td>Day 2 – FC</td>
<td>Day 2 – FC</td>
<td>Day 2 – FC</td>
</tr>
<tr>
<td>Day 3 – FCR (375 mg/m²)</td>
<td>Day 3 – FC</td>
<td>Day 3 – FC</td>
</tr>
<tr>
<td>Methylprednisolone 125 mg iv pre</td>
<td>Methylprednisolone 125 mg iv pre</td>
<td>No Methylprednisolone pre*</td>
</tr>
<tr>
<td>Acetaminophen 650 mg po pre</td>
<td>Acetaminophen 650 mg po pre</td>
<td>Acetaminophen 650 mg po pre</td>
</tr>
<tr>
<td>Diphenhydramine 50 mg po pre</td>
<td>Diphenhydramine 50 mg po pre</td>
<td>Diphenhydramine 50 mg po pre</td>
</tr>
<tr>
<td>Saline bolus 500 mL iv pre</td>
<td>Saline bolus 500 mL iv pre</td>
<td>Saline bolus 500 mL iv pre</td>
</tr>
<tr>
<td><strong>Rituximab prepared in 1 litre NS</strong></td>
<td><strong>Rituximab prepared in 250 mL NS</strong></td>
<td><strong>Rituximab prepared in 250 mL NS</strong></td>
</tr>
<tr>
<td>Rate starts at 50 mL/hr and if vitals and patient stable after 1 hr, ↑ by 50 mL/hr each 30 minutes. Rate capped at 400 mL/hr</td>
<td>Rate starts at 100 mL/hr and is capped at 100 mL/hr</td>
<td>Rate starts at 100 mL/hr x 30 minutes. If vitals and patient stable can ↑ to 300 mL/hr until infusion is complete</td>
</tr>
<tr>
<td>Acetaminophen 650 mg po Diphenhydramine 50 mg po/iv</td>
<td>Acetaminophen 650 mg po Diphenhydramine 50 mg po/iv</td>
<td>Acetaminophen 650 mg po Diphenhydramine 50 mg po/iv</td>
</tr>
<tr>
<td>Repeated every 4 hours straight during infusion</td>
<td>Repeated every 4 hours straight during infusion</td>
<td>Repeated every 4 hours if needed</td>
</tr>
</tbody>
</table>

*Methylprednisolone is omitted if patient did not have an infusion related or allergic reaction to cycle 2

$F = $ Fludarabine; $C = $ Cyclophosphamide; $R = $ Rituximab
Conclusions and Future Direction

The review of TOH patients who received rituximab for CLL showed it to be difficult to predict which patients would experience an infusion-related reaction. This observation is corroborated by the 2003 Byrd et al. study, which concluded that none of the pre-treatment variables (age, stage, β2M level, leukocyte count) could predict which patients would have severe infusion-related toxicity.9

Deferring rituximab to the final day of treatment for cycle 1 appeared to eliminate infusion-related reactions at TOH. The team at TOH will continue to collect data to determine if this trend continues and if further refinements to the treatment algorithm are needed.

Although the number of patients in the TOH review was small, the TOH experience may help improve tolerability so that patients can receive the proven benefit of the addition of rituximab to a fludarabine-based regimen. In the ongoing discussion toward a Canadian consensus on the administration of FCR in patients with CLL, the TOH experience is an important step.

Acknowledgement

The authors would like to acknowledge the contribution of Lisa Buchner, BSc Pharm, ACPR and Darcy McLurg, BSc Pharm, ACPR, malignant hematology pharmacists at TOH, for their aid in developing the TOH FCR administration protocol.

An Interview with Dr. James Johnston about FCR administration in CLL

At the CCOLD 2011 meeting, New Evidence spoke with Dr. James Johnston, Professor in the Department of Internal Medicine at the University of Manitoba and Hematologist at Cancer Care Manitoba, about the optimal administration protocol for FCR in CLL.

New Evidence: Which patients should receive FCR as first-line treatment for CLL?

Dr. Johnston: Including myself, there are two hematologists at Cancer Care Manitoba who run the CLL Clinic. Where possible, we use FCR as first-line treatment for CLL. To decide if a patient will be able to tolerate this regimen, we use the Cumulative Illness Rating Scale (CIRS), which is an assessment of co-morbidities as opposed to performance status. In addition to requiring adequate renal function, a CIRS score ≤6 was used as a cut-off point in the CLL-8 trial for selecting fit patients and we have also adopted this practice. Since a low CIRS score eliminates patients most likely to experience toxicities, we anticipate few problems in patients meeting this criterion for treatment. We have had no major difficulties with FCR using the CIRS scoring system and would thus encourage other physicians to use this simple measure to select patients for treatment.

New Evidence: What are the considerations for choosing oral versus intravenous fludarabine?

Dr. Johnston: Given the absorption of oral cyclophosphamide is highly variable, we tend to administer cyclophosphamide intravenously. Therefore, it also makes sense to give IV fludarabine as part of the FCR regimen. Giving fludarabine intravenously avoids the nausea we have observed with the oral formulation. Intravenous administration of FCR has the added advantage of allowing for closer monitoring of patients. The intravenous administration of fludarabine and cyclophosphamide does not require the presence of a physician and our clinic is open in the evenings and on weekends. In addition, these agents can be infused fairly rapidly, in approximately 90 minutes. Therefore, we choose to administer FCR intravenously at our centre. Conversely, we do give fludarabine orally as part of the FR regimen. Although patients often experience nausea by the fourth or fifth day, this can be managed with metoclopramide. Most patients prefer to cope with the nausea at home rather than coming back to the clinic every day to receive IV fludarabine.

New Evidence: What protocol do you follow for the administration of rituximab as combination treatment with FC in patients with CLL?

Dr. Johnston: At our institution, we give rituximab at a dose of 375 mg/m² for the first cycle and increase the dose to 500 mg/m² for subsequent cycles. We deliver the first infusion of rituximab at a slow rate (start infusion at 50 mg/hour for one hour and escalate infusion rate by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour) and monitor for infusion reactions. If there is no reaction, we gradually increase the infusion rate. If the patient has no reactions, rituximab is given over 90 minutes with subsequent cycles (20% dose given over 30 minutes, then remaining 80% dose given over 60 minutes).

If the patient reacts during the first infusion, we discontinue rituximab and give solumedrol (125 mg) or dexamethasone (40 mg) intravenously, along with benadryl. When the patient’s symptoms have resolved, we resume...
the infusion at a lower rate than when the patient had the reaction and gradually increase the infusion rate, as per the protocol. If rituximab cannot be given in one day, we keep it in the fridge overnight and give the rest of the infusion the following day. Patients are monitored for an additional one hour in the treatment room after rituximab infusion, or two hours if they had a reaction, to ensure there are no delayed reactions. While patients are being monitored, they receive IV fludarabine and cyclophosphamide.

New Evidence: What pre-medications are used before administering FCR?

Dr. Johnston: Before administering FCR, we give a number of pre-medications to minimize adverse reactions. During the first cycle, we give 40 mg of dexamethasone and will reduce the dose to 20 mg or 12 mg with subsequent cycles if the patient has no reactions. Before each treatment we give 650 mg of acetaminophen and 50 mg of benadryl. As we have observed fairly severe cases of shingles in patients on FCR, we treat our patients with 400 mg of acyclovir twice per day for the duration of chemotherapy and for several months following the last cycle.

We also give one tablet of double-strength trimethoprim-sulfamethoxazole, twice per day on Saturdays and Sundays, as prophylaxis against Pneumocystis jiroveci. If patients have an allergy to sulfa or are unable to tolerate trimethoprim-sulfamethoxazole, they will receive dapsone (100 mg) once daily on Mondays, Wednesdays and Fridays only. For patients who have a high tumour burden, we give 300 mg/day (dose adjusted for renal dysfunction) of allopurinol. Finally, because the FC component of the regimen can cause nausea, patients are also given an anti-emetic, such as ondansetron prior to chemotherapy administration.

New Evidence: How do you manage patients with a high tumour burden or elevated white blood cell counts?

Dr. Johnston: Although there are reports of patients with a high tumour burden having reactions to rituximab, we have not observed this at our clinic. This is perhaps because of the 40 mg of dexamethasone we give patients before the first administration of rituximab. In addition, we are inclined to keep the infusion rate low in patients that have a high tumour burden. If there is concern about the ability of a patient to tolerate a reaction (e.g., patients with significant cardiac disease and a lymphocyte count >50 x 10^9/L), we may give fludarabine alone for the first treatment and give FCR with the second cycle if the tumour burden has fallen. Alternatively, some centres will split the rituximab dose for the first treatment by giving 50 mg/m^2 on day 1 and 325 mg/m^2 on day 3.

New Evidence: How do you manage patients with grade 3/4 neutropenia, cytopenia, or infection?

Dr. Johnston: In general, there are few problems with blood counts for the first few cycles; this becomes more of an issue with later treatments. For patients whose neutrophil counts fall to <500 x 10^9/L and/or platelets to <50 x 10^9/L, we generally delay treatment for 1–2 weeks until the counts have recovered (neutrophils and platelets back to baseline or better). In subsequent cycles, we reduce the dose of FC by 25%.

We generally do not give filgrastim and have found that FCR can cause permanent thrombocytopenia or neutropenia, making it difficult to treat the patients in the future. Thus, if we need to delay treatments by longer than 2–3 treatments, we either discontinue chemotherapy or switch to a less marrow suppressive rituximab combination, such as FR, CRD (cyclophosphamide, rituximab, dexamethasone), or PCR (pentostatin, cyclophosphamide, rituximab). About 25% of first-line patients and 50% of relapsed patients are unable to complete the six treatment cycles because of marrow suppression.

New Evidence: Are there any other challenges you face with administering FCR for CLL?

Dr. Johnston: Approximately six percent of patients experience immune complications after treatment with FCR, such as hemolytic anemias, thrombocytopenia, neutropenia, and red cell aplasia. A tip-off that the neutropenia or thrombocytopenia is immune mediated, is that there is persistent neutropenia or thrombocytopenia even after the other counts have recovered. However, a marrow is required to confirm the diagnosis. The Coombs test is often negative for patients with typical features of hemolytic anemia. Patients with these immune problems usually respond well to steroids and patients with red cell aplasia do very well with cyclosporine.

A Canadian Perspective on the Use of Bisphosphonates in the Clinical Management of Multiple Myeloma

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Medical Writer: Anna Christofides, MSc, RD, New Evidence

Background

Multiple myeloma (MM) represents approximately 1% of all reported cancers worldwide and 12%–15% of hematological malignances. 1 In Canada, the average age at diagnosis is 62 years for men and 61 years for women, with only 4% of cases diagnosed in patients under 45. 2 Incidence rates are 5/100,000, with higher rates in men than in women (6/100,000 vs. 4/100,000). 3 Despite advances in the treatment of MM, the disease remains largely incurable, with an annual death rate of 4.1/100,000 and a five-year survival rate of 28%. 4 Improving survival in MM therefore remains the primary goal of treatment. 5

Patients commonly present with lytic bone disease, hypercalcemia, immunodeficiency, renal insufficiency, and anemia resulting from clonal expansion of plasma cells. 4 Destruction of bone occurs in approximately 79% of patients with MM and can result in significant bone pain, pathological fractures, spinal cord compression, hypercalcemia, and other skeletal-related events (SREs). 4, 6

The most common osteolytic lesions include the vertebrae, ribs, skull, femur, hip, and humerus, but in approximately 15% of patients, diffuse osteopenia is the only bone manifestation. 7 A number of these skeletal complications are associated with significant morbidity and can have a negative impact on survival, mobility, day-to-day independence, and quality of life (QoL), as well as increase treatment costs. 4 Given the primary goal to improve survival in patients with MM, appropriate treatment with supportive care is of paramount importance.

Preclinical studies suggest newer MM therapies, such as thalidomide, bortezomib, and lenalidomide, decrease bone resorption, principally by reducing tumour burden; these therapies may also have a direct effect on bone turnover. However, further research is needed to determine whether these agents can successfully reduce SREs. 8 Bisphosphonates are therefore the current standard of care to reduce and delay the skeletal morbidity caused by MM. 4

Bisphosphonates are synthetic, stable analogues of inorganic pyrophosphate, which are found in the bone matrix. They have an affinity for bone and are preferentially delivered to sites of increased bone formation or resorption. Once deposited, bisphosphonates are internalized by osteoclasts that are engaged in bone resorption and modulate signalling from osteoblasts to osteoclasts. As potent inhibitors of osteoclast-induced bone resorption, bisphosphonates are effective at preventing, reducing, and delaying SREs related to MM. 4, 9

There are two major classes of bisphosphonates: nitrogen-containing and non–nitrogen-containing. Non–nitrogen-containing bisphosphonates, such as clodronate (CLO), form non-hydrolyzable toxic adenosine triphosphate (ATP) analogues that inhibit ATP-dependent intracellular enzymes and induce apoptosis. Nitrogen-containing bisphosphonates, such as pamidronate (PAM) and zoledronic acid (ZOL), inhibit
farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway and an important mediator of osteoclast function and survival. Nitrogen-containing bisphosphonates have a unique mechanism of action and greater clinical activity than first-generation bisphosphonates. Of the second-generation bisphosphonates, ZOL is the most potent.10 ZOL, CLO, and PAM are all available in Canada, but reimbursement criteria differ across provinces and territories.

Purpose of this document

Currently, no uniform standard of care exists across Canada for the use of bisphosphonates in MM. Although a number of guidelines have been established worldwide, no Canadian recommendations have been developed for the use of bisphosphonates in these patients.

Dr. Donna Reece, Dr. Michael Sebag, Dr. Darrell White, and Dr. Kevin Song drafted this document, which presents a Canadian perspective on the use of bisphosphonates in MM. Topics addressed include diagnosis of bone disease; bisphosphonates and their relationship to SREs, bone pain, hypercalcemia, and overall survival (OS); and optimal duration of bisphosphonate treatment. In a separate document entitled A Canadian Perspective on the Management of Bisphosphonate-Related Complications in Multiple Myeloma, topics such as appropriate monitoring and the management of treatment-related complications are discussed.

The following paper describes a general consensus on the use of bisphosphonates in MM, but does not reflect a true evidence-based guideline process with a systematic literature review. In addition, patient preference should always be considered in any treatment decision.

Skeletal Complications

Assessment

Imaging studies

The standard diagnostic procedure for the detection of skeletal complications in MM is conventional radiography. A standard skeletal survey should include a postero-anterior (PA) view of the chest; antero-posterior (AP) and lateral views of the cervical spine, thoracic spine, lumbar spine, humeri, and femora; AP and lateral view of the skull; and AP view of the pelvis. Other symptomatic areas should be visualized using the appropriate views.11

Despite the advantages of radiography, bone destruction can occur in the absence of osteolytic lesions on skeletal radiography, suggesting diagnostic sensitivity is low in early stage disease. Studies have found that a loss of 30%–50% of the trabecular bone is required for detection of lytic lesions using this diagnostic method.7 Computed tomography (CT) scanning or magnetic resonance imaging (MRI) should therefore be used to clarify ambiguous findings, such as equivocal lytic lesions, especially in areas difficult to visualize, such as the ribs, sternum, and scapulae.11 When cord compression is suspected, MRI is the technique of choice. In patients with symptomatic MM, the number of focal lesions detected by MRI has been shown to be an independent prognostic factor for survival.7,11

However, bone scans typically underestimate myeloma bone lesions.4 In addition, evidence is insufficient to recommend positron-emission tomography (PET) or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging for the assessment of bone disease.4 Despite the existence of other promising imaging tests, the skeletal survey remains the recommended imaging modality at diagnosis.

Bone biomarkers

Biochemical markers of bone resorption, such as amino- and carboxy-terminal cross-linking telopeptide of type I collagen (NTX and CTX) and CTX generated by matrix metalloproteinases (ICTP), and bone formation are being evaluated in MM, but are not yet in routine use.7 Bone resorption and bone formation markers provide information on bone metabolism and reflect disease activity in bone. Bone biomarkers are useful in assessing the extent of bone destruction, risk of skeletal morbidity, and response to bisphosphonates. High levels of urinary NTX, serum CTX, and serum ICTP suggest advanced disease in MM patients with osteolytic lesions. In addition, high levels of urinary NTX and serum ICTP are associated with increased risk of SREs, disease progression, and OS. Bone markers have also been used for the early diagnosis of bone lesions.8

Measurement of bone turnover markers is non-invasive, relatively inexpensive, and can be useful in the assessment of bone disorders when applied and interpreted correctly. However, factors that influence bone biomarker levels, including circadian rhythm, diet, age, gender, renal function, and drugs need to be taken into account. In addition, these markers reflect whole-body bone turnover and give little information about the function of local changes in skeletal homeostasis. Given the above methodological difficulties, routine use of bone biomarkers is not currently recommended.8

Novel anti-myeloma agents

During the last decade, immunomodulatory drugs, including thalidomide and lenalidomide, and proteasome inhibitors, such as bortezomib, have significantly contributed to the improved...
OS of patients with MM. Thalidomide, lenalidomide, and bortezomib have proven to be effective agents for the treatment of both newly diagnosed and relapsed/refractory MM.\textsuperscript{12}

Some data suggest these MM therapies may also reduce bone destruction, presenting a possible alternative to standard bisphosphonate therapy. The role of these agents in bone metabolism has been evaluated in several studies, which are described in Table 1.\textsuperscript{8} However, clinically meaningful results have not been demonstrated with respect to the usefulness of these agents in reducing fractures, spinal cord compressions, or the need for surgery to bone. Use of these therapies to prevent bone destruction in MM is therefore premature and awaits the results of future research. Given the possible influence of these agents on bone metabolism, it is important to consider their impact when evaluating the efficacy of bisphosphonates.

| Table 1. Effect of anti-myeloma agents on bone biomarkers\textsuperscript{8} |
|-----------------------------|----------------|----------------|---------------------|---------------------|---------------------|
| **Agent**                   | **MM study population** | **N** | **Results** | **Subpopulation analysis** |
| **Thalidomide (+ dexamethasone)** |                           |       |             |                         |
| Tosi, et al.*               | Newly diagnosed          | 40    | ↓ Bone resorption markers  
                                 |                               |                      | (CTX, NTX)                       | In responders         |
|                            |                           |       | ↓ Bone formation markers  
                                 |                               |                      | (BALP, OC)                       | In all patients        |
| Terpos, et al.*             | Refractory/relapsed       | 35    | ↓ Bone resorption markers  
                                 |                               |                      | (CTX, TRACP-5b)                  | In all patients        |
|                            |                           |       | ↓ Osteoclast stimulators   
                                 |                               |                      | (sRANKL, sRANKL/OPG ratio)        | In all patients        |
|                            |                           |       | ↔ Bone formation markers   
                                 |                               |                      | (BALP, OC)                       | In all patients        |
| **Lenalidomide**            |                           |       |             |                         |
| Breitkreutz, et al.         | Refractory/relapsed       | 11    | ↓ Osteoclast numbers       | NA                   |
|                            |                           |       | ↓ Osteoclast differentiation| NA                   |
|                            |                           |       | ↓ Bone resorption          | NA                   |
| **Bortezomib (+ dexamethasone)** |                           |       |             |                         |
| Heider, et al.*             | Refractory/relapsed       | 58    | ↑ Bone formation markers   
                                 |                               |                      | (BALP, OC)                       | In all patients        |
| Terpos, et al.*             | Refractory/relapsed       | 34    | ↓ Bone resorption markers  
                                 |                               |                      | (CTX, TRACP-5b)                  | In all patients        |
|                            |                           |       | ↓ Osteoclast stimulators   
                                 |                               |                      | (sRANKL, sRANKL/OPG ratio)        | In all patients        |
|                            |                           |       | ↑ Bone formation markers   
                                 |                               |                      | (BALP, OC)                       | In responders\textsuperscript{\textdagger} |
|                            |                           |       | ↓ Osteoblast inhibitors    
                                 |                               |                      | (Dkk-1)                          | In all patients        |
| Giuliani, et al.*           | Refractory/relapsed       | 21    | ↓ Bone resorption markers  
                                 |                               |                      | (CTX)                            | In all patients        |
| Terpos, et al.*             | (VMDT regimen)            | 62    | ↓ Bone resorption markers  
                                 |                               |                      | (CTX, TRACP-5b)                  | In all patients        |
|                            |                           |       | ↓ Osteoclast stimulators   
                                 |                               |                      | (sRANKL, sRANKL/OPG, MIP-1 alpha ) | In all patients        |
|                            |                           |       | ↔ Bone formation markers   
                                 |                               |                      | (BALP, OC)                       | In all patients        |
|                            |                           |       | ↓ Osteoblast inhibitors    
                                 |                               |                      | (Dkk-1)                          | In all patients        |

Adapted from Terpos E, et al. Leukemia 2010.

*Concomitant bisphosphonates administration in the majority of patients.

\textsuperscript{\textdagger}BALP was increased only in responders, while OC was elevated in all patients.

\textsuperscript{1}This reduction did not reach statistical significance.

BALP = bone-specific alkaline phosphatase; CTX = carboxy-terminal cross-linking telopeptide of type I collagen; DKK-1 = dickkopf-1; MIP-1 alpha = macrophage inflammatory protein-1 alpha; MM = multiple myeloma; NA = not applicable; NTX = amino-terminal cross-linking telopeptide of type I collagen; OC = osteocalcin; OPG = osteoprotegerin; sRANKL = soluble form receptor activator of nuclear factor-KB ligand; TRACP-5b = tartrate-resistant acid phosphatase isofrom type Sb; VMDT = bortezomib, melphalan, dexamethasone, and thalidomide
Bisphosphonates

Quality of life in patients with MM is often compromised by pain, fatigue, and deteriorating physical function, with accompanying emotional and psychological difficulties and disrupted role functioning.13 A review of 1,027 patients diagnosed with MM at the Mayo Clinic between the years 1985 and 1998 showed that bone pain was present in 58% of patients at diagnosis. Conventional radiographs at diagnosis showed lytic lesions, osteoporosis, or fractures in 79% of patients.6 Bone pain is associated with significant morbidity and has a negative impact on activities of daily living. When the spine or lower limbs are involved, mobility may be impeded, significantly reducing patient QoL.14

The first bisphosphonate tested in a clinical setting was etidronate (ETI), a weak bisphosphonate, which showed no benefit in reducing SREs, bone pain, or fracture in MM patients.15–18 However, subsequent randomized studies using CLO, a bisphosphonate that is 10 times more potent than ETI, found significant reductions in the development of osteolytic lesions, bone pain, fracture rate, and the time to first non-vertebral fracture.18–22

PAM, a second-generation bisphosphonate, is 100-fold more potent than ETI and can be given orally or intravenously. A preliminary randomized study using oral PAM found no reduction in SREs, which the investigators attributed to low absorption of the oral formulation.17,18,23 Subsequently, a randomized study using IV PAM found a reduced number of SREs and time to first skeletal event. An extension of this study to a total of 21 cycles of PAM confirmed earlier results of a reduction in SREs with IV PAM.24,25

ZOL is 100 to 850 times more potent than PAM. A phase II trial comparing ZOL and PAM showed that both bisphosphonates significantly reduced SREs, and a large, phase III trial showed an increase in time to first SRE in both groups.17,18,26–28 However, the skeletal morbidity rate and normalization of the bone resorption marker NTX were improved in the ZOL group.27 A follow-up study showed that ZOL was more effective than PAM in reducing the risk of skeletal complications in patients with bone metastases from breast carcinoma by an additional 20% (p = 0.025). Efficacy of ZOL and PAM were similar in MM patients.28 Studies examining the effect of bisphosphonates on SREs are presented in Table 2.15,16,19,23,25–41

A recent Cochrane analysis by Mhaskar, et al. (2010) analyzed data from 17 trials, with 1,520 patients in bisphosphonate groups, and 1,490 in control groups. A total of seven studies were included in the pooled analysis examining the effect of bisphosphonates on SREs (1,497 patients) and vertebral fractures (1,116 patients). In comparison with placebo/no treatment, the pooled analysis demonstrated an overall beneficial effect of bisphosphonates for the prevention of pathological vertebral fractures (RR 0.74, 95% CI: 0.62–0.89; p = 0.001) and total SREs (RR 0.80, 95% CI: 0.72–0.89; p < 0.0001). However, the analysis found no benefit of one bisphosphonate over another for most comparisons.43

The Myeloma IX trial, a recently published randomized study by the UK Medical Research Council (MRC), compared ZOL and CLO with a median follow-up of 3.7 years. Groups were well balanced, with similar numbers of patients randomized to treatment with ZOL versus CLO (n = 981 vs. 979). Numbers of patients in the ZOL and CLO groups randomized to intensive therapy (n = 555 vs. 556) and non-intensive therapy (n = 426 vs. 423) were also well balanced. Results of the Myeloma IX trial showed significant benefits of ZOL over CLO in the reduction of SREs (27% vs. 35%; p = 0.0004).40,44 An updated Cochrane analysis by Mhaskar, et al. incorporated data from the Myeloma IX trial into the 2010 analysis to determine whether this study would influence results. Preliminary results of the updated analysis presented at ASH 2010 showed ZOL to be superior to CLO and PAM in the prevention of SREs in patients with MM.45

Results of clinical trials suggest bisphosphonates are effective at preventing, reducing, and delaying SREs related to MM. In addition, results of studies comparing ZOL to other bisphosphonates suggest ZOL may be superior to other agents for reducing skeletal complications associated with MM.

There is little evidence to support the use of bisphosphonates in asymptomatic patients with MM. A trial of monthly intravenous PAM versus placebo in newly diagnosed patients not requiring chemotherapy found a reduction in SREs; however, time to disease progression was not reduced.34 Use of bisphosphonates in asymptomatic patients is therefore not recommended by existing guideline committees, except as part of clinical trials.

Recommendations from existing guidelines on the use of bisphosphonates in MM are presented in Table 3.4,9,11,46–51
Table 2. Reduction in skeletal-related events with the use of bisphosphonates in multiple myeloma

<table>
<thead>
<tr>
<th>Author and year</th>
<th>BP</th>
<th>Dosage</th>
<th>MM patients (n)</th>
<th>Reduction of SREs*</th>
<th>Reduction in pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delmas, et al. (1982)</td>
<td>CLO</td>
<td>1600 mg/day, PO</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Belch, et al. (1991)</td>
<td>ETI</td>
<td>5 mg/kg/day, PO</td>
<td>173</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lahtinen, et al. (1992)</td>
<td>CLO</td>
<td>2400 mg/day, PO for 24 months</td>
<td>350</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Laakso, et al. (1994)</td>
<td>CLO</td>
<td>1600 mg/day, PO</td>
<td>170</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Daragon, et al. (1993)</td>
<td>ETI</td>
<td>10 mg/kg/day, PO for 4 months</td>
<td>94</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Heim, et al. (1995)</td>
<td>CLO</td>
<td>1600 mg/day, PO</td>
<td>170</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Berenson, et al. (1996)</td>
<td>PAM</td>
<td>90 mg, IV every 4 weeks for 21 cycles</td>
<td>392</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Berenson, et al. (1998)</td>
<td>CLO</td>
<td>1600 mg/day, PO</td>
<td>536</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>McCloskey, et al. (1998)</td>
<td>CLO</td>
<td>300 mg/day, PO</td>
<td>300</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Brincker, et al. (1998)</td>
<td>CLO</td>
<td>300 mg/day, PO</td>
<td>300</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Kraj, et al. (2000)</td>
<td>PAM</td>
<td>60 mg, IV every 4 weeks</td>
<td>46</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Terpos, et al. (2000)</td>
<td>ZOL</td>
<td>ZOL: 4 or 8 mg, IV or PAM: 90 mg, IV every 4 weeks for up to 10 months</td>
<td>108</td>
<td>Yes (ZOL non-inferior to PAM)</td>
<td>Yes</td>
</tr>
<tr>
<td>Rosen, et al. (2001)</td>
<td>ZOL</td>
<td>ZOL: 4 or 8 mg, IV or PAM: 90 mg, IV every 3–4 weeks for 24 months</td>
<td>353</td>
<td>Yes (ZOL&gt;PAM)</td>
<td>Yes</td>
</tr>
<tr>
<td>Musto, et al. (2003)</td>
<td>PAM</td>
<td>60 mg, IV every 4 weeks</td>
<td>90</td>
<td>Yes</td>
<td>NE</td>
</tr>
<tr>
<td>Attal, et al. (2006)</td>
<td>PAM</td>
<td>90 mg, IV every 4 weeks</td>
<td>597</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>Avilés, et al. (2007)</td>
<td>ZOL</td>
<td>4 mg, IV every 28 days</td>
<td>94</td>
<td>Yes</td>
<td>NE</td>
</tr>
<tr>
<td>Musto, et al. (2008)</td>
<td>ZOL</td>
<td>4 mg, IV every month</td>
<td>163</td>
<td>Yes</td>
<td>NE</td>
</tr>
<tr>
<td>Henk, et al. (ASH 2009)</td>
<td>ZOL</td>
<td>All dose variations</td>
<td>1655</td>
<td>Yes</td>
<td>NE</td>
</tr>
<tr>
<td>Gimsing, et al. (2010)</td>
<td>PAM</td>
<td>30 or 90 mg, IV every month for at least 3 years</td>
<td>504</td>
<td>No (difference between doses)</td>
<td>NE</td>
</tr>
<tr>
<td>Morgan, et al. (2010)</td>
<td>ZOL</td>
<td>ZOL: 4 mg, IV every 3–4 weeks or CLO: 1600 mg/day, PO</td>
<td>1960</td>
<td>Yes (ZOL&gt;CLO)</td>
<td>NE</td>
</tr>
<tr>
<td>Sezer, et al. (2010)</td>
<td>ZOL</td>
<td>4 mg, IV every 4 weeks</td>
<td>140</td>
<td>NS trend</td>
<td>NE</td>
</tr>
</tbody>
</table>

* SREs include new lytic lesions, vertebral and non-vertebral fractures, and need for radiation or surgery to the bone.
† PAM-controlled trial.
‡ CLO-controlled trial.
BP = bisphosphonate; CLO = clodronate; ETI = etidronate; IV = intravenous; MM = multiple myeloma; NE = not examined; NS = non-significant; PAM = pamidronate; PO = oral; SRE = skeletal-related event; ZOL = zoledronic acid
Table 3. Summary of recommendations for bisphosphonate use in multiple myeloma

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCSH/UKMF$^{11}$</td>
<td>2010</td>
<td>• BP therapy is recommended for all patients with symptomatic MM, regardless of whether bone lesions are evident.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ZOL and PAM both show efficacy in regards to SREs, but data from the Myeloma IX study showing an EFS and OS benefit of ZOL suggest ZOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>should be the treatment of choice.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• All patients with moderate-to-severe hypercalcemia should receive a BP; ZOL is the treatment of choice.</td>
</tr>
<tr>
<td>NCCN$^{46}$</td>
<td>2010</td>
<td>• BP therapy is recommended for all patients with MM who have bone disease, including osteopenia; PAM is favoured over ZOL due to risk of ONJ.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In smoldering or stage I disease, BP should preferably be used in the context of a clinical trial. These patients should have a bone survey yearly.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BP therapy is recommended for hypercalcemia.</td>
</tr>
<tr>
<td>EMN$^{4}$</td>
<td>2009</td>
<td>• BP therapy is recommended for all MM patients:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– with lytic bone disease on plain radiographs;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– with osteopenia or osteoporosis on BMD studies;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– on chemotherapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ZOL, CLO, or PAM should be used as indicated.</td>
</tr>
<tr>
<td>BCCA$^{47}$</td>
<td>2008</td>
<td>• Intravenous PAM should be given to all patients receiving chemotherapy for myeloma.</td>
</tr>
<tr>
<td>ASCO$^{48}$</td>
<td>2007</td>
<td>• BP therapy is recommended for MM patients:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– with lytic bone disease on plain radiographs or imaging studies;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– with osteopenia based on normal plain radiograph or BMD measurements.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PAM is favoured over ZOL due to risk of ONJ.</td>
</tr>
<tr>
<td>CCO$^{49}$</td>
<td>2007</td>
<td>• BP therapy is recommended for all MM patients who have lytic bone lesions, osteopenia, or osteoporosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients who do not have lytic lesions, osteopenia, or osteoporosis should be informed of the potential benefits and risks of therapy and offered BP treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral CLO and IV PAM or ZOL are reasonable choices. Patient preference, tolerance, and convenience will influence choice.</td>
</tr>
<tr>
<td>IMWG Reply to Mayo$^{50}$</td>
<td>2007</td>
<td>• Other imaging studies such as MRI, CT, and CT/PET recommended in addition to radiographs as basis for decision to initiate BP therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PAM generally favoured over ZOL due to risk of ONJ, but experts noted the shorter infusion time and possible survival benefits of ZOL and were awaiting further studies.</td>
</tr>
<tr>
<td>Mayo$^{3}$</td>
<td>2006</td>
<td>• BP therapy is recommended for MM patients:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– with lytic bone disease on plain radiographs;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– with osteopenia or osteoporosis on BMD studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PAM is favoured over ZOL in patients with newly diagnosed MM due to risk of ONJ, but guidelines do not necessarily advocate switching patients already on ZOL to PAM.</td>
</tr>
<tr>
<td>ESMO$^{51}$</td>
<td>2005</td>
<td>• BP therapy recommended for patients with stage III or relapsed MM receiving conventional-dose chemotherapy.</td>
</tr>
</tbody>
</table>

ASCO = American Society of Clinical Oncology; BCCA = British Columbia Cancer Agency; BCSH/UKMF = British Committee for Standards in Hematology/United Kingdom Myeloma Forum; CCO = Cancer Care Ontario; EMN = European Myeloma Network; ESMO = European Society for Medical Oncology; IMWG = International Myeloma Working Group; Mayo = Mayo Clinic; NCCN = National Comprehensive Cancer Network

BMD = bone mineral density; BP = bisphosphonate; CLO = clodronate; CT = computed tomography; EFS = event-free survival; MM = multiple myeloma; MRI = magnetic resonance imaging; ONJ = osteonecrosis of the jaw; OS = overall survival; PAM = pamidronate; PET = positron emission tomography; SRE = skeletal-related event; ZOL = zoledronic acid
Recommendations

Based on the evidence to date, the following is recommended for the assessment and treatment of skeletal complications in multiple myeloma:

- Currently, a skeletal survey is recommended for assessment of bone destruction in all patients with multiple myeloma.
- Additional imaging modalities should be considered in specific clinical situations, such as in patients with cord compression (MRI) or plasmacytomas (MRI/CT scan).
- Usefulness of new multiple myeloma treatments in the absence of bisphosphonates to prevent bone destruction awaits the results of future studies.
- All patients can be considered candidates for bisphosphonates, regardless of whether bone lesions are evident.
- The strength of the results of studies examining skeletal-related event outcomes with zoledronic acid, and findings from the recent Myeloma IX trial and the updated Cochrane analysis, suggest zoledronic acid may be the bisphosphonate of choice for reducing skeletal-related events in multiple myeloma.

Bone Pain

Pain is one of the most common symptoms of MM and is reported in up to 67% of patients at diagnosis. At diagnosis, pain may arise due to disease processes, such as destructive bone disease, or occasionally from plasmacytomas that directly affect neural tissues. Pain may also signify the presence of co-morbidities, such as degenerative arthritis or osteoporosis. Later in the disease course, pain often arises as a side effect of therapies, such as neuropathy associated with bortezomib treatment.14

Results of clinical trials show bisphosphonates are able to reduce bone pain and maintain the pain at a lower level.4,21,24 (Table 2) Evidence also suggests that bisphosphonates improve patient QoL and reduce analgesic consumption. However, the improvement in pain with bisphosphonates could be the result of a decrease in disease burden and may therefore reflect an indirect relationship.4 Randomized studies using CLO and PAM have demonstrated a significant reduction in bone pain as well as improvements in QoL, compared to placebo.21,24 In addition, the 2010 Cochrane analysis by Mhaskar, et al. pooled data from a total of eight studies (1,281 patients) examining the impact of bisphosphonates on pain compared to placebo/no treatment. Results of the pooled analysis demonstrated an overall amelioration of pain with bisphosphonates compared to placebo/no treatment (RR 0.75, 95% CI: 0.60 to 0.95; p = 0.01). However, there was no benefit of one bisphosphonate over another for most comparisons.43

Adding bisphosphonates to other pain management strategies, such as pharmacological treatments, radiotherapy, and psychological techniques, is therefore a reasonable option in patients with MM.

Recommendation

Based on the evidence to date, the following is recommended for the use of bisphosphonates in the management of bone pain in multiple myeloma:

- Pain arising in myeloma patients should be managed using a multi-modal approach that may include the addition of bisphosphonates as appropriate.
Overall Survival

Although novel therapies have resulted in improvements in response rates, time to progression, and survival, MM is still an incurable disease. The primary treatment goal remains the improvement of survival.

Preclinical studies

Results of in vitro and in vivo studies suggest nitrogen-containing bisphosphonates (N-BPs) have important anti-tumour effects against myeloma cells. In vitro studies show that N-BPs induce the proliferation of γδT cells and act as cytotoxic agents against myeloma cells. Stimulation of γδT cells results in a pronounced effect on the immune system, which may partly explain the anti-tumour effect of these agents. Studies in animal models have shown a relationship between myeloma cells and osteoclast activity. In addition, some evidence suggests that ZOL reduces tumour burden in bone and prevents osteolytic bone disease in mice. Results of PAM-based studies have also shown anti-myeloma activity in these animal models.

Recent animal studies suggest a potential anti-cancer effect of ZOL that is independent of osteoclast activity. Results of these studies suggest that ZOL interferes with a number of steps in the metastatic cascade, including tumour cell proliferation, adhesion and invasion, and angiogenesis.

Given the results of in vitro and animal studies showing a possible anti-tumour effect of N-BPs, it is important to determine whether these agents are capable of improving survival in patients with MM.

Clinical trials

Bisphosphonates have been a mainstay supportive care treatment for bone disease in patients with MM for over a decade. Evidence of ZOL’s anti-cancer activity has been shown in a number of studies across a broad range of malignancies. Recent evidence demonstrates that bisphosphonates may also have an important role to play in delaying disease progression and improving survival in patients with MM.

PAM was the first bisphosphonate to show a trend to improved survival in a subgroup of patients. In a study by Berenson, et al. (1998), survival in patients with more advanced disease was significantly increased in the PAM group (median survival 21 months vs. 14 months; \( p = 0.041 \), after adjusting for baseline serum, β2-microglobulin, and Eastern Cooperative Oncology Group [ECOG] performance status). An oral form of PAM, however, showed no survival benefit.

The impact of CLO on survival was also tested in a number of randomized trials. In a study by Lahtinen, et al. (1992), the proportion of patients who experienced a progression of lytic lesions was smaller in the CLO-treated group than in the placebo group. However, no significant effect on survival was seen. In an open label study by Heim, et al. (1995), there was a trend toward reduction in the number of new bone lesions in the CLO group. Again, no significant effect on survival was seen. Finally, a study by McCloskey, et al. (1998) concluded that there was no difference in OS for MM patients treated with CLO. However, in a post hoc analysis, patients without vertebral fracture at study entry survived significantly longer on CLO than on placebo (median survival 59 months vs. 37 months, \( p = 0.004 \)).

Studies examining survival outcomes with ZOL have been promising. A study by Rosen, et al. (2001 and 2003) compared ZOL to PAM in patients with bone lesions secondary to advanced breast carcinoma or MM. An exploratory, retrospective analysis using data from the Rosen study of a subset of MM patients who had information on baseline bone-specific alkaline phosphatase (BALP) levels showed that the OS rate at 25 months was significantly higher in ZOL-treated patients than in those treated with PAM (76% vs. 63%; \( p = 0.026 \), Cox regression). Among patients with low BALP levels, the survival rates were similar for both treatment groups. However, among patients with high baseline BALP levels, ZOL treatment significantly improved survival at study end compared with PAM (82% vs. 53%; \( p = 0.041 \), log-rank test). Subsequently, a randomized study comparing ZOL to no therapy showed an OS benefit of ZOL, with five-year OS rates of 80% and 46% for ZOL and placebo, respectively. Studies examining the effect of bisphosphonates on survival are presented in Table 4.

Results from CLO and PAM trials suggest some survival benefit from these agents, but improvements were limited to subgroup analyses. The 2010 Cochrane analysis by Mhaskar, et al. pooled data from a total of eleven studies (2,221 patients) examining the impact of bisphosphonates on mortality, compared to placebo/no treatment. Results of the pooled analysis also showed no reduction in the risk of mortality with bisphosphonates versus placebo/no treatment (HR 0.96, 95% CI: 0.80–1.14; \( p = 0.64 \)). No difference in survival outcomes were found between bisphosphonates.
Table 4. Improvement in survival with the use of bisphosphonates in multiple myeloma

<table>
<thead>
<tr>
<th>Author and year</th>
<th>BP</th>
<th>Dosage</th>
<th>MM patients (n)</th>
<th>Survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belch, et al. (1991)</td>
<td>ETI</td>
<td>5 mg/kg/day, PO</td>
<td>173</td>
<td>No</td>
</tr>
<tr>
<td>Daragon, et al (1993)</td>
<td>ETI</td>
<td>10 mg/kg/day, PO for 4 months</td>
<td>94</td>
<td>No</td>
</tr>
<tr>
<td>Berenson, et al. (1996)</td>
<td>PAM</td>
<td>90 mg, IV every 4 weeks for 21 cycles</td>
<td>392</td>
<td>Subset*</td>
</tr>
<tr>
<td>Berenson, et al. (1998)</td>
<td>CLO</td>
<td>1600 mg/day, PO</td>
<td>536</td>
<td>Subset†</td>
</tr>
<tr>
<td>McCloskey, et al (1998)</td>
<td>PAM</td>
<td>300 mg/day, PO</td>
<td>300</td>
<td>No</td>
</tr>
<tr>
<td>Rosen, et al. (2001)</td>
<td>ZOL</td>
<td>ZOL: 4 or 8 mg, IV or PAM: 90 mg, IV every 3–4 weeks for 24 months</td>
<td>353</td>
<td>Subset§</td>
</tr>
<tr>
<td>Attal, et al. (2006)</td>
<td>PAM</td>
<td>90 mg, IV every 4 weeks</td>
<td>597</td>
<td>No</td>
</tr>
<tr>
<td>Berenson, et al. (ASH 2006)</td>
<td>ZOL</td>
<td>ZOL: 4 or 8 mg, IV or PAM: 90 mg, IV every 3–4 weeks for 24 months</td>
<td>353</td>
<td>Subset§</td>
</tr>
<tr>
<td>Avilés, et al. (2007)</td>
<td>ZOL</td>
<td>4 mg, IV every 28 days</td>
<td>94</td>
<td>Yes</td>
</tr>
<tr>
<td>Henk, et al. (ASH 2009)</td>
<td>ZOL</td>
<td>All dose variations</td>
<td>1655</td>
<td>Yes</td>
</tr>
<tr>
<td>Morgan, et al. (2010)</td>
<td>ZOL</td>
<td>ZOL: 4 mg, IV every 3–4 weeks or CLO: 1600 mg/day, PO</td>
<td>1960</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Survival in patients with more advanced disease was significantly increased in the PAM group compared to placebo (median survival 21 months vs. 14 months; p = 0.041 adjusted for baseline serum \(\beta_2\)-microglobulin, and Eastern Cooperative Oncology Group [ECOG] performance status).
† In post hoc analysis, patients without vertebral fracture at study entry survived significantly longer on CLO than on placebo (median survival 59 months versus 37 months, p = 0.004).
§ Survival benefit with ZOL over PAM in a subgroup of patients who had elevated baseline BALP levels.
¶ CLO-controlled trial.
\(BP = \) bisphosphonate; \(CLO = \) clodronate; \(ETI = \) etidronate; \(IV = \) intravenous; \(MM = \) multiple myeloma; \(PAM = \) pamidronate; \(PO = \) oral; \(ZOL = \) zoledronic acid
Recently, the Myeloma IX trial reported that after a median follow-up of 3.7 years, a significant benefit of ZOL over CLO was found for OS (50 months vs. 44.5 months, \( p = 0.04 \)) and for overall progression-free survival (PFS) (HR 0.88; \( p = 0.0179 \)). A trend for increased median PFS with ZOL (19.5 months vs. 17.5 months, \( p = 0.07 \)) was also seen.\(^{40,44} \) (Figure 1) ZOL reduced mortality by 16% (95% CI: 4–26) versus CLO (HR 0.84, 95% CI: 0.74–0.96; \( p = 0.0118 \)). For non-intensive therapy, ZOL had a significantly increased rate of complete response (CR) or very good partial response (VGPR), compared to CLO (\( p = 0.018 \)). Moreover, ZOL improved OS independently of the reduction in SREs, suggesting that the drug has underlying anti-myeloma effects, which is consistent with the higher CR and VGPR rates. The Myeloma IX trial was the first study to show a survival advantage of one bisphosphonate over another. Results also showed that OS benefits remained even after controlling for baseline bone lesions and the reduction in risk for SREs, suggesting a possible anti-cancer effect of ZOL.

Incorporating data from the Myeloma IX trial, an update to the 2010 Cochrane analysis was presented at ASH 2010. For the outcome of OS, the pooled analysis demonstrated a beneficial effect of ZOL in comparison with CLO (HR 0.83, 95% CI: 0.73–0.94) and ETI (HR 0.48, 95% CI: 0.31–0.71). ZOL was also superior to CLO for PFS (HR 0.88, 95% CI: 0.78–0.99).\(^{45} \)

Thus far, ZOL is the only bisphosphonate to show a clear OS benefit in MM. Data from the Myeloma IX trial now demonstrate that ZOL has an OS advantage over CLO, even after controlling for baseline bone lesions and the reduction in risk of SREs. In addition, results of the 2010 Cochrane analysis showed no difference in survival outcomes between CLO and PAM. Therefore, the improvement in OS with ZOL shown by the recent Myeloma IX trial suggests ZOL has clinical benefits beyond the prevention of SREs and may be superior to other bisphosphonates in improving survival of patients with MM. Future research should help determine the efficacy of ZOL as a possible anti-cancer treatment in MM.

**Figure 1. Overall survival after treatment with ZOL versus CLO in multiple myeloma**

<table>
<thead>
<tr>
<th>Risk reduction</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (overall)</td>
<td>16%</td>
</tr>
<tr>
<td>(adjusted for SRE)*</td>
<td>15%</td>
</tr>
<tr>
<td>PFS (overall)</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Time to first SRE was included as a time-dependent covariate in an exploratory Cox model examining OS.

**Recommendation**

Based on the evidence to date, the following is recommended for the addition of bisphosphonates to multiple myeloma therapies for the treatment of multiple myeloma:

- Given the overall survival benefit seen with zoledronic acid in the recent Myeloma IX trial, zoledronic acid is the preferred bisphosphonate for newly diagnosed myeloma patients.
Hypercalcemia

Approximately 30% of patients with MM develop hypercalcemia, mostly occurring during active disease. Symptoms of acute hypercalcemia may include central nervous system dysfunction (confusion, coma, and obtundation), muscle weakness, pancreatitis, constipation, thirst, polyuria, shortening of the Q-T interval on an electrocardiogram (ECG), and acute renal insufficiency.

Hypercalcemia is typically treated with oral and/or intravenous rehydration. To avoid volume overload and heart failure, adequate urine output should be ensured. In addition, the use of intravenous loop diuretics may be considered to increase urinary calcium excretion once adequate volume repletion has been achieved.

A 2010 Cochrane analysis by Mhaskar, et al. pooled data from a total of eight studies (1,934 patients) examining the impact of bisphosphonates on hypercalcemia, compared to placebo/no treatment. Results of the pooled analysis found no overall reduction in the risk of hypercalcemia with bisphosphonates (RR 0.79, 95% CI: 0.56–1.11; p = 0.17). However, the 2010 Cochrane analysis did not include ZOL as one of the bisphosphonates in the analysis.

A pooled analysis of two randomized trials by Major, et al. (2001) compared the efficacy and safety of ZOL (4 or 8 mg IV) and PAM (90 mg IV) for treating hypercalcemia of malignancy. Both doses of ZOL were superior to PAM, with normalization of serum calcium levels by day 4 in approximately 50% of patients treated with ZOL and in only 33.3% of patients given PAM. Based on the results of the study by Major, et al., the British Committee for Standards in Haematology/United Kingdom Myeloma Forum (BCSH/UKMF) guidelines (2010) recommend the use of ZOL in patients with moderate-to-severe hypercalcemia.

Due to the absence of definitive survival data and because results from randomized trials on the incidence of osteonecrosis of the jaw (ONJ) were not available until recently, the Mayo Clinic, International Myeloma Working Group (IMWG), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guideline committees favoured the use of PAM over ZOL. However, landmark findings from the Myeloma IX trial have demonstrated that ZOL provides a significant survival benefit in newly diagnosed patients with MM. Similar results have been reported in patients with breast cancer. As a result of this recently released data regarding prolongation of event-free survival (EFS) and OS, the BCSH/UKMF has now recommended that ZOL be the bisphosphonate of choice in patients with MM. Recommendations from existing guidelines on the use of bisphosphonates in multiple myeloma are presented in Table 3.

Despite the strength of efficacy results with ZOL, the choice of a bisphosphonate should always consider patient compliance, choice of administration route, safety profile, as well as cost and availability.

Recommendations

Based on the evidence to date, the following is recommended for the use of bisphosphonates in multiple myeloma patients with hypercalcemia:

- All patients with hypercalcemia should be considered for hydration and the use of a loop diuretic.
- All patients with moderate-to-severe hypercalcemia should receive a bisphosphonate.
- Zoledronic acid is the bisphosphonate of choice for the treatment of moderate-to-severe hypercalcemia.

Choice of Bisphosphonate

Due to the absence of definitive survival data and because results from randomized trials on the incidence of osteonecrosis of the jaw (ONJ) were not available until recently, the Mayo Clinic, International Myeloma Working Group (IMWG), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guideline committees favoured the use of PAM over ZOL. However, landmark findings from the Myeloma IX trial have demonstrated that ZOL provides a significant survival benefit in newly diagnosed patients with MM. Similar results have been reported in patients with breast cancer. As a result of this recently released data regarding prolongation of event-free survival (EFS) and OS, the BCSH/UKMF has now recommended that ZOL be the bisphosphonate of choice in patients with MM. Recommendations from existing guidelines on the use of bisphosphonates in multiple myeloma are presented in Table 3.

Despite the strength of efficacy results with ZOL, the choice of a bisphosphonate should always consider patient compliance, choice of administration route, safety profile, as well as cost and availability.
Duration of Treatment

A single randomized trial found no benefit of treatment with PAM after tandem stem-cell transplantation. No difference was observed in the proportion of SREs in patients given PAM plus thalidomide (18%) or PAM alone (21%), compared with no maintenance (24%) after 29 months of follow-up. The majority of more recent guidelines for the use of bisphosphonates therefore recommend a standard duration of no more than two years of treatment in patients with MM.4,5,47-49 (Table 5)

Table 5. Guidelines for the duration of treatment with bisphosphonates in multiple myeloma

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Duration</th>
</tr>
</thead>
</table>
| BCSH/UKMF46                      | 2010 | • Given the risk of ONJ, it is reasonable to stop therapy in patients who have achieved a CR or VGPR with transplantation and/or a novel therapy combination and have no active bone disease; this should be at the discretion of the treating hematologist.  
  • Therapy should be reinstated at the time of relapse. |
| NCCN46                           | 2010 | NG                                                                       |
| EMN4                             | 2009 | • BPs should be given for 2 years.  
  • After 2 years, continue at physician’s discretion.  
  • BP therapy should restart upon relapse.  
  • Discontinue if patient develops ONJ and only re-initiate if the benefit of treating bone disease surpasses the risk of progressive ONJ. |
| BCCA47                           | 2008 | • For patients who undergo high-dose chemotherapy and stem-cell transplantation, PAM should be continued at approximately monthly intervals until assessment of response.  
  • For patients who do not undergo a stem-cell transplantation, PAM should be continued for 24 months, then stopped; it should only be resumed for another 24 month course if the myeloma again requires systemic treatment. |
| ASCO48                           | 2007 | • Give BPs monthly for 2 years. |
| CCO49                            | 2007 | • After 2 years of BP treatment:  
  – Patients who have achieved remission and are in a stable plateau phase off treatment should consider discontinuing the use of BPs.  
  – Patients who still require active treatment for myeloma should continue BPs, but may consider having the frequency decreased to every 3 months if on PAM or ZOL.  
  – Patients whose myeloma becomes active following initial response should resume monthly BP therapy. |
| IMWG Reply to Mayo50             | 2007 | • After 1 year of BP therapy, discontinue if patient has achieved CR or VGPR and has no active bone disease.  
  • Continue BP therapy if patient has achieved less than VGPR (<VGPR) and/or has ongoing active bone disease.  
  • After 2 years, discontinue BP therapy if patient has no active bone disease.  
  • If patient has active bone disease after 2 years of BP therapy, continue at discretion of primary physician.  
  • In patients who relapse with new bone disease, reinstitute BP therapy.  
  • Discontinue BP therapy if patient presents with ONJ. |
| Mayo9                            | 2006 | • Give monthly BP therapy for 2 years.  
  – After 2 years, discontinue if CR or in stable plateau phase.  
  – If disease is active after 2 years, decrease BP frequency to every 3 months. |
| ESMO41                           | 2005 | • Long-term BP is recommended. |

ASCO = American Society of Clinical Oncology; BCCA = British Columbia Cancer Agency; BCSH/UKMF = British Committee for Standards in Hematology/United Kingdom Myeloma Forum; CCO = Cancer Care Ontario; EMN = European Myeloma Network; ESMO = European Society for Medical Oncology; IMWG = International Myeloma Working Group; Mayo = Mayo Clinic; NCCN = National Comprehensive Cancer Network

BP = bisphosphonate; CR = complete response; NG = not given; ONJ = osteonecrosis of the jaw; PAM = pamidronate; VGPR = very good partial response; ZOL = zoledronic acid
To date, no clear evidence from clinical trials supports administration of bisphosphonates beyond two years. However, some patients may benefit from prolonged treatment using a reduced dose or dosing schedule. The Myeloma IX trial used bisphosphonate treatment at least until disease progression, with a median duration of 350 days on treatment. Although an early OS benefit was seen with ZOL, the OS curves separated throughout the study, suggesting a continued benefit of ZOL over time. The recent BCSH/UKMF guidelines (2010) recommend indefinite use of bisphosphonates until patients achieve a CR or VGPR with transplantation and/or a novel therapy combination, and have no active bone disease.

Most guideline committees agree that after stopping bisphosphonates, it is reasonable to restart these agents in patients who experience disease progression or bone pain. Relapse or progression in bone involvement may be present in patients with active MM who experience increasing bone pain, even in the absence of new SREs. However, to confirm myeloma bone progression, a full radiographic skeletal survey is required.

To minimize ONJ, an extensive dental evaluation and monitoring protocol should be followed prior to commencing treatment with bisphosphonates. In patients with signs of ONJ during treatment, the European Myeloma Network (EMN) guidelines recommend that bisphosphonates should only be re-initiated if the benefit of treating bone disease surpasses the risk of progressive ONJ. For these patients, a decision should be made at the discretion of the physician, based on the degree of bone destruction.

A full discussion on the management of bisphosphonate-induced ONJ is presented in the paper "A Canadian Perspective on the Management of Bisphosphonate-Related Complications in Multiple Myeloma. Recommendations from existing guidelines on the optimal duration of bisphosphonates in multiple myeloma are presented in Table 5.

### Recommendations

Based on the evidence to date, the following is recommended in relation to the duration of bisphosphonate treatment in multiple myeloma:

- In the first-line setting, bisphosphonates should be given for up to two years or discontinued earlier if a very good partial response or greater is achieved.
- Use of bisphosphonates may be considered in a relapse setting.
- Awareness of osteonecrosis of the jaw is recommended before and during bisphosphonate treatment.

### Adherence

Consideration of factors that influence patient adherence to bisphosphonates is necessary to ensure treatment is effective. CLO is administered orally as a single 1600–2400 mg dose or in two divided doses. Although randomized trials have found long-term compliance with CLO to be reasonable, results of studies in osteoporosis and metastatic bone disease suggest dosing compliance is poor. Poor levels of adherence have also been shown in patients with bone metastases in breast and prostate. Therefore, despite the convenience of oral bisphosphonates compared with IV preparations, compliance with these agents may be suboptimal and could contribute to a reduction in efficacy.

Greater levels of compliance have been found with IV bisphosphonates. The shorter infusion time (15 minutes) required for ZOL, as compared with other bisphosphonates, allows for administration with less disruption for the patient than the 2–4 hour time required for infusion of PAM. The shorter infusion time also means patients spend less time in the outpatient centre, and chairs or stations in the outpatient setting turn over at a faster rate. These time and resource savings may also translate into cost savings of personnel resources and provide a QoL benefit to patients. A study comparing patient preference for either ZOL or PAM showed a 92% preference for ZOL due to the shorter infusion time.
Conclusion

Destruction of bone occurs in the vast majority of patients with multiple myeloma, resulting in significant bone pain, hypercalcemia, and other skeletal-related complications.4,6 As potent inhibitors of osteoclast-induced bone resorption, bisphosphonates are effective at preventing, reducing, and delaying myeloma-related bone destruction.4,9 Although bisphosphonates are the standard of care in this setting, no Canadian guidelines are currently in place for their use. The purpose of this document was therefore to present a Canadian perspective on the use of bisphosphonates in multiple myeloma.

Given the methodological difficulties of measuring bone biomarkers, their routine use is not recommended for the assessment of myeloma-related bone destruction at this time. Diagnosis of bone destruction should be performed in all patients using skeletal surveys, with the addition of MRI and CT scans for specific clinical situations. Regardless of whether bone lesions are evident, all patients should be considered candidates for treatment with bisphosphonates.

Results of clinical trials suggest bisphosphonates are effective at preventing, reducing, and delaying skeletal-related complications related to multiple myeloma. In addition, studies comparing zoledronic acid to other bisphosphonates suggest zoledronic acid should be the bisphosphonate of choice for reducing these complications.

Other complications commonly seen in patients with multiple myeloma include bone pain and hypercalcemia.3 Bone pain should be managed using a multi-modal approach, which may include the addition of a bisphosphonate, as appropriate. Patients with hypercalcemia should be considered for treatment with rehydration and intravenous loop diuretics. In patients with moderate-to-severe hypercalcemia, zoledronic acid should be given as the bisphosphonate of choice.

To date, zoledronic acid is the only bisphosphonate to show a clear overall survival benefit in multiple myeloma.4 Data from the Myeloma IX trial now demonstrate that zoledronic acid has an overall survival advantage over clodronate, even after controlling for baseline bone lesions and the reduction in risk of skeletal-related events.40 In addition, results of the 2010 Cochrane analysis showed no difference in survival outcomes between clodronate and pamidronate.45 Given the strength of these results, zoledronic acid is currently the bisphosphonate of choice in multiple myeloma. It is important, however, to consider patient compliance, choice of administration route, safety profile, cost, and availability when making any treatment decision.

Some data show that certain anti-myeloma agents, such as thalidomide, bortezomib, and lenalidomide, influence bone metabolism. However, whether these agents also reduce myeloma-related skeletal complications is not clear.5 Denosumab, a fully human monoclonal antibody targeting RANKL, is being examined in a number of ongoing studies for the prevention of skeletal-related complications, but results are preliminary. Use of these therapies to prevent bone destruction in multiple myeloma is therefore premature and awaits the results of future research.

Progress in Mantle Cell Lymphoma: Summary of the Presentation by Dr. Martin Dreyling at CCOLD

As part of the lymphoma session at CCOLD 2011, Dr. Martin Dreyling, Associate Professor in the Medical Department of the University of Munich, Grosshadern, Germany, presented an update on mantle cell lymphoma. The presentation covered diagnosis and prognosis, and new approaches in the management of mantle cell lymphoma. The article below presents a summary of Dr. Dreyling’s presentation.

Diagnosis and prognosis of mantle cell lymphoma

Mantle cell lymphoma (MCL), a subtype of B-cell non-Hodgkin’s lymphoma (NHL), has a large variety of histomorphological appearances, including a classical type with typical irregular, cleaved nuclei and a diffuse, nodular, or mantle zone growth pattern; a chronic lymphocytic leukemia (CLL)-like round cell variant; and a blastoid variant with a high degree of cell proliferation. Approximately 80% of patients have classical, 15% have indolent, and 5% have transformed or blastoid MCL.

Given the variation in MCL, accurate diagnosis has proved difficult until recent years. In Germany, re-analysis of pathology samples from patients previously diagnosed with MCL has shown that an accurate diagnosis was made in only one third of cases. However, new discoveries in cytogenetics have dramatically improved the diagnosis of this disease.

Discovery of the characteristic t(11;14)(q13;q32) chromosomal translocation was a major breakthrough in the identification of MCL. This translocation causes the CCND1 gene on chromosome 11 to be co-localized with the immunoglobulin heavy chain gene on chromosome 14, resulting in increased expression of cyclin D1. Since mean cyclin D1 expression is increased in MCL, as compared with CLL and follicular lymphoma (FL), diagnosis of MCL can now be made with approximately 98% accuracy.

In contrast to other lymphomas, increased proliferation of tumour cells in MCL is strongly correlated with reduced survival. Thus, the proliferation index, as assessed by the percentage of Ki-67 positive cells, represents an important prognostic marker. Three risk groups can be identified based on the percentage of Ki-67 positive cells: low-risk (Ki-67 <10%), intermediate risk (Ki-67 10% to <30%), and high risk (Ki-67 ≥30%).

Factors associated with improved prognosis in patients with MCL include younger age (<65 years), normal lactose dehydrogenase (LDH) serum levels, and normal β2-microglobulin levels. Adverse prognostic factors include advanced-stage disease, high tumour burden, occurrence of B symptoms, and poor performance status. Based on data from over 450 patients participating in three clinical trials, the MCL international prognostic index (MIPI) was developed. The MIPI includes a number of key prognostic factors such as leukocyte count, LDH, age, and performance status, allowing for a more reliable estimate of the disease course, including overall survival (OS).

Treatment options in younger patients

The treatment of younger patients (<65 years) is somewhat counter-intuitive, as we often give dose-intensified therapy to this mostly low-risk group. In Europe, sequential dose intensification with CHOP-like induction therapy, followed by autologous stem cell transplant (ASCT), is the standard treatment. This standard is based on a number of studies showing the benefits of ASCT in younger patients.
A European MCL Network study by Dreyling, et al. compared consolidation with myeloablative radiochemotherapy followed by ASCT to maintenance with interferon-alpha (IFN-α) in first remission after CHOP-like induction treatment. Patients in the ASCT arm experienced a significantly longer progression-free survival (PFS), with a median of 39 months, compared to 17 months for patients in the IFN-α group \( (p = 0.01) \). The benefits of ASCT are independent of prior rituximab; however, the best outcomes in MCL have been shown for younger patients who received both ASCT and prior rituximab-containing induction treatment.\(^7\) (Figure 1)

A second treatment approach in younger patients with MCL is to treat with a regimen even more dose-intensified than R-CHOP, such as HyperCVAD/MA (hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone, alternating with high-dose methotrexate and cytarabine). This approach was introduced by the M.D. Anderson group and, with the addition of rituximab, demonstrated a response rate of 97% and a complete response (CR) rate of 87% in previously untreated patients with MCL.\(^8\) The five-year failure-free survival (FFS) and OS rates were 48% and 65%, respectively; in patients ≤65 years, the five-year FFS was 60%. However, relapses do still occur with this regimen, suggesting that even with such a dose-intensive approach, we are not able to cure patients with MCL.

To evaluate the potential superiority of a high dose cytarabine-containing regimen, Hermine, et al. initiated a randomized trial (MCL Younger) comparing:

- Arm A: 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy [12 Gray total body irradiation (TBI), 2 x 60 mg/kg cyclophosphamide] and ASCT;
- Arm B: alternating courses of 3 x CHOP and 3 x DHAP plus rituximab followed by a high dose cytarabine-containing myeloablative regimen (10 Gray TBI, 4 x 1.5 g/m\(^2\) cytarabine, 140 mg/m\(^2\) melphalan) and ASCT.\(^9\)

After induction, overall response (OR), including CR, unconfirmed CR (CRu), and partial response (PR), was similar in both arms. However, CR and combined CR/CRu rates were significantly higher in arm B (26% vs. 39%; \( p = 0.012 \) and 41% vs. 60%; \( p = 0.0003 \)). After a median follow up of 32 months, patients in arm B experienced a significantly longer time to treatment failure (TTF) [49 months vs. not reached (NR); \( p = 0.04 \), HR 0.68], mainly due to a lower number of relapses after CR/CRu/PR (20% vs. 10%). (Figure 2)

Although the CR rate after ASCT was comparable in both arms, remission duration (RD) after ASCT was superior in Arm B (48 months vs. NR; \( p = 0.047 \)). For patients in CR after ASCT, RD after ASCT was also presumably superior in arm B (51 months vs. NR; \( p = 0.077 \)). (Figure 3)
Figure 2. Time to treatment failure after R-CHOP/R-DHAP versus R-CHOP

![Graph showing time to treatment failure.](image)

- Median follow-up = 32 months
- Hazard ratio 0.68
- $p = 0.038$ (one sided sequential test)

Patients at risk:
- R-DHAP: 208, 147, 99, 67, 29, 11, 0
- R-CHOP: 212, 134, 95, 66, 36, 11, 0


Figure 3. Remission duration after ASCT in patients given R-CHOP/R-DHAP versus R-CHOP

![Graph showing remission duration.](image)

In addition to clinical response assessment, minimal residual disease (MRD) was prospectively monitored on the molecular level by real time quantitative polymerase chain reaction (PCR) in both arms. Potts, et al. reported that the proportion of patients in the MCL Younger trial who achieved MRD– at the end of induction was significantly higher in the R-CHOP/ R-DHAP arm versus the R-CHOP arm [60/82 (73%) vs. 29/92 (32%); \( p < 0.0001 \)].

Achievement of bone marrow (BM) MRD– after induction was associated with a significantly improved remission duration in the pooled treatment arms (89% vs. 74% at 24 months, \( p = 0.0017 \)). (Figure 4)

High-dose consolidation followed by ASCT demonstrated a high impact on tumour reduction in the pooled treatment arms and increased the BM MRD– rate from 50% to 75% (\( p = 0.0001 \), paired samples). This improvement was greater in the R-CHOP arm (29% to 65%; \( p = 0.0023 \)) than in the experimental arm (76% to 88%; \( p = 0.18 \)).

Results of the MCL Younger study suggest that high-dose cytarabine in addition to R-CHOP plus ASCT significantly improves outcomes, without a clinically relevant increase in toxicity. Therefore, alternating R-CHOP and R-DHAP followed by ASCT is another reasonable treatment option in younger patients with MCL.

In patients achieving a good response following ASCT, maintenance treatment with rituximab may improve remission duration. An ongoing study (LyMa) is examining the benefit of rituximab maintenance every two months for three years in younger patients (<65 years) with MCL.

**Treatment options in elderly patients**

The median OS of patients with advanced MCL has almost doubled in the past 30 years, mainly as a result of anthracycline-containing regimens and new treatment options, such as anti-lymphoma antibodies and stem cell transplantation.

However, although elderly MCL patients (>65 years) often fall into the high-risk MIPI category, we tend to treat them more conservatively.

In recent years, the addition of rituximab to CHOP (R-CHOP) has improved outcomes in patients with MCL. A study by Hoster, et al. showed a prolongation in the median time to treatment failure from 14 months with CHOP alone to 28 months with R-CHOP (\( p = 0.0003 \)) after a median follow-up of 65 months. (Figure 5) However, relapses do occur with R-CHOP; therefore, other agents are needed to improve the outcome in elderly patients with MCL.

Bendamustine is a purine analog/alkylator hybrid that was invented over 40 years ago in East Germany. Despite its use for other purposes, bendamustine was not studied extensively in cancer patients until the 1990s.
The addition of bendamustine to rituximab has shown promising results in MCL. A study by Rummel, et al. randomized patients with follicular, indolent, or mantle cell lymphoma to receive first-line rituximab plus bendamustine (90 mg/m² on days 1 and 2) (B-R) or R-CHOP. After a median observation time of 32 months, the median PFS was longer for B-R (54.8 months), compared to R-CHOP (34.8 months) \( (p = 0.0002) \). (Figure 6) The time to next treatment (TTNT) was 40.7 months in the R-CHOP group and not reached in the B-R group \( (p = 0.0002) \). R-CHOP was more frequently associated with serious adverse events (49 in B-R vs. 74 in R-CHOP). The reduced side effects associated with B-R, as compared with R-CHOP, is a major advantage for its use in elderly patients with MCL.

A second study by Rummel, et al. randomized patients with relapsed follicular, indolent, or mantle cell lymphoma to B-R or rituximab plus fludarabine (FR). After a median observation time of 33 months, median PFS was significantly prolonged with B-R compared to FR (30 vs. 11 months; \( p <0.0001 \)). (Figure 7) The OR rate was also significantly higher with B-R than with FR (82 vs. 49%, respectively; \( p <0.0001 \)).

The overall incidence of serious adverse events was similar for the B-R and FR groups (17.4% and 22.2%, respectively).

To extend remission duration in elderly patients with MCL, it is important to include some form of maintenance treatment after induction. An ongoing study (MCL Elderly) is examining the use of rituximab maintenance after induction with R-CHOP or fludarabine, cyclophosphamide, and rituximab (FCR) in elderly patients with MCL unsuitable for stem cell transplantation. Results of this ongoing study will be presented at EHA and ICML 2011.

A number of new agents are being examined for the treatment of MCL. The novel combination of the proteasome inhibitor bortezomib, a high-dose cytarabine, and dexamethasone was examined in a study by Weigert, et al. in eight heavily pre-treated MCL patients. An objective response were observed in four (50%) of eight patients, including two complete remissions. Median PFS and OS were 5 and 15.5 months, respectively.

Other promising new regimens being examined in ongoing clinical trials include everolimus (RAD-001); combination treatment with bendamustine, rituximab, and temsirolimus (BERT); CAL-101; and PCI-32765.
Figure 6. Progression-free survival after treatment with B-R or R-CHOP in the MCL subgroup


Figure 7. Progression-free survival after treatment with B-R or FR in the MCL subgroup

Median observation period 33 months

$p = 0.009$

Questions from the Audience

**Question #1:** Please discuss the effectiveness of flavopiridol for the treatment of MCL.

**Answer:** Results of studies using flavopiridol for the treatment of chronic lymphocytic leukemia (CLL) are promising. However, studies in MCL have been disappointing, given that flavopiridol is thought to down regulate Cyclin D1. In vitro data shows that if you turn off Cyclin D1 in MCL, cells do not undergo apoptosis, but instead turn on Cyclin D2 or D3. They may then be reactivated once treatment has been stopped. I would therefore be sceptical of the usefulness of flavopiridol for the treatment of MCL.

**Question #2:** Why did you think cytarabine would be so effective in MCL?

**Answer:** Based on the positive results seen with the use of R-HyperCVAD in MCL, we felt that the use of cytarabine might be effective in patients with a high degree of cell proliferation. Unfortunately, this was not the case. Cell proliferation remains a poor risk factor, even with the use of high-dose cytarabine. Therefore, for patients with blastic disease and a high degree of cell proliferation, experimental treatments should be considered. In patients who do not achieve MRD negativity after induction, we would like to give more experimental treatments before moving to ASCT.

**Question #3:** How do you treat patients with MCL who only have localized gastrointestinal involvement?

**Answer:** The scientific answer to this question is that a number of studies have shown a benefit of TBI conditioning prior to ASCT in patients with MCL. However, BEAM conditioning is a much better option than skipping ASCT in younger patients with MCL.

**Question #4:** What do you consider to be the best conditioning regimen to use before ASCT in patients with MCL?

**Answer:** Since hematologic toxicity is more profound with these regimens, patients must be followed more closely. However, administration of these regimens is feasible. In our study, a number of patients were not admitted to hospital in order to receive treatment, because the dose of cytarabine was split in two. One dose was given on day 2 and the second dose on day 3.
An Interview with Dr. Martin Dreyling about Mantle Cell Lymphoma

At the CCOLD 2011 meeting, New Evidence spoke with Dr. Martin Dreyling, Professor of Medicine and Head of the Lymphoma Program in the Department of Medicine III, University Hospital Grosshadern, Ludwig Maximilians-University, Munich, Germany about his presentation on advances in mantle cell lymphoma.

New Evidence: What have been the greatest milestones in mantle cell lymphoma that have been reached in recent years?

Dr. Dreyling: We have recently learned that mantle cell lymphoma (MCL) represents a heterogeneous spectrum of disease, which ranges from indolent and classical subtypes to very aggressive lymphoma similar to the secondary transformation seen in follicular lymphoma.

In the past year, we have been looking for markers of indolent MCL. Fernandez, et al. at the University of Barcelona presented data suggesting that SOX11-negative MCL represents the indolent form.1 In addition, SOX11-negative patients had very low-risk disease according to their mantle cell international prognostic index (MIPI) score, which also suggests indolent disease. However, the study by Fernandez, et al. used a retrospective design, and results therefore need to be confirmed in prospective studies.

The major development in the management of MCL in the past year has been the treatment of younger patients (≤65 years). This group is a low-risk cohort of patients; however, dose-intensified treatments remain the standard of care. At ASH 2010, we presented data showing that the addition of high-dose cytarabine (Ara-C) to R-CHOP plus autologous stem cell transplant (ASCT) increases progression-free survival (PFS) by around 15%.2

In elderly patients, we are looking forward to establishing a new standard of care. We are currently examining the role of post-induction interferon versus rituximab maintenance in patients >60 years (MCL elderly study). Results of the MCL elderly study are very promising and will be presented at EHA and ICML, 2011.

We have also learned that molecular targeted approaches play a major role in the treatment of MCL and should be used routinely in the relapsed setting. Thus far, most of these targeted approaches achieve response rates (RRs) of around 30%, indicating that we need to combine these regimens with conventional chemotherapy. Recently, we have discovered that the B-cell receptor pathway plays a critical role in MCL. Treatments that target the B-cell pathway therefore look promising, but, to date, results are only available from phase I/II studies.

New Evidence: Have you changed your clinical practice based on the results of recent studies?

Dr. Dreyling: In clinical routine, we have adopted a new standard in younger patients that includes the use of high-dose Ara-C. In elderly patients, post-induction treatment is critical and should be included routinely in clinical practice. When it comes to study concepts, we are looking forward to the development of new compounds targeting the B-cell receptor pathway.
**New Evidence:** How do you use the mantle cell international prognostic index (MIPI) to make treatment decisions?

**Dr. Dreyling:** MIPI is crucial to identify the prognostic features of our patients, but is not sufficient alone for making treatment decisions. For example, in younger patients with low-risk disease, we give intensive treatment and therefore do not base decisions on risk profile alone. In addition, although high leukocyte counts do represent a MIPI risk factor, patients with exclusively leukemic disease tend to have a more indolent course. Therefore, we try to include clinical as well as biological factors to define our patients’ individual risks.

In our institution, we follow different risk markers including MIPI, as well as identifying unusual clinical features characteristic of indolent lymphomas. Importantly, cell proliferation is the most reliable prognostic factor in MCL.

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**New Evidence:** In which patients do you use a watch and wait strategy?

**Dr. Dreyling:** We tend to use a watch and wait approach primarily in patients with low cell proliferation (Ki67 <10%), including younger patients with no major tumour load. We also tend to observe patients who have an exclusively leukemic disease or only gastrointestinal (GI) involvement. In elderly patients >70 years, we are more reluctant to start treatment, even though they are generally high-risk according to MIPI. Thus, in cases with no major lymph nodes, we tend to observe the clinical course for at least three months. However, in around 80%-85% of patients, it is appropriate to start treatment at diagnosis.

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**New Evidence:** Do the benefits outweigh the risks of R-DHAP/R-CHOP compared with R-CHOP alone?

**Dr. Dreyling:** In our study presented at ASH 2010, we saw a significant difference in RRs between patients given R-DHAP/R-CHOP versus those given R-CHOP as induction treatment. However, after autologous transplant, response was similar in both treatment groups. The lack of difference in response between the two groups is most likely because RRs are an inadequate measure of the quality of remission in MCL. When looking at minimal residual disease (MRD), PFS, and duration of remission, the R-DHAP/R-CHOP group was superior to the R-CHOP group, even after transplant.

Given the higher rates of hematologic toxicity seen in our study, it is fair to say that the R-DHAP/R-CHOP regimen is more toxic than R-CHOP alone. However, only a modest increase in grade 3/4 non-hematological toxicity occurred in the R-DHAP/R-CHOP group. As PFS increased by 15% with R-DHAP/R-CHOP, I consider the benefits definitely outweigh the risks of this regimen.

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**New Evidence:** What are the key treatment considerations for young patients with mantle cell lymphoma?

**Dr. Dreyling:** Independent of the risk profile of a younger patient, dose-intensified treatment represents the current standard of care. In select cases, watch and wait is a reasonable strategy, based primarily on low Ki67 and occasionally on unusual clinical features of the disease, such as patients with only GI involvement or leukemic disease. In the future, SOX11 may become a more reliable marker that can be used to guide treatment decisions. The French LYMA study is an ongoing trial investigating the role of R-maintenance in younger patients after transplant and should help determine whether maintenance treatment is useful in these patients.

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**New Evidence:** What are the key treatment considerations in older patients with mantle cell lymphoma?

**Dr. Dreyling:** The most important question in elderly patients with MCL is when to start treatment. As the majority of these patients are high-risk, we might consider starting treatment earlier; however, these patients are also more vulnerable to side effects, so the efficacy of treatment needs to be balanced against safety. Risk factors, such as Ki67 and clinical manifestations, need to be considered. In some patients, it is best to observe the clinical course of the disease for three months before initiating treatment. In contrast, treatment should be started right away in patients with elevated lactose dehydrogenase (LDH) levels or with high tumour burden. Again, based on the results of our studies, post-induction maintenance should be considered in all elderly patients.
New Evidence: Of the potential new treatments for MCL, which are the most promising?

Dr. Dreyling: The combination of rituximab and bendamustine (R-bendamustine) is an exciting new treatment option in MCL, showing similar or greater efficacy as R-CHOP (first-line) or FR (relapsed MCL). In Germany, this treatment option has been available for decades. After reducing the dose of bendamustine to 60% of the original (300 mg/m² to 180 mg/m²), this regimen has displayed a favourable side effect profile. The favourable side effect profile is a major advantage of R-bendamustine, especially in elderly patients with MCL. Moreover, we usually apply only four cycles in patients with predominant leukemic disease, since we know the hematological reserve in these patients is impaired. However, even with the use of R-bendamustine, patients are not cured. Post-induction treatment is therefore still needed in older patients unable to undergo transplant.

Bortezomib and temsirolimus, when combined with conventional chemotherapy, have also shown a major treatment advantage, and lenalidomide maintenance has achieved promising results in early studies.

Small molecules targeting the B-cell receptor pathway, such as BTK or PI3K inhibitors, are showing promising results in pre-clinical trials. We hope to be able to achieve synergism between these agents and conventional chemotherapy, potentially achieving long-term benefits.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see CONTRAINDICATIONS and ADVERSE REACTIONS).

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

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

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

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

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

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

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

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

Blood and Lymphatic System: thrombocytopenia, thrombocytopenia

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

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

Injury, Poisoning and Procedural Complications: spinal or epidural hematoma

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

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

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

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

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

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

**Administration**

**DOSAGE AND ADMINISTRATION**

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

**Dosing**

Thrombophrophaxis in Conjunction with Surgery

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

General surgery with associated risk of thromboembolic complications: 2500 IU s.c. administered 1-2 hours before the operation, and thereafter 2500 IU s.c. each morning until the patient is mobilized, in general 5-7 days or longer.

General surgery associated with other risk factors: 5000 IU s.c. is given in 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.

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 >0.1 IU anti-Xa/mL before injection and <1.0 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.

Use in Patients with Renal Impairment

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

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

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

Anticoagulation for Hemodialysis and Hemofiltration

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

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.

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

### 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 prefilled syringes), depending on the patient’s weight (table below). Once the platelet count recovers to ≥100,000/mm³, FRAGMIN should be re-instated at full dose.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Scheduled Dose (IU)</th>
<th>Reduced Dose (IU)</th>
<th>Mean Dose Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤56</td>
<td>7500</td>
<td>5000</td>
<td>33</td>
</tr>
<tr>
<td>57-68</td>
<td>10,000</td>
<td>7,500</td>
<td>25</td>
</tr>
<tr>
<td>69-82</td>
<td>12,500</td>
<td>10,000</td>
<td>20</td>
</tr>
<tr>
<td>83-98</td>
<td>15,000</td>
<td>12,500</td>
<td>17</td>
</tr>
<tr>
<td>≥99</td>
<td>18,000</td>
<td>15,000</td>
<td>17</td>
</tr>
</tbody>
</table>

### Dosing

To report an adverse event, please contact: your physician, pharmacist or Pfizer Medical Information: 1-800-463-6001.

**Weight (kg) Dosage (IU)**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dosage (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46-56</td>
<td>10,000</td>
</tr>
<tr>
<td>57-68</td>
<td>12,500</td>
</tr>
<tr>
<td>69-82</td>
<td>15,000</td>
</tr>
<tr>
<td>83 and above*</td>
<td>18,000</td>
</tr>
</tbody>
</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, FIX, FX) have decreased to a therapeutic level, in general for approximately 5 days.

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

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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.

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.

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.

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, FIX, FX) have decreased to a therapeutic level, in general for approximately 5 days.
Acute renal failure, patients with high bleeding risk: i.v. bolus injection of 5-10 IU/kg body weight, followed by i.v. infusion of 4-5 IU/kg body weight per hour. Plasma level should lie within the range of 0.2-0.4 IU anti-Xa/mL.

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

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

1 mL 10 000 IU

Isotonic NaCl Infusion (9 mg/mL) 500 mL
or
Isotonic Glucose Infusion (50 mg/mL) 500 mL

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

Cancer-associated thrombosis

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

SUPPLEMENTAL PRODUCT INFORMATION

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

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

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

Product Monograph available on request.

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