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A Canadian perspective by:

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NEWEVIDENCE
In Supportive Care Oncology

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A CANADIAN PERSPECTIVE

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Overview

The 47th American Society of Hematology's (ASH) annual meeting and exposition, held from December 10 to 13, 2005, provided hematologists from around the world a forum for discussing critical issues in hematology. Nearly 20,000 clinicians, scientists, and others attended the four-day meeting, which consisted of educational programs and cutting-edge scientific sessions as well as oral and poster presentations containing the latest and most exciting developments in scientific research. Highlighted in this issue of *New Evidence in Supportive Care Oncology* are data reported during ASH 2005 regarding supportive care concerns in hematological malignancies.

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Managing Oral Mucositis: Mitigating Negative Clinical and Economic Outcomes

Mucositis is a serious complication of cancer treatment. The severity of oral mucositis (OM) can range from a mild erythematous, atrophic lesion in which the mucosa remains intact to the more critical form where ulcerations penetrate the submucosa and cause severe pain.[1] Furthermore, the compromised mucosal barrier is susceptible to bacterial infection that can amplify the inflammatory process, leading to further injury. Mucositis-associated pain is the primary source of cancer treatment-related pain, particularly during eating and swallowing. Pain from OM afflicts as many as 40–70% of patients receiving chemotherapy or radiotherapy,[2] and can cause treatment to be terminated or delayed.

Oral mucositis is also associated with poorer clinical and economic outcomes in patients undergoing autologous hematopoietic stem-cell transplantation (HSCT), according to one study presented in a poster at the 2005 ASH meeting.[3] Forty-eight percent of patients with multiple myeloma (mean age: 54 years), who tended to be overweight (average weight: 81.6 kg), and had a history of alcohol and tobacco use (56% and 26% of patients, respectively), experienced OM of grade 2 or higher within 28 days of conditioning, while 14% had OM grade 4 or 5. Advanced age and a low Karnofsky score at enrolment were associated with a significantly worse OM score (P=0.02). Interestingly, neither the conditioning agent used nor patient characteristics such as weight and alcohol or tobacco use were predictive of a higher OM grade in this study. Increased length of hospital stays resulting in higher total inpatient charges were attributed to a more severe grade of OM, as well as days with fever, percentage of patients with infection, and use of injectable narcotics.

Data on the long-term consequences of OM after autologous HSCT in patients with lymphoid malignancies is sparse. However, a retrospective study that assessed the clinical outcomes of patients with lymphoid malignancies who underwent autologous HSCT at a single institution over a five-year period found that the severity of OM directly correlated with mortality within 100 days of transplant.[4] Patients with a maximal OMAS (Oral Mucositis Assessment Scale) score of <1.0 had 99% 100-day survival (103/104) as compared to 92% (80/87) for those with an OMAS scale ≥1.0 (P=0.015). At 54 months following transplant, severe mucositis was associated with poorer survival (P=0.002), and with the death of eight patients with severe mucositis related to toxicities, as compared to zero deaths in the less severe mucositis group. Bolwell and colleagues acknowledge that survival following transplant is most likely multifactorial, as elevated lactate dehydrogenase (LDH) at transplant (P=0.03), number of prior chemotherapy regimens (for one regimen increase, P=0.024), and severe mucositis (P=0.003) were all significant risk factors for overall survival (OS). A similarly designed study by Montserrat et al. found comparable OM severity-related outcomes in patients undergoing allogeneic HSCT.[5] While mucositis may directly contribute to mortality risk, it may also be a surrogate marker of other organ toxicities. It is still unclear, therefore, whether preventing or controlling oral mucositis will have a positive effect on OS outcomes in lymphoma patients undergoing transplant.

The prevention and treatment of mucositis have been a focus of research in recent years. In the last decade alone, more than 25 prophylactic or therapeutic treatment interventions based on biological attenuation were under investigation for reducing chemotherapy- or radiotherapy-induced mucositis. Therapies that are in preclinical or clinical development include glutamine, amifostine, keratinocyte growth factors, laser therapy, and cryotherapy. What is becoming increasingly evident is that the biological complexity of the condition requires not one but several approaches to therapy.[1]

In the spring of 2005, the Food and Drug Administration (FDA) approved the first therapeutic agent for severe OM, palifermin (rHu-KGF), for the prevention and treatment of OM in patients with hematologic cancers who are undergoing high-dose chemotherapy prior to bone marrow transplantation. The drug was approved for this indication by Health Canada on December 9, 2005. Palifermin is a recombinant keratinocyte growth factor (KGF) that was shown in animal models of chemotherapy, radiotherapy, and autologous HSCT to stimulate the growth of epithelial cells in the skin and on the surface layer of the mouth, stomach, and colon.[6,7,8] In humans, the results of a double-blind placebo-controlled phase III study showed that palifermin decreased the incidence and duration of severe OM for up to one year of follow-up in patients with lymphoid malignancies who received total body

irradiation-based high-dose chemotherapy regimens and HSCT.[9] The drug was administered three days prior to conditioning and three days after stem cell transfusion. The incidence of grade 3 or 4 mucositis in the palifermin-treated group was 63% (67 of 106 patients), considerably lower than the 98% in the placebo group (104 of 106 patients). The median duration of OM was six days in the palifermin group and nine days in the placebo group.

The development of any therapy intended to lessen radiation- or chemotherapy-associated toxicity needs to ensure that it targets normal tissue effectively without diminishing the therapeutic impact of the cancer therapy. According to follow-up data for the trial published by Spielberger and colleagues presented in a poster at the 2005 ASH meeting,[10] palifermin appears to have had neither a positive nor a negative impact on disease outcomes in patients after a median follow-up of two years. Data from an earlier double-blind placebo-controlled phase II study (n=86) and the aforementioned phase III study (n=212) were pooled; in all, 152 patients treated with palifermin (60 mcg per kg of body weight for six doses), and 146 patients treated with placebo were monitored for a median of 23 months. No differences were noted in the number of deaths (30% palifermin; 27% placebo) for the palifermin and placebo groups, which were attributed to the underlying cancer, nor did the investigators observe any difference in the OS and progression-free survival curves (P=0.474 and P=0.253, respectively). Secondary malignancies (nine patients with diagnoses of non-Hodgkin's lymphoma [NHL] and two patients with Hodgkin's lymphoma) were reported to occur in only 3% of palifermin and 4% of placebo patients.

When evaluating studies of OM therapies, variations in the study protocols make comparisons of clinically meaningful outcomes a challenge, and, more importantly, the lack of an agreed-upon scoring system for mucositis results in non-uniformity across studies. Scales that combine objective signs of mucositis (erythema and ulceration) with subjective symptomatic outcomes (pain and swallowing) are common, and this approach may result in underscoring and underreporting of symptomatic outcome measures, particularly as a result of inter-evaluator variability.[11] In future, it is hoped that large controlled studies using validated scoring instruments will reveal which supportive care interventions have a clinically meaningful influence on mucositis in cancer patients without impacting treatment, and will help to determine the impact of mucositis on OS.

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Dr. Bredeson's perspective:

Most traditional ablative pre-transplant conditioning regimens cause some degree of mucositis in all patients. However, predicting the high-risk patients before a transplant is conducted presents a challenge. Being able to identify the subgroup of patients who are susceptible to developing severe mucositis post-transplant would allow an agent like KGF to play a larger preventative role.

Currently, there is no evidence that patients suffering from mucositis have worse survival or progression-free survival as a result of this complication. While Bolwell's presentation[4] demonstrated that people with severe mucositis had poorer survival than those with mild mucositis, it did not establish a causal relationship between the mucositis and the mortality. The Spielberger et al. study[10] suggests that KGF does not protect against mortality in the short to medium term, presenting similar survival curves for palifermin and non-palifermin groups. Despite the apparent lack of survival benefit, palifermin may result in decreased inpatient costs and total days in hospital and/or on antibiotics, parenteral narcotics, and enteral nutrition.

The question regarding the relationship between mucositis, its prevention and post-transplant survival remains unanswered in the absence of a large prospective randomized trial. Until a validated scoring system becomes globally accepted and an appropriate high-risk group can be identified, such a study would be difficult to conduct. Further effort needs to go into identifying at-risk populations who can benefit from this novel agent.

With the recent approved indication for palifermin in Canada, use of KGF therapy will be considered by transplant programs across the country. However, until studies that include cost-effectiveness in the context of the Canadian healthcare system are conducted to appropriately define the role of KGF, it is unlikely Canadian transplant programs will introduce general use of KGF in the autologous transplant setting. More likely, specific populations thought to be at higher risk will be targeted. My approach to using KGF treatment will be to consider its use in patients who have experienced prior episodes of severe mucositis with salvage therapy or with prior autologous transplant. At our centre, we also will be using KGF therapy for patients with amyloidosis, as this patient population is known to have a high risk of regimen-related morbidity including mucositis and bleeding with high-dose chemotherapy.

Supportive Care of Chemotherapy-induced Neutropenic Toxicity

Effective management of chemotherapy-associated toxicities, such as febrile neutropenia (FN), with appropriate supportive care is crucial, particularly in the elderly population for whom complications of cytotoxic effects are reportedly more common.[1] Neutropenic events occur most frequently during the first cycle of chemotherapy when patients are often treated with full-dose chemotherapy without supportive care, as evidenced by previous studies in patients with NHL treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy.[1] Prevention of neutropenic complications has typically involved dose reduction or delay strategies, selective use of prophylactic antibiotics, and primary prophylaxis with myeloid growth factors (e.g., granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], filgrastim [rmethG-CSF], and pegfilgrastim [pegylated filgrastim]). Myeloid growth factors, as demonstrated in several studies, not only make treatment with standard-dose chemotherapy possible but may also lead to reduced hospital stays and lower use of parenteral antibiotics, two costly areas of cancer treatment. Evidence supporting the importance of maintaining full-dose on-schedule chemotherapy varies considerably according to cancer type, and is still a subject of debate. However, some clinical studies have shown that dose reductions and delays result in poorer outcomes in patients with NHL, and in many cases, higher dose intensity appears to result in greater overall and progression-free survival.[2]

The cost of myeloid growth factors has led to discussion about their appropriate use. Moreover, not all patients benefit from or need the prophylactic administration of growth factors. While the type of chemotherapy regimen is a factor in the development of first-cycle neutropenia complications, anthracycline use, poor performance status, and low pretreatment blood counts are other predictors of FN risk.[3] A prospective registry database was set up recently by Lyman and colleagues to analyze the incidence of and associated risk factors for FN episodes in cancer patients treated in a community setting.[4] The investigators studied the data on 357 patients of the more than 3,600 patients who were registered; most of the subgroup had NHL and 47% of them were over age 65. A logistic regression model was developed to examine predictors for first-cycle severe neutropenia (SN) or FN. SN or FN occurred in 123 patients during their treatment, with 81 of these cases (66%) in cycle 1. Clinical factors that predicted cycle-1 FN included anthracycline use (OR=6.9, P<0.001), recent infection (OR=12.41, P=0.035), pretreatment anemia (OR=2.41, P=0.043), elevated bilirubin (OR=2.25, P=0.051), Causcasian (OR=4.13, P=0.053), renal disease (OR=33.15, P=0.011), baseline absolute neutrophil count (OR=0.95, P<0.001) and lymphocyte count (OR=0.95, P<0.001), and elevated LDH (OR=2.0, P=0.040). Many of these factors are intuitive, particularly evidence of pretreatment myelosuppression, and some have been shown previously to identify patients at risk for

FN. This model was highly predictive in its dataset of which patients were at low risk for FN (negative predictive value = 94%), but the positive predictive value was lower, around 32% (sensitivity 92% and specificity 40%). Before it can guide physicians in deciding which patients are at high enough risk to justify the prophylactic use of myeloid growth factors, this model is being validated in a separate population of patients.

Age-related physiologic changes such as decreased stem-cell reserves, decreased ability to repair cell damage, progressive loss of body protein, and accumulation of body fat can increase the toxicity of chemotherapy. A natural decline in liver or renal function can alter the pharmacokinetics of many of the commonly used chemotherapeutic agents in some elderly patients, making toxicity less predictable. Using the same prospective registry cited above, researchers were able to determine that advanced age, and a more advanced stage of disease at the time of treatment, were associated with fewer neutropenic events in all chemotherapy cycles (P=0.017) and lower relative dose intensity (RDI) (P=0.041).[5] In the 50% of patients age 70 years and older who received almost full-dose intensity chemotherapy (≥85% RDI), increasing age alone did not appear to increase the risk of hematologic toxicity. Nevertheless, older patients who received ≥85% actual RDI experienced more frequent SN or FN in all cycles of chemotherapy (27% vs. 22%, P=0.041) Not surprisingly, anthracycline-containing regimens were associated with a higher risk of hematologic toxicity, particularly anemia and thrombocytopenia (P<0.001). Independent risk factors for neutropenic events in older patients were similar to those that affect the younger population. The salient finding of this study is that age is not a barrier to treatment. Older patients may do just as well as younger patients if the toxicities associated with chemotherapy are effectively managed with appropriate supportive care. With further development of these models, it is hoped that clinicians will be able to integrate this information into clinical decision-making for the individual patient.

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Dr. Bredeson's perspective:

Based on the rationale that dose intensity is important for progression-free survival and OS, researchers continue to evaluate the effectiveness of filgrastim and pegfilgrastim in helping to maintain dose intensity of chemotherapy by preventing neutropenic complications. The model used by Lyman et al.[4] suggested that two-thirds of patients were in the high-risk category for neutropenic events; however, only 23% of patients went on to develop neutropenia. While this study showed that too many patients would require treatment to make a prophylactic approach reasonable, it remains a worthy goal to develop clinical parameters for identifying at-risk patients.

What was surprising about the second study to come out of the prospective registry[5] was that approximately half of the cancer patients aged 70–79 were able to receive 85% or more of the planned dose intensity for their malignancy and did not experience more adverse events than the younger population who received the same dose intensity. For patients with reasonable performance status and lab results at presentation, it would be wonderful to have a robust tool that could help identify those who would be able to tolerate full-dose therapy.

A readily available risk factor assessment tool would be invaluable to physicians, particularly when data supporting a long-term benefit in survival outcomes can be clearly demonstrated. This would enable the development of a cost-effective strategy for the use of myeloid growth factors that would be attractive to patients, physicians, and third-party payers. In the absence of such a tool or data, the institutional policy at CancerCare Manitoba continues to include primary prophylaxis for patients thought to have a risk of FN of ≥40%. This differs from the recommendations of the National Comprehensive Cancer Network (NCCN) in

the US where the threshold has been dropped to 20%. The NCCN change was made to reduce the number of hospital admissions, as hospital days in the US are increasingly expensive. Secondary prophylaxis remains an option for patients receiving chemotherapy with curative intent if they have an episode of FN or a delay of therapy due to neutropenia.

The use of pegfilgrastim was introduced primarily as an alternative to filgrastim following chemotherapy for either primary or secondary prophylaxis. Our transplant program is interested in the potential of pegfilgrastim as an alternative to filgrastim in the setting of graft mobilization and autologous transplantation as reported in several abstracts at ASH 2005. We hope soon to be studying these approaches in the Canadian context, where, along with efficacy and patient preference, the ever important issue of cost-effectiveness must be addressed.

Rituximab and the Clinical Management of Lymphoid Malignancies

Regarding the clinical management of B-cell lymphomas, discussion about the monoclonal antibody rituximab could not have been more highly anticipated than at the 47th meeting of ASH. A good indication of this was that no fewer than 325 abstracts on this therapeutic agent were presented.

Rituximab (R) is a chimeric human/murine IgG1 monoclonal antibody that binds specifically to CD20, an antigen that is expressed exclusively on the surface of normal B cells and most B-cell malignancies.[1] A large number of trials with rituximab, with or without chemotherapy, for lymphoid malignancies are currently underway worldwide to determine the optimum conditions in which this monoclonal antibody exerts its effect. To date, the data collected on rituximab in combination with CHOP chemotherapy confirm that the addition of this biological agent to full-dose standard chemotherapy results in higher rates of complete response (CR), lower rates of relapse, prolonged survival, little additional toxicity, and no compromise of the dose intensity of standard chemotherapy regardless of age and risk group. Moreover, the safety profile of rituximab combined with chemotherapy resembles that expected with chemotherapy alone.[2,3] Thus far, trials with rituximab have largely been conducted in low-risk patient groups.

Two major studies established R-CHOP-21 as the worldwide standard regimen for newly diagnosed elderly patients with diffuse large B-cell lymphoma (DLBCL). In 2002, the Groupe d'Étude des Lymphomes de l'Adulte (GELA) study reported that rituximab added to standard CHOP conferred a higher OS rate for older patients (>60 years) with advanced-stage DLBCL.[2] Eight cycles of CHOP alone or CHOP with rituximab produced CR rates of 63% and 76%, respectively (P=0.005), and a two-year OS of 57% and 70% (P=0.007). The survival benefit was maintained and actually continued to improve through five years of follow-up, as demonstrated in a recent update of this trial;[4] however, the data fell short of significance in high-risk patients. The benefit of R-CHOP-21 treatment was consistent across all subgroups of patients tested, including both low- and high-risk patients. However, a subgroup analysis of this large study revealed that two groups of patients appear to derive particular benefit from rituximab: (1) those with a low age-adjusted International Prognostic Index (IPI) risk and (2) those with DLBCL positive for Bcl-2 overexpression, historically a poor prognostic factor.[5]

The second study is the as-yet-unpublished larger US Intergroup study (CALGB 9793/ECOG-SWOG 4494), which randomized a population of 632 elderly patients to eight cycles of CHOP or R-CHOP given every other cycle, following which responding patients were randomly assigned to receive either rituximab as maintenance or no maintenance therapy.[6] The magnitude of the OS benefit of induction therapy with CHOP plus rituximab parallels that in the GELA trial. The US Intergroup study, reported — perhaps the most salient finding — no additional benefit from rituximab as maintenance therapy in patients who had received the monoclonal antibody as part of their initial chemotherapy regimen.

The preliminary findings of the MabThera International Trial (MInT) demonstrated the benefit of R-CHOP-21 over CHOP-like regimens in low-risk patients between 18 and 60 years of age.[7] As in the GELA trial, patients who received rituximab plus chemotherapy had a significantly longer two-year time to treatment failure (81% vs. 58%) than patients receiving chemotherapy alone. In addition, the two-year OS rates also significantly favoured chemotherapy plus rituximab (95% vs. 85%).

Data is continuing to accumulate on whether the use of rituximab in chemotherapy regimens translates into survival benefit. The combination of cyclophosphamide, vincristine, and prednisone (CVP) for eight cycles is one of several standard treatment options for advanced follicular lymphoma (FL); however, the addition of rituximab has been demonstrated to significantly improve the clinical outcome of previously untreated patients with stage III/IV $CD20^+$ FL when compared to standard CVP therapy alone.[8] Further analysis of the data from this study after 42 months of follow-up confirmed the results of the combination treatment, with the median time to progression for patients receiving R-CVP more than double that of CVP alone (33 months vs. 14 months, $P<0.0001$).[9] In addition, the time to new lymphoma treatment or death was significantly longer in the rituximab group than in the CVP arm, and the median duration of response was almost four times higher, at 37.7 months. Fewer than half the number of patients in the R-CVP died due to lymphoma progression compared to patients receiving CVP (12 vs. 25 deaths, $P=0.02$). However, the toxicity of the rituximab regimen was evident in that the incidence of neutropenia was almost double in the R-CVP group (39/162 vs. 23/159 patients).

The role of monoclonal antibody-based therapies in dose-intense regimens is unclear, and trials incorporating rituximab therapy into dose-dense, dose-intensified regimens are ongoing. Two recently published trials, NHL-B1 and NHL-B2, suggest that modifications to the CHOP regimen may improve survival;[10,11] however, results of several new studies presented at the 2005 ASH meeting have been mixed. Additionally, the question of whether to subject patients to eight cycles of chemotherapy, or whether six is enough, remains to be decided.

The highly anticipated oral presentation given by Dr. Michael Pfreundschuh on the results of the RICOVER trial shed some light on the latter issue.[12] In the random two-by-two factorial designed RICOVER-60 (R-CHOP over 60) trial, 828 evaluable patients with $CD20^+$ DLBCL (median age 68, balanced for IPI prognostic factors) were assigned to receive six or eight cycles of CHOP-14 with or without eight applications of rituximab. The relative dose intensity for all four arms reached 96–99%. The primary endpoint was freedom from treatment failure (FFTF) with events defined as additional therapy, failure to achieve complete remission, progressive disease, relapse, or death. At a planned interim analysis, the data and safety monitoring committee closed the study because of an improvement in FFTF in the rituximab cohort. After a median follow-up of 26 months, the primary outcome following six cycles of either the CHOP-14 or R-CHOP-14 treatments was similar to that of eight cycles in this setting (70% FFTF for both six [n=211] and eight cycles [n=203]). Toxic deaths in the CHOP-14 arm were reported at 6%, while the rate of hematotoxicity was 40–45%; toxicities were reported to worsen with the addition of rituximab. The advantage of R-CHOP-14 over CHOP-14 with respect to OS is not yet significant (74% vs. 78%; $P=0.13$). Before the routine use of dose-intense regimens can become accepted practice, longer observation is required to draw definitive conclusions.

A study presented by Dr. Leo Verdonck on behalf of the Dutch HOVON trial group found intensified (I) CHOP-14 not to be significantly better than standard CHOP-21 in patients with intermediate-risk aggressive NHL in terms of clinical outcomes after five years of follow-up, and noted higher toxicity associated with the intensified regimen.[13] The prospective randomized HOVON-26 trial was conducted from 1994–2004 and enrolled 513 untreated patients aged 16–65 years. Patients were assigned to receive either six cycles of I-CHOP plus G-CSF or eight cycles of standard CHOP-21. The incidence of grade 3 and 4 toxicities at 40% in the I-CHOP arm was double that of the CHOP arm, while treatment-related mortality (8%) was similar between groups. Although results show that I-CHOP did not offer a significant improvement over CHOP in intermediate-risk NHL patients, a post hoc subgroup analysis revealed a possible benefit in overall, disease-free, and event-free survival in the low-intermediate group. The clinical significance of this observation, including duration of response, awaits further testing.

In contrast, rituximab in an intensified CHOP regimen resulted in improved failure-free survival in elderly patients without an increase in toxicity.[14] In the HOVON-46 study, patients with intermediate or high-risk NHL were treated with either eight cycles of CHOP-14 (n=99) or CHOP-14 plus six administrations of rituximab (n=98). The two treatment arms were balanced in terms of histology, age, WHO (World Health Organization) classification of NHL, age-adjusted IPI score, Ann Arbor stage, WHO performance status, and serum LDH. After a median follow-up of 15 months, tolerability and the rate of toxicity (n=21, CHOP-14 vs. n=16, R-CHOP-14) and CR (n=30 vs. 33) were similar between the two treatment arms. Event-free survival (EFS) and OS were significantly improved in the R-CHOP-14 treatment arm, and at two years, EFS was reported at 51% in the R-CHOP-14, double that for CHOP alone (23%, P=0.005).

As evidence grows that rituximab added to chemotherapy translates into longer response durations and increases in overall response rates, a potentially valuable role for rituximab in maintenance therapy may also exist, although studies that have used single-agent rituximab maintenance have been inconclusive. Some studies have suggested that rituximab maintenance therapy is precluded if the antibody was part of the induction regimen, but it may have a role after standard or high-dose chemotherapy. In a recent study presented at ASH 2005, Hiddemann and colleagues showed that rituximab maintenance after rituximab plus fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) salvage therapy is highly effective and improves the outcome of patients with relapsed or refractory FL and mantle cell lymphoma (MCL).[15] A prolonged response duration was observed in patients with FL following rituximab maintenance therapy after induction treatment with R-FCM (P=0.035). Patients were randomly assigned to four courses of chemotherapy with FCM vs. R-FCM. The first randomization was stopped after 147 patients demonstrated a significant improvement for the R-FCM therapy in response rate (79% vs. 58%, P=0.01), response duration (P=0.038), and OS (P=0.003). In spite of the small number of patients with MCL who had received R-FCM before (11 out of 22 patients), response duration was prolonged by rituximab maintenance (P=0.048). The authors conclude that rituximab increases CR rates and duration of response for indolent lymphomas, even after induction R-FCM.

Another notable study by Van Oers et al. at this year's ASH meeting presented supporting data for the use of rituximab maintenance therapy in patients with advanced FL who have received rituximab-based induction chemotherapy.[16] However, no data exist for this maintenance therapy following R-CVP or R-CHOP. All completed trials with maintenance rituximab have shown improvement in progression-free survival with minimal additional toxicity. Questions that remain unanswered include the optimal scheduling and duration of maintenance therapy and whether repeated exposures to rituximab as a single agent may lead to biologic resistance, leading to poorer results with subsequent rituximab-based salvage regimens.

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Dr. White's perspective:

In the RICOVER-60 trial,[12] data results comparing six to eight cycles of CHOP-14 with rituximab were quite similar. While no OS benefit was shown with the addition of rituximab to CHOP, FFTF was improved with R-CHOP-14. Follow-up at 26 months may be too short a time period to make definitive conclusions. RICOVER-60 wasn't a randomized trial designed to demonstrate whether R-CHOP-21 or dose-dense R-CHOP-14 was superior. Ideally, it would now be useful to see data directly comparing the two regimens in a head-to-head trial. Nonetheless, this was a compelling study that addresses the important question of whether to administer six or eight cycles of R-CHOP therapy and adds to our knowledge of the effectiveness of rituximab in chemotherapy.

Because the addition of rituximab to standard chemotherapy was accepted several years ago, the HOVON-26 trial[13] comparing intensified CHOP-14 with standard CHOP is already out of date. Also, the study was started before the use of the IPI was common, and hence it was not initially designed to compare patients according to low-, intermediate-, and high-risk factors. In this regard, it may not be valid to accept a post hoc analysis of the data suggesting that low to intermediate-risk patients benefit from the dose-intense regimen. While the follow-up at 15 months is very short, it will be interesting to watch the data mature. Significant OS rates need to be clearly shown before the increased grade 3 and 4 toxicity rates in the dose-intense regimen can be considered acceptable. Once significantly improved OS rates can be demonstrated, the additional expense of G-CSF treatment may be considered cost-effective and accepted in the Canadian supportive care environment.

In the HOVON-46 study data presented,[14] where eight cycles of CHOP-14 were compared with the same regimen plus six administrations of rituximab, only 51% of the patients in the CHOP-14 arm and 57% of patients in the R-CHOP-14 arm completed the treatment. While investigators state that toxicity was similar in both arms, the low rate of trial completion needs to be evaluated.

In Canada, six to eight cycles of R-CHOP-21 remains the standard of care for elderly patients. Randomized controlled data comparing R-CHOP-14 to R-CHOP-21 would be required before any changes could be expected in the Canadian guidelines for management of lymphoma patients with respect to dosing intervals. The patient population that may benefit most from a shorter dosing interval would be the elderly or those with high-risk disease — the segment of the population that the investigators have tried to capture in these studies.

Safely and Effectively Managing Anemia with Erythropoietin-Stimulating Agents

Several studies have shown that quality of life (QoL) is substantially improved by therapy that raises the hemoglobin (Hb) level to between 110 and 120 g/L. Cancer-induced anemia can be corrected by blood transfusion, or by pharmacologically increasing the erythropoietin level with recombinant human erythropoietin-stimulating agents (ESAs) such as epoetin alfa (EPO) and darbepoetin alfa (DA). Studies have shown that long-term improvement, including a progressive and stable Hb level, can be achieved in a number of patients by giving recombinant erythropoietin on a regular schedule.[1,2] However, only about 60% of patients respond to erythropoietin treatment (Hb increase of at least 20 g/L), pointing to the need for accurate predictive models to help determine who will respond.[3,4]

In all randomized controlled clinical trials to date, erythropoietic agents have consistently increased hematocrit or Hb levels and reduced the need for blood transfusion. Associated improvements in QoL have also been reported. Head-to-head trials comparing efficacy, safety, and optimal dosage schedules of available erythropoietic agents are ongoing.[5]

Two recent trials have raised concerns about the safety of ESAs in cancer patients with regards to thrombosis, tumour progression, and survival. One randomized controlled trial (RCT) in breast cancer patients, which was terminated early at four months, reported increased thrombotic and cardiovascular events (2.3% in the ESA group vs. 0.4% in the placebo group).[6] The trial by Henke et al.[7] added epoetin beta to head/neck patients with anemia undergoing radiotherapy and found the outcome favoured the non-ESA-treated groups with regard to OS and disease-free survival. Both trials were criticized for design flaws and because ESA treatments were initiated at higher Hb levels than those used in other studies or needed in clinical practice. The trials also set out to achieve higher target Hb levels — levels that are now considered unsafe.

In a poster session at ASH 2005, researchers Freemantle et al. presented a meta-analysis of data from four RCTs examining DA in chemotherapy-induced anemia.[8] Results indicated no detrimental effect on survival or tumour progression, and the thrombotic event rate was consistent across pre- and post-approval studies. A second meta-analysis of all available clinical trial data on EPO and DA presented by Bohlius and colleagues suggests a significant risk of thromboembolic events with these agents (relative risk 1.67; 95% CI 1.35–2.06; 35 trials, n=6,769), though effects on tumour response and OS could not be determined from available data.[9] Ongoing well-controlled randomized trials across multiple tumour types should provide more conclusive data on the effect of erythropoietic agents on endpoints such as survival, adverse events, and tumour response. The evidence so far suggests that, if used as indicated for patients with a Hb level <120 g/L, erythropoietic agents are safe.

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Dr. White's perspective:

The ASH 2005 study data evaluating the safety of ESAs in cancer patients with regards to tumour progression and survival provided information that was reassuring and would not warrant change in the current Canadian practice guidelines. The researchers showed that although there is some evidence of risk of thromboembolic events, it is more common for Hb levels above 120 g/L — levels not recommended by most clinical guidelines. The data in terms of QoL is sufficient to warrant using ESA medications in symptomatic anemic patients.

The question of which drug to use, EPO or DA, is currently up for debate in hematology circles. To date, there have been few head-to-head studies completed. In terms of safety, both drugs are similar and the varying endpoints of the available study data make efficacy comparison difficult. Currently, criteria such as provincial guidelines or third-party insurance coverage influence which drug to choose for specific patient populations. If the evolving evidence supporting Q2W or Q3W dosing clearly demonstrates that less frequent dosing is effective, guidelines will be revisited. Another factor to consider is cost. ESA treatments are expensive. Less frequent dosing may prove to be more cost-efficient, as well as providing an obvious benefit to patients.

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