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Advancing the options for treatment and support of patients with haematological disorders

Chair: J.-L. Harousseau (Nantes, FR)

Treatment strategies for diffuse large B-cell lymphoma: the GELA experience

B. Coiffier (Pierre Bénite, FR)

Supporting the way towards a cure in multiple myeloma

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M. Rummel (Giessen, DE)

TREATMENT STRATEGIES FOR DIFFUSE LARGE B-CELL LYMPHOMA: THE GELA EXPERIENCE

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Over 74,000 patients in Europe (ie, the European Economic Area plus Switzerland) were diagnosed with non-Hodgkin's lymphoma (NHL) in 2006 [Finlay, Ann Oncol. 2007; 18:581]. Most patients (31%) newly diagnosed with NHL are diagnosed with the aggressive diffuse large B-cell lymphoma subtype. Of these, most are over 60 years old. Since the 1970s these patients had been treated with CHOP chemotherapy, administered on a 21-day schedule (ie, CHOP-21). Within the past 5 years, however, options for the treatment of aggressive NHL have evolved. Phase 3 trials have demonstrated that adding rituximab, a chimeric anti-CD20 monoclonal antibody, to CHOP-21 increases survival, without a notable increase in toxicity, in all groups studied [Coiffier, NEJM 2002; 346:235]. Recently, results were presented confirming these observations after 7 years follow-up. Another approach has been to administer CHOP more frequently, every 14 days; this CHOP-14 regimen was effective in all patients between the ages of 18 and 75 [Pfreundschuh, Blood 2004; 104:626; Pfreundschuh, Blood 2004;104:634]. Addition of rituximab to CHOP-14 has been examined in the 4-arm RICOVER-60 trial, 2 arms each comparing 6 and 8 cycles of the regimens: superior survival was observed when patients aged 60 to 81 years received 6 cycles of R-CHOP-14 compared with 6 cycles of CHOP-14 alone. Additional ongoing trials are investigating whether R-CHOP-14 should become the new gold standard for older patients. Outcomes observed with chemotherapy regimens such as these indicate that it is important that chemotherapy be delivered on-time and at full dose to optimise response.

Patients receiving these agents, especially patients on dose-dense regimens, frequently suffer from haematological toxicities such as neutropenia and anaemia. Febrile neutropenia and grade 3/4 anaemia have been reported as occurring in approximately 20% and 14%, respectively, of patients on R-CHOP 21 [Coiffier, NEJM 2002; 346:235]. Both of these toxicities may either delay chemotherapy or result in dose reduction, potentially affecting long-term outcome, and anaemia can significantly affect quality of life in these (often elderly) patients. Guidelines for the management of neutropenia with granulocyte-colony stimulating factor recommend their use with dose-dense regimens and recommend primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) when the overall risk of febrile neutropenia from chemotherapy and patient risk factors is ≥ 20%. Guidelines for anaemia treatment recommend the use of erythropoiesis-stimulating agents (ESAs) for symptomatic anaemic patients receiving chemotherapy. In the current GELA study evaluating R-CHOP-14 vs R-CHOP-21 in patients with aggressive NHL (a 2x2 factorial design) [LNH 03-6B], the benefit of mandated prophylactic use of darbepoetin alfa versus standard of care, which includes therapeutic use of darbepoetin alfa or transfusions depending on patient status, is also being assessed. Early safety results of this study have been reassuring.

In conclusion, choice of treatment should be made based on an evaluation of age, outcome, and, for some patients, location of tumours. Similarly, choice of supportive care regimen should be made based on chosen treatment regimen and patient risk factors.

SUPPORTING THE WAY TOWARDS A CURE FOR MULTIPLE MYELOMA

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For many years there has been a clear unmet need for novel agents to treat multiple myeloma (MM). Autologous stem cell transplantation (ASCT) improves response rate and progression free survival (PFS), but it is only offered to younger patients (<65–70 years) and MM is primarily a disease of the elderly. For patients who are not candidates for ASCT, the standard of care is conventional dose chemotherapy regimens (such as melphalan-prednisone) that have remained essentially unchanged since the 1960's. At last, we have newer agents that potentially offer better outcomes – beginning with the reintroduction of thalidomide, and followed by lenalidomide and bortezomib.

Firstly, these agents offer new possibilities for relapsed patients. In heavily pre-treated patients they can induce impressive response rates and prolong PFS, particularly when given at first relapse. In this setting, these agents are mainly used in combination either with dexamethasone or chemotherapy. Thalidomide, bortezomib and lenalidomide have also been evaluated as frontline therapy in older patients unsuitable for ASCT. Randomized studies have shown that melphalan-prednisone + thalidomide or bortezomib is significantly superior to melphalan-prednisone alone for inducing remission. Preliminary results with melphalan-prednisone + lenalidomide, or lenalidomide + low-dose dexamethasone are also encouraging. Although these combinations yield complete remission and PFS rates similar to those achieved with high-dose chemotherapy + ASCT, newer agents do not signal the end of ASCT. Patients can experience a long period of remission post ASCT without the requirement for maintenance therapy, while prolonged treatment with newer agents is needed. Newer agents can, however, improve outcomes in ASCT either as part of the induction regimen or when used after transplantation. For instance, the use of novel agents prior to ASCT may increase complete and very good partial remission rates to 70–80%. Maintenance therapy with thalidomide further increases the complete remission rate, translating into significantly longer PFS and overall survival. The tolerability of novel regimens is a key question. Trials suggest that lenalidomide is associated with clinically significant severe neutropenia in a substantial proportion of patients, particularly when used at higher doses. To a slightly lesser extent this is also true of bortezomib-containing regimens, while both agents can be associated with anaemia (≥grade 2). Thus, appropriate supportive care (e.g. with growth factors) should be considered to ensure maximum benefit is gained from these important advances in treatment.

INNOVATIVE APPROACHES IN THE TREATMENT AND SUPPORT OF ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is a genetically heterogeneous disease characterized by an accumulation of acquired mutations in hematopoietic progenitor cells. At present, well-established chemotherapy regimens, such as the '7+3' induction regimen of cytarabine plus an anthracycline, are the standard of care for all AML subtypes. New induction and consolidation regimens are, however, being investigated. Supportive care with growth factors can be important to aid recovery from treatment-related aplasia. Filgrastim has been used in this setting, and data now show that pegfilgrastim is also effective. Perhaps the greatest benefit from growth factor support is observed following consolidation therapy. For example, use of pegfilgrastim after high-dose cytarabine consolidation therapy reduced time to neutrophil recovery, incidence of neutropenic fever and time in hospital compared with controls.

Looking to the future, our improving knowledge of leukemogenesis will increasingly translate into more accurate prognostic assessment and genotype-specific treatment strategies. In a recent metaanalysis we attributed induction success in AML patients exhibiting a normal karyotype to those having mutations either in *NPM1* in the absence of *FLT3*-ITD or in *CEBPA*. These favorable genotypes emerged as highly significant prognostic markers for relapse-free and overall survival; they also acted as predictive markers with the beneficial effects of an allogeneic stem cell transplant in first complete remission being evident only in patients without a favorable genotype. The utility of genotyping has been further demonstrated in core binding factor (CBF) leukemias, which exhibit a higher expression of *KIT* compared to other AML subtypes. Here, *KIT* mutations have been associated with an unfavorable prognosis.

New drugs are being developed to specifically inhibit molecularly-defined targets. The efficacy of tyrosine kinase inhibitors is being investigated in $FLT3^{mut}$ and CBF AML, while other examples include the use of all-trans retinoic acid in $NPM1^{mut}$ AML. It is of note, however, that nearly all new targeted treatments combine innovative agents with a backbone of chemotherapy such as the 7+3 induction regimen and consolidation therapy with high-dose cytarabine.

In conclusion, the future of AML treatment lies in genotype-specific strategies. Since most new agents will be combined with conventional chemotherapy appropriate supportive care, including growth factors, will remain a consideration in management of AML.

ROMIPLOSTIM: A BREAKTHROUGH IN THE TREATMENT OF IMMUNE THROMBOCYTOPENIC PURPURA

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Immune thrombocytopenic purpura (ITP) is an immune-mediated, haematologic disorder of increased platelet destruction and concomitant sub-optimal platelet production. Patients typically have abnormally low platelet counts (<50 x 10^9/L). Clinical signs and symptoms include bleeding, purpura, petechiae, and at very low platelet counts, there is a risk of major non-fatal and fatal bleed events. ITP affects patients of all ages and ethnic groups, and there are approximately 390 new cases of ITP per million people per year. (1) Current approved treatment options include corticosteroids whose long-term use can be associated with various side effects, including hypertension, diabetes, and osteoporosis. Splenectomy is an option for patients with severe ITP refractory to corticosteroids, but the trend is now for more conservative management of patients.

Romiplostim is a thrombopoiesis-stimulating Fc-peptide fusion protein (peptibody) that binds to and activates the thrombopoetin receptor on megakaryocytes in the bone marrow, thereby increasing platelet production. The efficacy and safety of romiplostim as a new treatment option for ITP was investigated in two parallel, multicentre, double-blind, randomised, placebo-controlled, phase III studies conducted in the US and Europe. (2) Romiplostim was administered as a weekly subcutaneous injection (starting dose 1μg/kg/week, adjusted to maintain platelet counts between 50-200 x 10^9/L) for 24 weeks to 83 adults with ITP (splenectomised N=42; non-splenectomised N=41). Altogether 88% of the non-splenectomised patients and 79% of the splenectomised patients receiving romiplostim achieved either a durable or transient platelet response during the study period compared with placebo-treated patients ($p<0.0001$). Patients receiving romiplostim required fewer ITP rescue medications and were able to discontinue or reduce the use of concurrent ITP drugs such as corticosteroids.

Headache was the most frequently reported adverse event in the romiplostim-treated patients (35% vs 32% placebo). Significant bleeding events occurred in 12% and 7% of the patients receiving placebo and romiplostim, respectively; there was a 42% reduction in ≥ grade 3 bleeding events in favour of the romiplostim-treated patients. (3)

These phase III data indicate that romiplostim offers a promising breakthrough in the treatment of ITP in splenectomised and non- splenectomised adults.

1. Kaye et al. Haematologica 2007; 92 (Suppl 1): 280
2. Kuter et al. Lancet 2008; 371: 395-403
3. Lyons et al. The American Society of Hematology Annual Meeting 2007; Abstract 1300