risk factors each experienced a transient ischemic attack without sequelae while their platelet counts were \(< 100 \times 10^9/L\). The results of this study lend to some considerations. It is now clear that the response rates to romiplostim in the published trials are fairly superimposable to what one can achieve in the clinical arena. There is often the concern that because of selection criteria and stricter control of administration of the drug, results of trials may be better than those observed in real life. However, in the French study, in which patients were unselected and romiplostim was administered at home in 74% of the patients, the overall response rate was nearly as good as that obtained in the pivotal studies.5 That said, there are still roughly one-third of patients for whom the use of romiplostim results in no sustained improvement of the platelet count. In Khellaf et al’s study these were the patients presenting with the most severe bleeding manifestations, a finding that is somewhat diminutive of the role of this drug in managing difficult cases. However, this is the first time that a bleeding score in ITP is found to have a predictive value. Because previous trials with either romiplostim or eltrombopag used the World Health Organization bleeding score, this observation needs to be confirmed prospectively.

With regard to side effects of treatment, romiplostim has consistently shown a favorable profile. Nevertheless, because the absolute safety of this drug in the very long term is yet to be defined, its use in young, nonplenectomy individuals should be carefully pondered. The same concerns, however, also apply to many immunosuppressive agents that need chronic administration. Finally, to minimize the possible increased risk of thromboembolic events,7 a sensible approach is to set the target platelet count range between 50–100 \( \times 10^9/L \). For the majority of patients with a cardiovascular risk this will be a hemostatically safe range even on anticoagulants or antiaggregants.

Despite some of the limitations that we have described, there is little doubt that romiplostim represents a major breakthrough in the management of chronic ITP. In addition to an increase in platelet count, decreased risk of bleeding, and reduction or discontinuation of concomitant ITP medications, patients responding to romiplostim also experience an often dramatic improvement of health-related quality of life.8,9 This aspect could not be adequately addressed in the retrospective French study, but clinicians treating patients with ITP are aware that it is as important as the platelet count.

Future strategies for the development of romiplostim in chronic ITP may involve its use in combination therapies, with the aim of targeting both the increased platelet destruction and the impaired platelet production that is typical of this disease.10 Conflict-of-interest disclosure: The author has served as a consultant for Amgen, Glaxo-SmithKline, and Suppremol and has participated on advisory boards and/or as a speaker at medical education events supported by Amgen, Glaxo-SmithKline, Nycovac, Novo, Bayer, and Baxter.

REFERENCES

© 2017 American Society for Blood and Marrow Transplantation

Impression of long hematologic remission, event-free survival (EFS) and overall survival (OS) of 12.7 years, 8.3 years, and 13.2 years, respectively. U pfront treatment of patients with systemic AL amyloidosis remains challenging. Before the era of novel agents and availability of serum-free light chain measurements for response assessment, outcomes with alkylator-based chemotherapy were poor. Taking a lead from myeloma, patients with amyloidosis followed the high-dose melphalan ASCT path, but the multisystem nature of the disease lead to unacceptably high treatment-related mortality (TRM) in early series. Review of criteria for patient selection reduced TRM2 but raised questions as to whether patient selection and not treatment was the reason for better outcomes. Troubled waters were further muddied by results of the only randomized trial that failed to demonstrate improved outcomes with ASCT over chemotherapy, but the study was relatively small with a high TRM.3 Less than a quarter of all patients with AL amyloidosis are deemed suitable for ASCT, and a significant proportion of those selected need dose reduction of melphalan in the conditioning regime. Chemotherapy is used to treat a majority of patients with AL amyloidosis with oral melphalan and dexamethasone considered the standard of care for patients not eligible for

Comment on Cibeira et al, page 4346

ASCT for AL: all’s well that ends well

Ashutosh D. Wechalekar
UNIVERSITY COLLEGE LONDON MEDICAL SCHOOL

In this issue of Blood, Cibeira et al report long-term outcomes of 421 patients with AL amyloidosis undergoing autologous stem cell transplantation (ASCT) at a single center.1 Patients who achieved a complete hematologic response (CR) had impressively long hematologic remission, event-free survival (EFS) and overall survival (OS) of 12.7 years, 8.3 years, and 13.2 years, respectively.
ASCT. It achieves a hematologic response, CR, and organ response in ~60%, 20%–25%, and 40%, respectively. Hematologic response rates with bortezomib are high in both relapsed and upfront settings, especially in combination with dexamethasone and alkylators. The latter can produce very good partial responses or better in over 65% patients, with nearly half achieving a rapid organ response. The numbers are small, and long-term durability of responses remains to be determined.

Among the 421 patients after high-dose melphalan and ASCT reported by Gibeira et al, on an intention to treat basis, EFS for patients in CR (34%) and not in CR was (66%) was 8.3 years versus 1 year while the OS was 13.2 years versus 3.2 years, respectively. Forty-five percent had cardiac involvement with a median OS of 3.4 years. The median time to hematologic relapse was 12.7 years for CR and 2.7 years for non-CR with more frequent organ responses in the CR group (78.6% vs 39%). Although the overall TRM in the study was low (11.4%), especially so in the previous 5 years (5.6%), one-year mortality was still high at 19.1%, and remains a concern with 69% of these deaths occurring among cardiac cases. The long-term relapse-free data and OS in CR patients looks very promising indeed but the problem of early deaths still remains.

One-third of the selected good-risk patients undergoing ASCT will achieve the desired result of a hematologic CR, but what about the other two-thirds that don’t achieve a CR? Not all patients need a CR to improve organ function but early identification of those who do is critical. Early changes in cardiac biomarkers are potentially useful tools in this context. Clinical trials of adjuvant chemotherapy after ASCT could be an option if an improved response is deemed desirable. TRM was a major obstacle for ASCT. This seems to have been largely overcome in experienced centers, but will centers that do not routinely perform transplants on large numbers of AL patients achieve similar results? This remains to be seen.

Dose-adapted melphalan (melphalan 100–140 mg/m²) conditioning has allowed older patients or patients with more advanced disease to undergo ASCT but with a significant compromise in the efficacy: an ~50% decrease in CR, EFS, and OS compared with the melphalan 200 mg/m²–approach in the current study. Chemotherapy outcomes have improved over the past 10 years and oral melphalan-dexamethasone appears to achieve comparable results. The hematologic and possible organ responses with dose-reduced ASCT appear inferior to novel agent combination regimes such as bortezomib-alkylator-dexamethasone, although data on long-term outcomes are lacking. Novel conditioning regimes, such as addition of bortezomib or 90Y-labeled CD66, need to be explored in this setting to allow lower melphalan doses to be used with better efficacy and lower toxicity. The role of melphalan 100–140 mg/m²–conditioned ASCT in AL amyloidosis is highly questionable.

Where does this leave a clinician making decisions and counseling a newly diagnosed patient with AL amyloidosis? Most patients treated with chemotherapy will need repeated courses during which there is a risk of treatment toxicity, organ progression at each relapse, and risk of inducing clonal resistance. The prospect of long-term disease control makes ASCT with melphalan 200 mg/m² conditioning attractive for a younger amyloid patient without significant cardiac involvement, good performance status, and organ function, where outcome after ASCT, if a CR is achieved, appears superior to chemotherapy. Making a decision to undergo ASCT is difficult for a newly diagnosed AL patient. Chemotherapy with novel agent combinations appears attractive with no need for hospital stay and less toxicity and TRM compared with ASCT. A prospective randomized comparison between novel agent combinations and ASCT is clearly needed but is very challenging. A United Kingdom randomized trial comparing cyclophosphamide-thalidomide-dexamethasone with ASCT failed to recruit any patients. Most patients opted for chemotherapy outside the trial, knowing they could have ASCT later if needed. In the current study, prior chemotherapy improved CR rate by 10%. An important question that needs to be answered is the role of delayed or consolidation ASCT in patients achieving good responses to chemotherapy. Markers like calreticulin appear interesting in preliminary studies for predicting melphalan response. A priori knowledge of melphalan responsiveness would be of great help in the decision-making process, as would predictors of organ toxicity during ASCT. ASCT with melphalan 200 mg/m²–conditioning remains an important treatment option for younger, fitter patients with AL amyloidosis but much remains unanswered. All’s well that ends well, but we still need a crystal ball at the beginning!
ASCT for AL: all's well that ends well

Ashutosh D. Wechalekar