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A Short Review of Hematopoietic Transplantation for AL Amyloidosis

Ivetta Danylesko

Abstract

AL amyloidosis is an uncommon disease with variable clinical presentations; as such, it is often initially unrecognized and diagnosis is therefore frequently delayed. As a result of diagnosis at a point in their disease when patients often have significant end-organ damage, aggressive therapy with major toxicities can be extremely challenging. Nonetheless, clinical data have been accumulating over the past several decades that have demonstrated that patients who were taken to high-dose therapy—typically using single-agent L-phenylalanine mustard—with autologous hematopoietic rescue, have a dramatically improved overall survival than otherwise. In this chapter, the critical clinical data that demonstrate this, and the risk-adjusted approach to optimize the outcome for patients, are reviewed.

Keywords: AL amyloidosis, hematopoietic transplant, plasma cell dyscrasias

1. Introduction

AL amyloidosis, the consequence of the three-dimensional misfolding and aggregation of serum immunoglobulin light chains, with consequent end-organ damage due to the deposition of the amyloid, is an uncommon disorder, resulting from a clonal proliferation of lymphoid cells of B cell lineage. As such, it shares many pathobiological characteristics with multiple myeloma, and drugs that have antineoplastic activity in myeloma and other plasma cell dyscrasias typically are active in the treatment of AL amyloidosis. However, in large part, because the early clinical manifestations of AL amyloidosis can be insidious and nonspecific, a majority of patients with AL amyloidosis are not diagnosed until there has been significant end-organ damage. The presence of end-organ damage, often in multiple organ systems critical for the tolerance of antineoplastic therapy, has limited the feasible treatment options for patients with significant amyloid burden, particularly with regard to cardiac, hepatic, and renal involvement by amyloid.

Despite the barriers to treatment, however, significant progress has been made, especially at centers with deep experience in the management of AL amyloidosis. Clinical data have been accumulated in the past several decades that convincingly demonstrates—despite little in the way of prospective, randomized trials—that high-dose antineoplastic therapy with hematopoietic rescue, and most specifically high-dose melphalan chemotherapy with autologous stem cell rescue—“ABMT,” improves overall survival in patients with AL amyloidosis. As of this writing,

criteria for selecting patients for ABMT are evolving, as risk stratification becomes better defined, and supportive care improves. For patients who are considered for transplant, these factors also impact the decision as to whether a particular patient is an appropriate candidate for upfront ABMT, versus induction therapy followed by ABMT. Similarly, post-transplant maintenance therapy is also the subject of ongoing clinical research. This review summarizes the data from a number of important papers published in the peer-reviewed medical literature, all of which are indexed in the National Library of Medicine of the United States' searchable database, PubMed.

2. Evolution of transplant for AL amyloidosis

The historical evolution of the treatment of AL amyloidosis is reviewed elsewhere in this volume. The first peer-reviewed report of the efficacy of conventional doses of L-phenylalanine mustard—melphalan—dates to 1958, when Blokhin and colleagues in the former Soviet Union reported benefit from the use of melphalan in a variety of disease states [1]. Shortly thereafter, in 1962, Mass reported some degree of efficacy of prednisone as a single agent in the treatment of myeloma, as compared to placebo [2]. However, it was not until 1997 that the efficacy of melphalan and prednisone for the treatment of AL amyloidosis was reported in the context of a formal clinical trial. In that year, Kyle and colleagues at the Mayo Clinic reported the results of a prospective, randomized clinical trial, comparing colchicine alone, melphalan together with prednisone, or the combination of all three drugs, in treating AL amyloidosis. That study randomized 220 patients who had biopsy documentation of AL amyloidosis. The authors reported median survival of 18 months for patients randomized to melphalan and prednisone, the median survival of 17 months for patients randomized to the three-drug combination, and median survival of 8.5 months for those treated using colchicine alone [3]. This study established melphalan with prednisone as a standard of care, although this approach had by then been in use for more than two decades.

ABMT for patients with amyloidosis began to be explored extensively in the final decade of the twentieth century at a number of centers around the world. In 1996, in the journal *Blood*, Comenzo and colleagues at Boston City Hospital reported their experience with their first five AL amyloidosis patients treated using intravenous melphalan at a dose of 100 mg/meter square body surface area per day for two consecutive days, followed by rescue with autologous peripheral blood hematopoietic progenitor cells that were collected after filgrastim priming [4]. Patients underwent this therapy between 2 and 18 months after diagnosis, with a median of transplant at 5 months from diagnosis; median age was 46 years. All five patients were alive at the time of publishing follow up, with favorable hematologic responses—clearing of monoclonal light chains, and clinical improvements with respect to their manifestations of disease, including peripheral neuropathy in the three patients so affected, gastrointestinal dysfunction in the one patient so affected, and resolution of hepatomegaly in the one patient so affected. Performance status either was improved or stable for all five patients. Similarly, Moreau reported a retrospective examination of a series of 21 patients with AL amyloidosis treated in France, published in 1998 [5]. In this series, 18 patients received single-agent high-dose melphalan, in the range of 200 mg/meter square body surface area, and three patients received the combination of high-dose melphalan together with total body radiation. Up to 43% of these patients died within the first month after transplant, an extremely high mortality rate attributable to toxicity, as opposed to the progression of the disease. However, among the surviving

12 patients in this series, 10 patients had an objective response to therapy, demonstrating that the therapy did have efficacy for those who tolerated the treatment. Overall survival was 57% at a median follow up of 14 months, and Event-free survival was 29.9% [4]. Importantly, they noted five clinical features at the time of transplant that was associated with outcome. Patient results were significantly worse if there was (a) greater than 3 grams per 24 hours' proteinuria; (b) creatinine clearance less than 30 mL/minute; (c) congestive heart failure syndrome; (d) neuropathy; or (e) hepatomegaly together with alkaline phosphatase greater than 200. As would be expected, patients with two or more of these adverse clinical findings had significantly poorer outcomes, with overall survival at 4 years of 11.1%, as compared to the overall survival of 91.7% for patients with fewer than two of these adverse findings.

Reports such as those by Comenzo and Moreau, and from a number of other centers around the world regarding the early experiences with autologous transplant for treatment of AL amyloidosis, led the Intergroupe Francophone du Myelome (IFM) to conduct a prospective, randomized multicenter clinical trial, comparing high-dose melphalan with autologous hematopoietic rescue—ABMT—to conventional-dose melphalan given with dexamethasone. The findings from this study were reported by Jaccard and colleagues on behalf of the IFM in the year 2007 [6]. Between the years 2000 and 2005, 100 patients were accrued who had Eastern Cooperative Oncology Group performance status score of 2 or lower, with biopsy-proven AL amyloidosis, in the absence of symptomatic multiple myeloma. In the transplant group, peripheral blood hematopoietic progenitor cells were collected by cytapheresis following a five-day course of granulocyte-colony stimulating factor, with a minimum target collection of 2 million CD34 cells per kg body weight. Conditioning was with melphalan 200 mg/meter square but was reduced to 140 mg/meter square for patients 65 years of age and older, for those with left ventricular cardiac ejection fraction less than 30%, those with calculated creatinine clearance less than 30 mL per minute, and those with liver disease who had significantly prolonged prothrombin time, elevated total bilirubin greater than five times the upper limit of normal, or alkaline phosphatase elevated to greater than five times upper limit of normal. The granulocyte-colony stimulating factor was administered to accelerate granulocyte recovery following stem cell infusion. Patients in the control arm were treated using monthly cycles of oral melphalan 10 mg per meter square body surface area on days 1–4 each month, together with oral dexamethasone 40 mg daily for days 1–4 each month, for up to 18 months, later emended to stop therapy after 12 months if complete remission obtained. Dose adjustments were permitted for oral melphalan if clinically appropriate. In this study, criteria for organ involvement and organ response were meticulously defined. The two cohorts were fairly well balanced for age, performance status, the number of organs clinically involved by disease, and organ function.

Among the 50 subjects randomized to the ABMT arm, 13 did not proceed to transplant, of whom 10 died from complications of the amyloidosis prior to transplant. Of the 37 patients who did proceed to ABMT, nine died within 100 days of receiving the melphalan conditioning; transplant-related mortality was 24%. Among the patients assigned to conventional-dose melphalan, two patients died from cardiac arrhythmias prior to completing the first month of therapy, and five additional patients died within the first 130 days after randomization—all from the progression of the underlying amyloid disease. The results reported showed that hematologic responses did not differ significantly between the two treatment groups. Up to 69% of the patients in the conventional-dose therapy group demonstrated favorable reductions in light chain levels, as compared to 62% in the transplant arm. However, the complete remission rate was 47% in the conventional-dose

group, as compared to 61% in the high-dose melphalan group. As of the time of data analysis in August 2006, 51 patients had died out of the initial 100, 20 patients in the conventional-dose group, and 31 patients in the group assigned to transplant. With respect to intention-to-treat analysis, the estimated median overall survival was 56.9 months in the conventional dose cohort, as compared to 22.2 months in the group assigned to ABMT. The study was powered to detect at 25% survival advantage for ABMT as compared to conventional-dose melphalan with dexamethasone; the study failed to demonstrate the superiority of ABMT. Indeed, in this study, median overall survival was significantly longer in the conventional-dose control group, as compared to the autologous transplant group. The authors noted that had the trial been conducted exclusively at a tertiary referral center with a very high level of expertise, the mortality in the transplant arm might have been lower. This study did appear to have a somewhat chilling effect on enthusiasm for high-dose therapy with the autologous hematopoietic rescue for the treatment of AL amyloidosis for a brief period of time, but centers with experience continued to investigate this approach, particularly as supportive care improved and the experience was gained.

As clinical experience accrued, demonstrating that end-organ function at the time of transplant largely determined early survival during and shortly after the transplant, along with the observation that patients who survived the acute toxicities of transplant showed a very high likelihood of a favorable response, it became clear that selecting appropriate patients for transplant based on organ function, performance status, and risk stratification was essential to optimize outcome from high-dose therapy. Over the past 25 years, the application of risk stratification to patient selection for transplant has translated into decreased acute mortality in published reports of ABMT for AL amyloidosis. Gertz and colleagues published a consensus opinion on the definition of organ involvement and treatment response in AL amyloidosis from the 10th international symposium on amyloid and amyloidosis [7], in 2005. The investigators who participated in writing this report carefully specified criteria for the diagnosis of AL amyloid—as distinct from other potential diagnoses, such as myeloma. They also specified the formal definition of specific organ involvement—for most organs by biopsy documentation but for some organs noninvasive findings (e.g., for definitive lung involvement, classic diffuse interstitial lung disease on CT imaging together with biopsy-proven AL amyloidosis in a different organ). Further, they defined criteria for evaluating treatment response by organ, including definitions of complete response, partial response, stable disease, and progression of the disease. The rigorous application of these types of definitions helped to harmonize patient assessment in the context of data reporting, and analysis of patient responses to ABMT as well as conventional therapies and investigational agents. Formalizing the criteria for diagnosis, organ involvement, and response to treatment, in turn, enhanced the analysis of risk stratification of patients.

Many of the prominent early series of patients with AL amyloidosis treated by ABMT were reviewed in a paper published by Comenzo and Gertz, two leaders in Amyloidosis research and treatment, in the journal *Blood* in the year 2002 [7]. These authors summarized from four single-center clinical trials, totaling 87 patients, and from two multicenter reports, totaling 61 patients. Among the 87 patients reported from the four single-center experiences, transplant-related mortality (TRM) was 16 patients, a rate of 21% at that time. A summation of responses for the four single-center series was a 62% response rate overall. In the two multicenter series summarized by Comenzo and Gertz (Table 1 in their manuscript) TRM was measured as 24 patients out of 61 subjects, for transplant-related mortality of 39% in these two reports, and with overall response rate reported also at 62%.

During the first two decades of the twenty-first century, increasing numbers of centers reported their experiences with a series of AL amyloidosis patients undergoing ABMT, and with increased experience, as well as more refined selection criteria were applied, transplant-related mortality fell over time.

In 2015, D'Souza and her colleagues published an important summary of data compiled by the Center for International Blood and Marrow Transplant Research (CIBMTR) regarding the outcome for autologous transplantation to treat AL amyloidosis. This report analyzed data from 1536 patients with a diagnosis of AL amyloidosis who underwent ABMT at 134 transplant centers between the years 1995 and 2012, as entered into the CIBMTR database [8]. Data from these patients were grouped into three chronologic cohorts—the group of patients transplanted between the years 1995 and 2000; patients transplanted between the years 2001 and 2006; and finally, patients transplanted between the years 2007 and 2012. The median age at transplantation was 56 for the cohort as a whole, with the median age gradually rising in successive chronologic cohorts, with most patients undergoing autologous transplants within 6 months of diagnosis. The underlying plasma cell clone was lambda in 72% of transplant patients. The median melphalan dose was 175 mg/meter square body surface area for the cohort transplanted between 2001 to 2006 but fell to 143 mg/m² body surface area during 2007–2012. The percentage of patients that received antineoplastic therapy prior to transplant was 85% between 2001 and 2006, but the percentage of patients receiving antineoplastic therapy prior to transplant fell to 67% for those transplanted between 2007 and 2012. Early mortality—that is, death by day 30 and by day 100, declined significantly over time. Mortality by day 30 was 11%, and mortality by day 100 was 20%, in the patients transplanted between 1995 and 2000. However, mortality by day 30 fell to 3%, and mortality by day 100 fell to 5%, for the cohort transplanted between the years 2007 and 2012. Consistent with the improved outcome associated with decreased early mortality from transplant over time, overall survival also improved substantially over time. Five-year overall survival was 55% in the cohort of patients transplanted between the years 1995 and 2000. This improved to a 5-year survival of 77% for the cohort transplanted between the years 2007 and 2012. In their discussion, the authors of this paper attributed improvements in outcome both to improvements in supportive care, as well as increasing clinical expertise at managing patients through the transplant process. They also remarked that the best results for ABMT in AL amyloidosis as of that writing came from high-volume transplant centers, and noted that in the data set analyzed, ABMT centers performing fewer than four transplants per year for treatment of AL amyloidosis had higher early mortality rates than centers that performed a number greater than four transplants per year. Multivariate analysis in this study indicated that the presence of cardiac involvement, the presence of poor renal function, the presence of poor performance status (Karnofsky performance status of less than 80%), and use of melphalan conditioning at a dose of less than 180 mg/meter square body surface area—were all associated with worse outcome. **Figure 1** illustrates an approximation of the Kaplan–Meier survival curves for patients in the analysis of the CIBMTR data referenced above.

The conditioning regimen that has become standard over the past quarter-century for myeloma patients undergoing autologous transplant is melphalan as a single agent, at 200 mg/meter square body surface area, given either as a single dose, or divided over 2 consecutive days. Tandon and colleagues from the Mayo Clinic examined their experience with making adjustments to the melphalan dose [9]. In this retrospective analysis of 457 patients, 314 of these—69%—received full-intensity therapy with melphalan given at 200 mg/meter square. Up to 143 patients, that is, 31%, were treated using reduced-intensity therapy, defined as less

Figure 1.
Probability of overall survival after autologous transplantation in AL amyloidosis for three different time periods: European bone marrow transplant registry data (after D’Souza et al, J clinical oncology 2015 [8]).

than 180 mg/meter square; most often, the reduced dose cohort were treated using melphalan at 140 mg/meter square. The authors stated that the conditioning dose of melphalan was adjusted depending on performance status, the patient’s comorbidities, and the presence of renal insufficiency, defined as serum creatinine greater than or equal to 2 mg/dL. In their analysis, patients who received full-intensity therapy were, as expected, overall younger, with better average performance status, and with less multi-organ involvement by amyloidosis and, in especial, less cardiac disease, than patients who received dose reduced melphalan. Progression-free survival was significantly longer in the full-intensity therapy group as compared to the reduced-intensity therapy group, with four-year progression-free survival of 55% for those receiving full-dose therapy, as compared to 31% for those receiving dose reduced melphalan. Overall survival was also significantly longer, reported as 86% overall survival at 4 years for the patients receiving full intensity melphalan, as compared to 54% overall survival at 4 years for the patients who received dose reduced melphalan. To date, there has been relatively little investigation into alternative conditioning regimens. Sanchorawala and colleagues from Boston did report a small pilot study in which bortezomib at a dose of 1 mg/meter square on days minus 6, minus 3, plus 1, and plus 4, was added to the conditioning regimen of melphalan. In this study, melphalan was given at either 200 mg/meter square divided over 2 days—for 8 patients, and melphalan was given at 140 mg/meter square divided over 2 days for 1 patient who was aged over 65. Hematologic responses were achieved in 89% of the patients, with no toxic deaths [10]. No long-term follow-up data were provided. This approach has not been adopted in general, and indeed, single-agent melphalan at 200 mg/meter square remains the conventional dose applied to patients for conditioning in the setting of ABMT for AL amyloidosis.

Allogeneic hematopoietic transplantation has very rarely been performed as therapy of systemic AL amyloidosis [11, 12]. The majority of patients with AL amyloidosis have a low plasma cell burden. Further, there is a very low risk of contamination of peripheral blood hematopoietic progenitor cells by the malignant plasma cell clone. Finally, there is a significantly greater risk of severe complications from allogeneic as compared to autologous transplant. On the basis of these

considerations, allogeneic hematopoietic transplant continues to be applied rarely to the management of systemic AL amyloidosis.

3. Evolution of risk stratification

Clinical prognosis at any point in time for a patient diagnosed with AL amyloidosis correlates, on the one hand, with the biological features of the clone of cells producing the pathogenic immunoglobulin light chain, and, on the other hand, with the damage to the end organs that has resulted from the amyloid deposition. Although the characteristics of the abnormal clone (most often a plasma cell but in a minority of cases a B cell giving rise to an IgM-associated light chain) may correlate with parameters of end-organ damage, it tends to be the measures of end-organ damage that impact the most on risk stratification useful for assessing patients' risk of morbidity and mortality at ABMT. Dittrich and colleagues, from Heidelberg, Germany, recently reviewed the prognosis and staging of AL amyloidosis [13]. Adverse features of the underlying plasma cell clone that are particularly statistically significant include bone marrow plasmacytosis greater than 10% morphologically, and elevation of the involved free light chain, greater than 125 mg/liter in the plasma, especially when greater than 180 mg/liter [14]. Chromosomal abnormalities identified by karyotype or by fluorescent *in situ* hybridization are also of prognostic significance [15].

However, with respect to risk for transplant-related morbidity and mortality, biomarkers of end-organ damage are particularly important to assessing patients as candidates for high-dose therapy. Numerous organ features and biomarkers have been examined, but the most prominent markers relate to cardiac function and renal function, with hepatic and pulmonary function, as well as nutritional status, also becoming important if impaired. The Mayo Clinic group published a cardiac staging system for AL amyloidosis patients in 2004, using the two parameters of (a) elevated circulating serum troponin level as a measure of myocardial cell damage, and (b) elevated N-terminal pro-B type natriuretic peptide (NT-proBNP) level [16]. In this system, patients with high-sensitivity troponin levels greater than 54 pg./microliter, or NT-proBNP greater than 332 ng/liter, but not both, were categorized as stage I, with a median survival of 130 months. Patients with troponin level and NT-proBNP above both thresholds were categorized as Stage III disease and had a median survival of only 10 months. In 2012, the Mayo Clinic group revised their system to expand the grouping to four stages [17], in the process of raising the threshold for the NT-proBNP to greater than 1800 ng/liter and adding the criterion of the difference between the involved free light chain and the uninvolved free light chain (termed Δ FLC) being greater than 180 mg/liter being an adverse prognostic factor. In this staging system, patients with all the adverse factors—stage IV disease—had a median overall survival of only 6 months; those with only the two cardiac adverse parameters had stage III disease with median overall survival of 24 months. Since then, additional staging systems have been proposed for assessing cardiac status, but are variations on the Mayo approach. One means of addressing severe cardiac disease due to amyloid infiltration has been to take selected patients to heart transplantation, and, upon recovery, follow heart transplantation by ABMT. Less dramatic approaches that have been widely applied have included, where appropriate, pre-ABMT implantation of an automated cardiac defibrillator, and use of ventricular support devices in severe heart failure that is expected to improve after ABMT. Cardiac support in patients with AL amyloidosis was recently reviewed in detail by Macedo and colleagues from Brazil [18].

Similarly, staging systems to categorize renal end-organ damage in AL amyloidosis have been developed. Kastritis and colleagues published a staging system for renal disease in this setting [19] using the ratio of 24-hour proteinuria (24-hour UPr) to estimate glomerular filtration rate (e GFR). Patients with a 24-hour UPr/e GFR ratio less than 30 were defined as Stage I renal disease, and none of these patients required renal dialysis at 3 years from staging. Patients with the ratio of 30–99, defined as Stage II, had an 11% rate of requiring renal dialysis at 3 years, and among those with Stage III disease, defined as a ratio of 100 or greater, 46% required renal dialysis at 3 years. It must be noted, however, that ABMT has been performed successfully for AL amyloid patients with end-stage renal failure already requiring renal dialysis pre-transplant. This, of course, requires very careful attention to fluid and electrolyte balance, as well as dosing of medications. Batalini and colleagues reported on the Boston Medical Center experience with 32 AL amyloidosis patients with dialysis-dependent end-stage renal failure who underwent autologous hematopoietic transplants between 1994 and 2016 [20].

Compromised hepatic function obviously can impact medication metabolism, and severe liver dysfunction will also increase morbidity risks associated with high-dose therapy. Markers of hepatic function, including prothrombin time, bilirubin level, and transaminases are critical in assessing the degree of liver dysfunction. Although hepatomegaly and splenomegaly are common in AL amyloidosis, severe liver dysfunction due to amyloid is relatively uncommon [21]. However, hypoalbuminemia is common and may be due to either renal involvement by amyloid resulting in proteinuria with loss of albumin in the urine; or hypoalbuminemia may be due to gut malabsorption due to intestinal tract involvement by amyloidosis—as well as the less likely possibility of impaired hepatic synthesis. If gut malabsorption is a significant issue, and ABMT is a consideration, then temporary parenteral nutrition would appear a reasonable means to support a patient until the production of new amyloid can be stopped through antineoplastic therapy.

Pulmonary involvement by AL amyloidosis is a frequent finding but is often clinically silent. When pulmonary amyloidosis does manifest, it most commonly manifests as diffuse alveolar-septal deposition [22]. This can cause ventilation-perfusion mismatch and shunting physiology requiring supplemental oxygen and may improve after ABMT, although the improvement may not manifest until months after transplant.

Gertz from the Mayo Clinic recently published a review of immunoglobulin light chain amyloidosis, in which, he highlighted general criteria for transplant [23]. In his paper, he described patient characteristics associated with a safe outcome—that is, low transplant-related mortality—including systolic blood pressure above 90 mm Hg; troponin level less than 0.06 ng/mL; age below 70 years, and serum creatinine of less than 1.8 mg/dL. For AL amyloid patients who are not deemed transplant candidates, regimens such as conventional-dose melphalan with corticosteroids, the regimen of cyclophosphamide with bortezomib and dexamethasone (“CyBorD”), and the monoclonal antibody daratumumab were suggested. Indeed, early results from the safety run-in portion of the international, multicenter phase III ANDROMEDA study were recently published [24]. In this study, newly diagnosed AL amyloidosis patients are randomized to either CyBorD or CyBorD with subcutaneous daratumumab. Palladini and colleagues reported their outcome data from 28 patients treated in the context of the safety run-in therapy of the arm consisting of CyBorD plus daratumumab, with the daratumumab administered subcutaneously weekly in cycles 1 and 2, then every 2 weeks during cycles 3–6, and then once every 4 weeks for up to 2 years. Patients included in the analysis received a median of 16 treatment cycles at the time of analysis for publication. No grade 5 treatment-related adverse events occurred. Of the 28 patients, 5 died, of whom

3 had proceeded to transplant. The overall hematologic response rate was 96% in this cohort, with a complete hematologic response of 54%. Thus, the approach of CyBorD with daratumumab appears to be a promising bridge to transplant for patients who are deemed not eligible for ABMT as upfront therapy.

Huang and colleagues at Nanjing University performed a prospective, randomized trial comparing induction therapy using two cycles of bortezomib with dexamethasone followed by ABMT, versus ABMT alone. In this study, 56 patients were enrolled, with 28 patients in each arm [25]. With a median follow up of 28 months, the survival at 24 months after the initiation of treatment was 95% in the group that was treated using induction followed by transplant, versus 69.4% survival at 24 months for the group that received transplant without induction. These investigators stated that their preliminary data suggested that the outcome was superior with induction followed by ABMT as compared to ABMT alone. However, data regarding the nature and the role of induction therapy is evolving rapidly with the introduction of newer treatments, and as of this writing, for patients with adequate organ function as delineated by Gertz above, upfront transplant appears to remain an appropriate approach.

A general application of risk stratification to decision-making regarding ABMT for AL amyloidosis has been incorporated into practice guidelines published by the National Cancer Center Network (NCCN), a consortium of cancer centers in the United States that have the designation of Comprehensive Cancer Center from the National Cancer Institute of the United States federal government. Thought leaders from these institutions have, for several decades, been publishing clinical practice guidelines for the management of the relatively common malignancies. In a recent iteration of these guidelines, labeled “NCCN Guidelines Version 1.2021 Systemic Light Chain Amyloidosis,” the guidelines use the Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements, as published by Kumar, Dispenzieri, Lacy, et al., published in the *Journal of Clinical Oncology* in 2012 (17, **op cit**). These guidelines recommend primary therapy using the combination of daratumumab—in the subcutaneous form—together with the regimen of cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD). This is then followed by ABMT if the patient is deemed appropriate for ABMT. For patients with very small clonal burdens, induction therapy may not be necessary, and ABMT as initial therapy may be the optimal approach (web address: nccnb.org/professionals/physician_gls/pdf/amyloidosis.pdf).

4. Stem cell harvesting

There is a significant body of literature detailing experiences with various approaches to priming for peripheral blood hematopoietic progenitor collection for AL amyloidosis. Due to end-organ damage by the amyloid protein deposition, the morbidity of stem cell collection is significantly higher for patients with AL amyloidosis as compared to patients with multiple myeloma; in one relatively early study, mortality from stem cell collection was as high as 4% of patients [26]. In a recent review paper, Gertz and Schonland summarized nine clinical reports that included analysis of clinical experience with various mobilization approaches [27]. The majority of these reports describe the use of granulocyte-colony stimulating factor (G-CSF) as a single agent (most often 10 mg/kg body weight subcutaneously daily beginning 4–5 days prior to the start of harvesting and continuing until target stem cell collection is obtained, with a goal usually of 5–10 million CD34 cells per kg body weight), with grade 2 or greater toxicities ranging between approximately 4%

and 25%. The most frequent significant toxicity reported is fluid retention, which is attributed to the G-CSF use in the setting of cardiac and/or renal disease. For patients who fail to attain target CD34 cell collection, the protein drug plerixafor—breaks the bond between CXCR-4 and SDF-1 that anchors hematopoietic progenitor cells to the marrow microenvironment—has been used successfully, adding only modestly to reported toxicity. Regimens using chemotherapy agents in addition to recombinant cytokines to stimulate the mobilization of stem cells into the peripheral circulation have been associated with increased morbidity [28].

5. Post-transplant therapy

Investigators at the Ohio State University reported a retrospective analysis of 50 patients with AL amyloidosis who underwent ABMT at that institution. Of this series, 28 patients received post-ABMT maintenance therapy and 22 patients did not. Kaplan–Meier analysis was employed to examine the effect of maintenance versus no maintenance, and found no statistical difference between the groups with respect to either progression-free survival or with respect to overall survival [29]. However, a number of clinical trials have been ongoing to examine the role of post-transplant maintenance therapy. Investigators at Memorial Sloan Kettering Cancer Center have been studying bortezomib with dexamethasone as induction therapy, followed by ABMT, and then followed by maintenance bortezomib with dexamethasone. Preliminary data from this approach has been listed on the Clinical Trials.Gov website for the study. For the 19 patients with AL amyloidosis enrolled, approximately 37% achieved a complete response, with an additional 21% achieving a partial response, and approximately 5% found to have the stable disease; progression of disease was reported in only approximately 5% of patients (clinicaltrials.gov, identifier NCT 01383759). As of this writing, it is too soon to make a definitive statement regarding the role of post-ABMT maintenance therapy, and currently, practices vary between different transplant centers.

6. Future directions

The introduction of new antineoplastic therapies effective in treating plasma cell dyscrasias with novel mechanisms of action, which has occurred over the past two decades—in especial the proteasome inhibitors and more recently monoclonal antibodies—has had a substantial impact on the management approach to multiple myeloma. It is anticipated that just as the landscape has changed for patients with myeloma, changes in the management of patients with systemic AL amyloidosis will follow. However, as is evident from the discussion above, myeloma patients and systemic AL amyloidosis patients are very different clinically, even though they share common biological features. In part because of the relative rarity of systemic AL amyloidosis, and in part because so many patients are diagnosed at a point in time when end-organ dysfunction precludes safe application of ABMT, large, prospective randomized clinical trials will continue to be a challenge for advancing improvements in therapy for this disease. However, much progress has been made in the past quarter-century, and with better recognition of AL amyloidosis and earlier diagnosis, along with new therapeutic modalities, continued improvements in outcome may be anticipated.

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