Educational Review

Re-Examining the Role of High-Dose Chemotherapy in the Treatment of Light Chain Amyloidosis

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INTRODUCTION

Systemic light chain amyloidosis (LCA) is a rare monoclonal B cell disorder characterized by the accumulation of misfolded monoclonal light chain fragments within the heart, kidney, liver, gut, peripheral nerves, and other tissues, resulting in damage to these organs. Median survival is poor (less than 3 years in many series) and most closely associated with the degree of cardiac involvement [1-5]. However, recent progress in the diagnosis, characterization, and management of patients with LCA necessitates thoughtful reassessment of the role of high-dose chemotherapy in the management of this challenging disease. For years, the pace of improvement has been hampered to some degree by the rarity of the condition, lack of good preclinical models, heterogeneity in clinical presentation, and less than enthusiastic support from pharmaceutical companies and national organizations. Accrual to prospective clinical trials, critically important to evaluate several of the newer treatment approaches, has often been sluggish at many centers or trials have not been available. Thus, high-dose chemotherapy and autologous hematopoietic cell transplantation (HCT) continues to be considered a suitable frontline therapy for appropriate LCA patients.

The role of high-dose melphalan and HCT in LCA was initially explored in the early 1990s [6]. Although treatment-related mortality (TRM) was frighteningly high (>30%) in these early experiences, long-term survivors enjoying good quality of life were observed and, eventually, this treatment became an established part of the amyloidosis therapeutic armamentarium more than a decade ago [1,7,8]. Notwithstanding, the only prospective randomized trial completed to date comparing high-dose therapy to conventional chemotherapy failed to demonstrate a benefit for LCA patients who underwent transplantation early in the course of the disease, and even suggested they may do worse, with median overall survival of 22.2 months in the high-dose chemotherapy group and 56.9 months in the group treated conventionally (P = .04) [9]. The trial results were reported in 2007 and fell under heavy criticism because of the extremely high rate of TRM in the group who underwent transplantation (24%) and the inclusion of patients who underwent transplantation at centers with little to no experience using high-dose chemotherapy in patients with LCA [10]. Nevertheless, a landmark analysis with long-term follow-up failed to demonstrate an advantage to high-dose chemotherapy, even in those patients surviving the first 100 days of HCT [10]. Further, a subsequent meta-analysis, also heavily criticized, again failed to demonstrate a benefit to HCT [11,12]. With the advent of immunomodulatory drugs and proteasome inhibitors, hematological response rates and organ function improvements have increased and demand that we question the value of high-dose chemotherapy and HCT, even in less risky patients with LCA, given the availability of effective and potentially less toxic therapies [5,13].

The greatest number of autologous HCT for patients with LCA are performed within the United States [14]. Notwithstanding, the US National Comprehensive Cancer Network 2013 guidelines for treatment of systemic LCA do not make firm recommendations for first line therapy and instead include high-dose chemotherapy as 1 of a number of therapeutic considerations for the management of these patients (all recommendations being category 2a) [15]. They conclude that “the optimal therapy for systemic LCA still remains unknown, the National Comprehensive Cancer Network panel members strongly encourage treatment in the context of a clinical trial when possible.” Unfortunately, most patients are either ineligible for or not offered clinical trials [5,13,16]. So, which patients are appropriate candidates for HCT outside the context of a clinical trial? Should these patients undergo transplantation only at specialized centers with significant experience providing transplantsations for patients with LCA, or is it appropriate for them to undergo HCT at centers that perform fewer than 5 transplantsations for LCA annually? Should there be more stringent guidelines established for selecting appropriate candidates, and should each center performing such transplantations follow established guidelines for all aspects of supportive care, including stem cell mobilization and procurement, chemotherapy administration, and post-
transplantation management? We will address some of these questions here.

Many within the amyloidosis treatment community have questioned the value of high-dose chemotherapy, given the high risk of TRM and in light of the results of the only randomized study [5,13,17]. As mentioned, the French prospective study was believed to be highly flawed by several members of the blood and marrow transplantation community, who may themselves be biased toward the value of high-dose chemotherapy [9,10]. Appropriately, issues were raised about patient selection; the inclusion of high-risk patients with cardiac involvement, who in retrospect should probably have been excluded; the lack of inclusion of biomarkers to predict prognosis; the lack of experience at many of the participating centers; the dose of melphalan used; and the protracted length of time required to complete the study. Many have pointed toward these criticisms to downplay the significance of the study results. In rebuttal, the study authors performed a follow-up landmark analysis that accounted for patients who died early after transplantation [10]. This analysis still failed to show an advantage for patients who had received high-dose melphalan, once again questioning the overall value of melphalan dose escalation. On the positive side, the findings forced the transplantation community to reconsider the salient issues and to better establish guidelines for patient eligibility and supportive care. This has resulted in substantial improvements in the risk of TRM in recent years [18-21]. Thus, it is reasonable to re-examine the critical questions that each center must consider when evaluating the role of high-dose chemotherapy in the treatment of their patients with LCA. Much of the current decision making requires a clear understanding of the goals of therapy, a comprehensive assessment of the extent of disease in any 1 individual, and based on that, the overall prognosis and degree of risk of morbidity and mortality related to the primary therapy chosen [13,17-19,21-24]. An extensive discussion of the pathophysiology of LCA, as well as its diagnosis and management, is beyond the scope of this review, but the reader is referred to several excellent recent reviews covering these topics [3-5,7,13,16,25-32].

WHAT ARE THE PRIMARY GOALS OF THERAPY IN THIS DISEASE?

Systemic therapy designed to destroy the plasma cell clones responsible for the synthesis of immunoglobulin light chain remains the primary approach [1,7,13,20,21,29,33-40]. The goal is to promptly eradiate the misfolded amyloid light chains, resulting in improvement in the function of the involved organ(s). The importance of a good hematological response has been well established over the last several years [13,38]. Hematological response (HR) is considered essential for the establishment of an organ response, although HR does not always translate into organ improvement. Consensus criteria have been developed for the assessment of HR and organ response [37]. The inclusion of the serum-free light chain assay has greatly improved the assessment of HR, as has the use of cardiac biomarkers such as cardiac troponin and NT-proBNP [41,42]. As is the case with multiple myeloma, there is some controversy as to whether a complete HR is necessary for long-term clinical benefit, particularly if organ response is observed and organ dysfunction is stabilized or improved [5,13,16,38,40,43]. Notwithstanding, long-term responses have been seen, particularly in patients achieving a complete response to high-dose chemotherapy [43]. In addition to depth of response, the rapidity of response is also an important factor influencing the likelihood of achieving organ stabilization or improvement.

Achievement of a rapid HR certainly pertains to patients receiving high-dose chemotherapy, but it is also relevant when one considers nontransplantation therapies and the decision to use a regimen containing immunomodulatory agents (eg, thalidomide, lenalidomide, or pomalidomide) versus a proteasome inhibitor (bortezomib, carfilzomib) [5,13,16,18,44-55]. Data suggest HR and even organ responses may be observed more rapidly with regimens incorporating a proteasome inhibitor [5,49,50]. The addition of bortezomib may improve the rapidity of response and is currently being studied in a randomized prospective trial comparing bortezomib added to standard melphalan and dexamethasone [46,51,56,57]. Whether the addition of cyclophosphamide to bortezomib and dexamethasone improves the depth and rapidity of response remains an open question, but many of the best responses have been seen with the so-called CyBord (cyclophosphamide, bortezomib, and dexamethasone) regimen [49,51]. As with multiple myeloma, numerous combinations of novel agents are currently being evaluated in patients who are not considered candidates for HCT, but may also prove effective in patients traditionally considered for high dose chemotherapy as primary treatment.

Older studies failed to establish the benefit of induction chemotherapy before high-dose chemotherapy and HCT in LCA, but given the availability of potentially better induction regimens that work rapidly, the value of both induction and consolidation chemotherapy in the context of high-dose chemotherapy is being revisited in ongoing clinical trials [7,16,58,59]. Most would agree that depth of response influences the potential for prolonged survival and should also translate into an improved quality of life. This remains to be established prospectively. For those who would advocate high-dose chemotherapy, depth of response is the critical factor in establishing an overall benefit in these patients [16,43].

WHAT ROLE HAS PATIENT SELECTION PLAYED IN THE FAVORABLE OUTCOMES OBSERVED AFTER HCT?

Patient selection exerts a profound influence on treatment outcome in virtually any clinical trial setting. Given the very high rates of TRM (particularly within 100 days of transplantation) reported in the early trials, which established a role for high-dose melphalan in the treatment of LCA, it is hard to imagine that the pioneering centers were “cherry picking” the best patients [6,58-61]. Much was learned through these preliminary explorations of high-dose chemotherapy. Early on, and not surprisingly, it became clear that the number and extent of organ involvement, patient age, performance status, and, in particular, the severity of cardiac involvement exerted a heavy influence on the risk of TRM [6,58-61]. Retrospective analyses demonstrated that many of the early deaths were in patients with the most severe cardiac involvement and established the basic tenet that patients with very advanced cardiac involvement should probably not undergo high-dose chemotherapy [1,2,11,20,21,29]. However, even that statement has been questioned by recent data from the Mayo Clinic [7,29,47]. The establishment of the Mayo staging system has provided a universally accepted method for evaluating patient characteristics across centers [24]. The use of cardiac biomarkers (troponin, NT-proBNP) before HCT has provided the most
objective criteria for both patient stratification as well as inclusion and/or exclusion from high-dose chemotherapy. A recent report from Mayo Clinic established that patients with NT-proBNP levels greater than 5000 pg/mL should not undergo HCT given their extremely high risk of TRM [47]. The use of serum biomarkers provides a more objective means to predict a patient’s risk and to compare results across studies rather than number of organs involved, given the potential variability in assessing organ involvement from center to center. Beyond risk of TRM, recent data also suggest that the extent of bone marrow plasma cell involvement heavily influences the likelihood of long-term survival, and patients with greater than 10% marrow plasma cell involvement seem to have worse overall survival [62-64].

The issue of TRM (as high as 30% in some series) becomes even more important now that there are other potentially effective therapies available to these patients [5,7,13]. So, what should be considered an acceptable rate of TRM, at least within the first 100 days of transplantation? Clearly, rates above 10% seem unacceptably high except for certain exceptional situations. It would seem reasonable that rates approaching those observed with other hematological malignancies amenable to autografting (<5%) should be the goal. However, if such stringent criteria are used, the vast majority of patients are unlikely to be candidates for HCT, even at the experienced transplantation centers using well-established supportive care guidelines. It has been estimated that no more than 20% to 30% of all patients diagnosed with primary LCA would be eligible for upfront HCT if the goal is to maintain a low risk of TRM [5,13,16]. From the perspective of this reviewer, the availability of potentially effective conventional therapies necessitates that we accept only a low risk of TRM. Given these concerns, randomized prospective trials comparing HCT with conventional regimens are even more urgently needed than before, but they are unlikely to be performed. For instance, a recent trial in the United Kingdom comparing cyclophosphamide, thalidomide, and dexamethasone to high-dose chemotherapy was closed because of lack of accrual [5]. Whether this was due to the lack of equipoise on this issue or other matters in unclear. In the United States, where the majority of upfront transplantsations are performed, there are currently no plans for a prospective trial comparing high-dose to more conventional chemotherapy. Unfortunately, this leaves both patients and the physicians caring for them in a quandary over the best initial approach. A conservative management approach would be to embark initially on a less toxic, better tolerated conventional regimen first, to be followed by high-dose chemotherapy if certain response goals are not met. This approach has recently been advocated by some, but it could be risky if a patient then misses the opportunity to benefit from high-dose chemotherapy [5]. In the absence of clinical trials, the Mayo Clinic guidelines for selecting transplantation candidates should be adopted by most centers until better treatments are available [47].

IF THE DECISION HAS BEEN MADE TO MOVE FORWARD WITH HIGH-DOSE CHEMOTHERAPY, ARE THERE ESTABLISHED “BEST PRACTICES” FOR THE MANAGEMENT OF THESE PATIENTS? DOES CENTER EXPERIENCE MATTER AND, IF SO, HOW MUCH?

Fortuitously, the centers with the greatest longitudinal experience in providing transplantations to patients with LCA have developed and published guidelines to mitigate the risk of morbidity and mortality throughout the process of stem cell mobilization and procurement and after high-dose chemotherapy [1,2,16,18,29,31,58]. At both the Mayo Clinic and Boston University, TRM has markedly improved over the last several years, based on experience in supporting these patients, as well as on the establishment of better selection criteria [2,43,47]. Typically these go hand in hand. Centers performing fewer than 5 to 10 transplantations annually for amyloidosis are well advised to follow guidelines established by these larger programs. A recent review of registrations to the Center for International Blood and Marrow Transplant Research determined that the majority of centers in the United States that perform transplantations in patients with LCA do so in less than 5 patients annually (Marcelo Pasquini, personal communication). At Ohio State University, where we perform transplantations on no more than 5 LCA patients annually (but perform 80 to 100 multiple myeloma autografts yearly), we have carefully reviewed the Mayo Clinic and Boston University experiences, adopted many of their practices, and have developed our own criteria for supporting patients through stem cell mobilization and procurement, determining the dosage of melphalan, and the use of blood product and growth factor support after peripheral blood stem cell transplantation (PBCT). The outcomes for these patients are continuously reviewed at our site, and guidelines are revised according to outcomes, based on a process of continuous quality improvement. Based on a combination of strict selection criteria and stringent supportive care guidelines, only 1 of 29 LCA patients undergoing PBCT at our center has experienced TRM before day 100 (Yvonne Efebera, unpublished observation).

HOW SHOULD WE MOBILIZE STEM CELLS?

Akin to patients with multiple myeloma, most patients treated in the early days of transplantation for LCA underwent stem cell mobilization following high-dose cyclophosphamide [1,6,9,11,60,61,65,66]. Unfortunately, many patients did not tolerate this approach nearly as well as their myeloma counterparts, primarily because of a high risk of mortality, secondary to cardiac events, infection, or bleeding episodes. Alternative strategies were sought and a shift towards cytokine-based mobilization using granulocyte colony-stimulating factor (G-CSF) appears to have substantially lowered substantially the risk of morbidity and mortality during stem cell mobilization [1,2,21,58]. G-CSF–based mobilization has become the standard method by which hematopoietic-reconstituting cells are obtained from LCA patients. Meticulous attention to volume shifts and other apheresis techniques are critical, as well, as many of these patients have suffered severe complications during the process of leukapheresis. Given that most of these patients have not received prior chemotherapy or, if they have, it has been of limited duration, G-CSF should be adequate to mobilize a sufficient stem cell dose in the majority of these patients. The presence of amyloid deposition within the bone marrow does not appear to adversely affect stem cell mobilization [67]. Plerixafor has been added to G-CSF in a small number of LCA patients, and its use appears to be safe [68]. However, plerixafor administration should probably be reserved for patients failing to mobilize adequately with G-CSF alone. Because the use of tandem transplantation has not been established in patients with LCA, sufficient hematopoietic progenitor cells to support 1 course of high-dose chemotherapy is generally adequate [58,66]. However, given concerns about added toxicity with the routine use of G-CSF post transplantation, it may be wise to procure at least 4 to 5 × 10^6
CD34+ cells/kg in these patients to promote prompt neutrophil recovery in the absence of G-CSF use after HCT. The optimal CD34 dose for infusion following high-dose melphalan in LCA patients has not been well established.

WHAT IS THE APPROPRIATE MELPHALAN DOSE AND SHOULD THAT DOSE BE PATIENT SPECIFIC?

The prospective French randomized trial used melphalan 200 mg/m² as the standard dose, with reduction to 140 mg/m² for older patients and for those with poor cardiac or renal function [9]. Others have advocated for adjustments in the dose of high-dose melphalan, based on the presence or absence of organ involvement and/or age, with doses ranging from 100 mg/m² to 200 mg/m² reported in the published studies [18-20,22]. Given that hematological response may be related to dose received, there is a potential downside with the use of doses reduced to levels lower than typically used in multiple myeloma. This is once again controversial, particularly now that the ultimate benefit of high-dose melphalan in LCA is being questioned. Further, the pharmacology of high-dose melphalan in patients with LCA has not been well studied. In multiple myeloma patients, there are data to suggest that pharmacogenomic factors may significantly influence exposure to high-dose melphalan [69]. At Ohio State University, a pharmacogenomics study in multiple myeloma is ongoing. We hypothesize that there may be important differences in melphalan handling among patients and that toxicity may be related either to peak concentrations achieved or, alternatively, to area under the curve and that, perhaps, melphalan may be better dosed based on measured or predicted pharmacokinetics, similar to dosing for busulfan. This may be even more important in LCA patients, given the high risk of TRM. In this high-risk group of patients, it would be interesting to consider individualized dosing of melphalan based not only on clinical characteristics such as age, renal function, and cardiac reserve, but also based on pharmacogenetics. The value of pursuing this strategy further will ultimately rest with the issue of whether any dose escalation of melphalan is warranted.

The role of other types of high-dose chemotherapy drugs for conditioning, the addition of other drugs, such as bortezomib, to a melphalan-based conditioning regimen, and the use of other approaches, such as total body irradiation, have been reported mainly from single centers with varying degrees of success [46,58,59,70]. Total body irradiation seems excessively toxic in these patients [70]. However, no firm recommendations can be made and it seems that high-dose melphalan alone should remain the baseline conditioning regimen outside the context of a clinical trial.

IS THERE A ROLE FOR CONSOLIDATION AND MAINTENANCE AFTER TRANSPLANTATION, AS THERE IS FOR MULTIPLE MYELOMA?

Depth of response is associated with benefit from high-dose chemotherapy, and data from multiple myeloma patients suggest that depth of response can be improved with both consolidation and maintenance treatment after autograft. Thus, there are currently studies evaluating the use of consolidation and maintenance strategies in LCA patients not achieving complete response after 1 course of high-dose melphalan [5,16,46,71]. Clearly, issues related to tolerability are paramount, but given the availability of immunomodulatory drugs and proteasome inhibitors that have been relatively well tolerated, the question is, indeed, relevant. One study from Memorial Sloan Kettering suggested consolidation with bortezomib was both feasible and effective in this setting [46]. Others have reached similar conclusions [16]. Outside the context of a clinical trial, the use of maintenance treatment, particularly with a drug like lenalidomide, which has been associated with a potentially higher risk of secondary malignancies, should be considered on a case-by-case basis and the pros and cons discussed in detail with the patient [71,72]. There are insufficient data at present to make any firm recommendations regarding maintenance treatment in LCA after high-dose chemotherapy.

HOW MUCH GUIDANCE CAN WE EXPECT FROM ONGOING CLINICAL TRIALS?

It seems as if most manuscripts published on the topic of treatment of systemic LCA incorporate the conclusion that prospective clinical trials are urgently needed. It is certainly difficult to argue with this conclusion, but what is the evidence that sufficient clinical trials are available or that they are relevant to the majority of patients diagnosed with LCA? A recent review of the ClinicalTrials.gov database (performed on September 22, 2013), searching for either phase II or III trials involving patients with systemic LCA, revealed a total of 8 phase II and 2 phase III studies. The pace of progress in this disease may remain slow as a result, particularly given the current NIH funding climate. Unfortunately, a number of prospective trials have had to close because of poor accrual. Whether this is due to study design issues, feasibility, lack of relevance for the majority of LCA patients seen in practice, the advanced nature of disease in many newly diagnosed patients, lack of publicity, or other factors is unclear. However, the dearth of available trials represents a significant impediment toward further progress in the treatment of this very difficult disease. At a minimum, reports of experience with high-dose therapy should include results not only for the patients who had undergone transplantation, but also for those in whom an unsuccessful effort was made to procure cells that could be used for transplantation. The prospective French study accounted for both groups, but many retrospective reports have included results only for patients who underwent transplantation and did not account for the complications associated with unsuccessful stem cell mobilization [5].

PUTTING IT ALL INTO CONTEXT: WHAT IS THE ROLE OF HIGH-DOSE CHEMOTHERAPY IN 2014?

The role of high-dose chemotherapy remains unclear, particularly for those patients with LCA who may be deemed to be at anything more than a low risk for mortality related to high-dose melphalan. It is difficult to discount the fact that many LCA patients have enjoyed prolonged progression-free survival with good quality of life after high-dose chemotherapy and autologous HCT [13,16,43]. Clearly, the majority of patients newly diagnosed with LCA are not candidates for high-dose chemotherapy. Among the estimated 20% to 30% of patients who have a low enough risk of TRM to be considered for this procedure, who are best treated with this approach? Patients should be placed on prospective clinical trials whenever possible. Patients with newly diagnosed LCA should be considered for referral to centers focusing on this disease. When that is not possible, patients should be referred to and placed on LCA-specific clinical trials approved at local/regional NCI-designated cancer centers within the United States, whenever possible. A clinical trial, whether evaluating conventional or high-dose chemotherapy as a strategy, would be preferable to high-dose chemotherapy performed outside of a clinical trial. Clearly not everyone would agree, and
Unfortunately, the reality is that the majority of LCA patients will either not be offered a clinical trial or will not be eligible. For those who would be eligible for a clinical trial but cannot participate or choose not to participate, high-dose chemotherapy should be offered to those patients willing to accept up to 5% to 10% risk of TRM within the first 100 days after transplantation. Such patients should be deemed fit and good candidates based on criteria established at the large referral centers. Preferably, patients would undergo transplantation at centers that perform 5 to 10 or more transplants for this disease annually, although this is admittedly an arbitrary number. Each center willing to offer HCT to a patient with LCA should, if they have not already, adopt well-established criteria for transplantation candidacy and should strongly consider the development of LCA-specific supportive care guidelines within their center for every aspect of the procedure, from stem cell mobilization to supportive care, within the first 3 to 4 months after HCT.

The United States’ blood and marrow transplantation community should consider clarifying the role of PBCT in LCA. The feasibility of a prospective trial supported by the US government, perhaps by the NIH-funded Blood and Marrow Transplant Clinical Trials Network, should be seriously considered. Unfortunately, given the rarity of this disorder and heterogeneity of the patients at diagnosis, together with the low proportion of patients eligible, such a study may not be feasible, particularly if overall survival were chosen as the primary endpoint. Short of that, consistent registration of LCA patients undergoing transplantation at centers within the Center for International Blood and Marrow Transplant Research should be mandatory, and outcomes at individual centers should be scrutinized closely, particularly because many centers perform fewer than five transplantations in these patients annually (Marcelo Pasquini, personal communication). The use of cardiac and other biomarkers to establish candidacy for high-dose chemotherapy should become the standard of care throughout centers and establishment of newer biomarkers and genetic signatures should continue to be pursued.

After more than 20 years of studying the role of high-dose chemotherapy in LCA, much has been learned. We know who should probably not undergo transplantation, and we know that there is certainly a significant fraction of patients who derive long-term benefit from this approach. Better precision in the identification of those LCA patients who derive long-term benefit from high-dose chemotherapy in preference to less toxic therapies should be a major goal in the next decade, as should continued improvement in supportive care, such that LCA patients undergoing HCT do not suffer rates of TRM substantially higher than their counterparts with multiple myeloma.

With the advent of novel therapies, it remains unclear whether high-dose chemotherapy will maintain an established role in the planned upfront therapy of LCA or if its use will be relegated to a treatment for patients who have failed to respond to 1 or a number of more conventional and less toxic therapies. This is conceivable, given the recent development of novel therapies, including antibody treatments and methods to absorb amyloid fibrils, which hold promise for the future [73–76].

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References


