Biol Blood Marrow Transplant 20 (2014) S2–S7

Educational Review

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

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Article history:
Received 11 November 2013
Accepted 11 November 2013

Key Words:
Light chain amyloidosis
Transplantation
Stem cell
Therapy

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 transplantations for patients with LCA, or is it appropriate for them to undergo HCT at centers that perform fewer than 5

DOI of original article: http://dx.doi.org/10.1016/j.bbmt.2013.11.015.
☆ This article is a reprint of a previously published article. For citation purposes, please use the original publication details; Biol Blood Marrow Transplant. 2014;20:14–19.
Financial disclosure: See Acknowledgments on page S6.
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http://dx.doi.org/10.1016/j.bbmt.2013.11.035

transplantations 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 eradicate 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 proteosome 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