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REVIEW ARTICLE

Autologous Stem Cell Transplant in the Era of Bortezomib-Based Induction for AL Amyloidosis – A Single Institution 11 Year Experience

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Abstract:

A single-institution retrospective outcome analysis was performed on a cohort of 52 patients with systemic light-chain amyloidosis comparing bortezomib-based induction versus no induction before autologous stem cell transplantation (ASCT). Thirteen patients underwent ASCT without induction, 33 received bortezomib-based induction, and 6 received non-bortezomib-based induction. Thirty patients received melphalan 200 mg/m², while 22 received dose-reduced melphalan. Treatment-related mortality at 100-days was 3.8%. Overall hematologic (ORR) and organ response rates (OR) in the entire cohort were 85% and 67%, respectively. ORR was 94% in those receiving bortezomib-based induction versus 69% with no induction (p=0.04). Median time to maximum hematologic response post ASCT was significantly shorter with bortezomib-based induction (3 months versus 14 months). Five-year progression-free survival (PFS) and overall survival (OS) in the entire cohort were 50% and 73%, respectively. Between groups there were no statistically significant differences in depth of hematologic response, cardiac or renal response rate, or 5-year PFS or OS. This study supports ASCT, with bortezomib-based induction as a well-tolerated therapy, with higher ORR and shorter time to maximum hematologic response than no induction. Larger-scale multi-center randomized trials would be beneficial to confirm these observations.

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Introduction:

Systemic immunoglobulin light chain (AL) amyloidosis is a monoclonal plasma cell disorder characterized by the deposition of insoluble light (AL) or heavy-chain (AH) fragments into tissues, often resulting in progressive organ dysfunction if left untreated. Although novel agents directly targeting amyloid protein are currently being studied, treatment has historically been directed at suppressing bone marrow plasma cell growth given that these are the source of the pathologic protein.

With few exceptions, patients with AL amyloidosis require systemic treatment at the time of diagnosis including consideration of autologous stem cell transplantation (ASCT), for which eligibility criteria are largely country- and institution-dependent.¹ The combination of high-dose melphalan (HDM) conditioning with ASCT for selected patients has shown considerable success, with upfront ASCT without induction carrying hematologic responses ranging from 32-66% and organ responses ranging from 33-78%.²⁻⁷ Deeper hematologic responses have been associated with longer survival.^{2, 8}

Outcomes of ASCT have improved over time, likely due to advancements and peri-transplant supportive care, as well as improved center experience in patient selection and in managing those with complex medical conditions. Notably, a large retrospective analysis of the Center for International Blood and Marrow Transplant Research (CIBMTR) database, which assessed outcomes of AL amyloidosis patients treated in various time periods, has shown that early post-transplantation mortality and survival have improved in recent years (100-day mortality of 5% and 5-year overall survival of 77% for patients treated from 2007-2012, compared to 100-day mortality of 11% and 5-year overall survival of 61% in 2001-2006).¹ However, patients with cardiac amyloidosis did not share these similar improvements.

Currently, there are no agents approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) for induction prior to ASCT in patients with AL amyloidosis. It therefore remains largely institution-dependent regarding decision-making on proceeding directly to ASCT without induction versus use of front-line therapy (e.g., chemotherapy, immunomodulatory agents, proteasome inhibitors) in an off-label manner for the purposes of improving organ function prior to transplant. One agent that has received considerable attention in this setting is bortezomib, a proteasome inhibitor currently FDA-approved for treatment of multiple myeloma.⁹ Though most efficacy data are largely limited to case series, bortezomib appears to be active in patients with AL amyloidosis, and has received consideration in the setting of induction, consolidation, and as stand-alone therapy for those ineligible for transplant or with relapsed disease.¹⁰

Our group previously published a retrospective analysis of 31 patients comparing bortezomib-based induction versus no induction prior to ASCT.¹¹ This preliminary analysis showed that compared to no induction, bortezomib-based induction was associated with higher hematologic, organ, and cardiac response rates with shorter time to maximum hematologic response (though testing for statistical significance was not performed due to sample size). Here we report an update, with an increase in sample size to 52 patients and with a long-term follow-up extending to 11 years.

Subjects and Methods:

This study was designed as a retrospective cohort analysis that was conducted at a single tertiary care academic medical center (Oregon Health & Science University). Prior to data collection, this study received institutional review board approval. All patients with biopsy-confirmed systemic immunoglobulin AL amyloidosis who received HDM + ASCT at Oregon Health & Science University (OHSU) from 2006 to 2017 were included (n = 52).

All patients had a detectable monoclonal protein in the serum and/or urine. Amyloidosis was detected on organ or bone marrow biopsy specimens by positive Congo red or toluidine blue staining, and then confirmed histologically via immunohistochemical staining or mass spectroscopy (Mayo Clinic Laboratories, 200 1st Street SW, Rochester, MN 55905).

Institutional eligibility criteria for performing HDM + ASCT for AL amyloidosis patients included: biopsy-proven AL amyloid, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , left ventricular ejection fraction $\geq 45\%$, New York Heart Association class I or II, Mayo clinic cardiac biomarker criteria stage I or II, carbon monoxide diffusing capacity $>50\%$, and serum creatinine ≤ 3.0 mg/dL unless receiving dialysis. There was no upper age limit.

Patients received melphalan 200 mg/m^2 or dose-reduced melphalan ($100\text{--}140 \text{ mg/m}^2$) for higher-risk patients: 140 mg/m^2 was provided for those ≥ 70 years of age, NYHA class $\geq \text{II}$ heart failure, serum creatinine >2.0 mg/dL or dialysis dependence, or ECOG score of 2; 100 mg/m^2 was provided for those with NYHA class III heart failure. HDM was administered over 2 days (day -2 and -1) in divided dose in the setting of oral cryotherapy. Peripheral blood stem cells were then mobilized with granulocyte colony-stimulating factor (G-CSF) while monitoring for toxicity. If there was predicted lower stem cell yield with G-CSF alone, plerixafor was added based on institutional protocol.¹²

Prior to ASCT, those receiving bortezomib induction could have received one of several bortezomib-containing regimens, including (but not limited to) bortezomib with dexamethasone (VD), bortezomib with lenalidomide and dexamethasone (RVD), or bortezomib with cyclophosphamide and dexamethasone (CyBorD). VD treatment schedules were: IV bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 or days 1, 8, and 15 with oral dexamethasone 20 to 40 mg on each day of bortezomib on 21-day cycles; or subcutaneous bortezomib 1.5 mg/m^2 on days 1, 8, and 15 with oral dexamethasone 20 to 40 mg on each day of bortezomib on 28-day cycles.¹³ The RVD treatment schedule was lenalidomide 15 to 25 mg orally on days 1-21; bortezomib 1.3 to 1.5 mg/m^2 on days 1, 8, 15, 22, with oral dexamethasone 20 to 40 mg with each dose of bortezomib. The CyBorD treatment schedule was subcutaneous bortezomib 1.5 mg/m^2 , oral cyclophosphamide 300 mg/m^2 , oral dexamethasone 40 mg on days 1, 8, and 15 on 28-day cycles.¹⁴ Assessment of hematologic and organ involvement, response, and progression were based on consensus criteria reported in the 10th International Symposium on Amyloid and Amyloidosis and the updated criteria from the Roundtable on Clinical Research in Immunoglobulin Light-Chain Amyloidosis.¹⁵⁻¹⁷ Complete hematologic response (CR) was defined as normalization of the free light chains levels and ratio, with negative serum and urine immunofixation. Very good partial response (VGPR) was defined as a reduction in the difference between involved and uninvolved free light chain (dFLC) to $<40 \text{ mg/L}$. Partial response (PR) was defined as a greater than 50% reduction in the dFLC. No

response (NR) was defined as less than a PR but without progressive disease. Organ response was evaluated on the basis of improvement of one or more affected organs. Only one parameter was required to satisfy the organ response criteria, and the response needed to be maintained for a minimum of 3 months to be considered valid. Renal response required a 30% reduction in 24-hour urine protein excretion (at least 0.5 g/d) with stable creatinine. Cardiac response required one of (1) improvement by 1 NYHA classes if baseline class 2 or 2 NYHA classes if baseline class 3 or 4 without an increase in diuretic use; (2) NT-proBNP improvement by >30% and >300 ng/L decrease if baseline NT-proBNP level $\geq$ 650 ng/L. Hepatic response required either (1) 50% decrease in (or normalization of) an initially elevated alkaline phosphatase level or (2) reduction in the size of the liver by at least 2 cm by radiographic determination. A neurologic response was defined as either a reduction in the Neuropathy Impairment Score (NIS) by 10 points, Gastrointestinal tract improvement was defined as reduction of diarrhea to 50% of previous movements per day, or decrease in fecal fat excretion by 50%.

Statistical Analysis

Data analysis was performed comparing patients who received a bortezomib-containing induction regimen versus no induction prior to ASCT. Categorical data for both groups were analyzed by using a two-tailed Fisher exact test. A Student t test was used for continuous data. Hematologic response rate (ORR) was defined as the percentage of patients having a partial hematologic response or greater. Organ response rate (OR) was defined as the percentage of patients who had a response of *any* involved organ per consensus criteria. Progression-free survival (PFS) was defined as the time from day 0 of ASCT to the date of relapse or progression of disease or death from any cause; observation was censored at the date of last follow-up for patients alive at last contact. Overall survival (OS) was defined as the time from day 0 of ASCT to death from any cause; observation was censored at the date of last follow-up for patients alive without relapse/progression of disease at last contact. These were estimated using Kaplan-Meier analysis. Survival curves were compared using log-rank analysis. Prism 3.02 statistical software was used for statistical analysis.

Results:

Clinical Characteristics

Baseline characteristics, including disease features and organ involvement, are shown in Table 1. A total of 52 patients with systemic AL amyloidosis who underwent ASCT were identified between January 1, 2005 and December 31, 2017. Thirty-two patients underwent ASCT in the recent years of 2005-2012, the time period of our original study. Twenty additional patients were treated in the years of 2013-2017. Median patient age at the time of transplant was 61.5 years (range 41-72 years). Renal involvement was the most common organ involved (31 patients, 59%), followed by cardiac (23 patients, 43%), and peripheral nerve (9 patients, 17%). Thirty-one patients (60%) had involvement of multiple organs; 14 patients (27%) had involvement of three or more organs. Thirty patients (58%) received a melphalan dose of 200 mg/m² prior to ASCT, whereas 22 patients (42%) required dose-reduction.

Table 1. Baseline characteristics of 52 patients with AL amyloidosis before autologous stem cell transplantation

Characteristic	Value
Age at Transplant, Mean Years (SD)	61.0 (7.2)
Sex, n (%)	
Male	31 (58)
Female	22 (42)
Hematopoietic Cell Transplant Co-Morbidity Index, Mean Score (SD)	3.1 (2.2)
Karnofsky Performance Status, Mean Score (SD)	83.3 (9.0)
Light Chain Type, n (%)	
Kappa light chain	15 (29)
Lambda light chain	37 (71)
Organ Involvement, n (%)	
Single organ	21 (40)
Two organs	17 (33)
Three or more organs	14 (27)
Cardiac	23 (43)
Renal	31 (59)
Gastrointestinal	11 (21)
Peripheral neuropathy	9 (17)
Liver	8 (15)
Autonomic neuropathy	5 (09)
Skin	3 (06)
Macroglossia	2 (04)
Melphalan Dose Received, n (%)	
200 mg/m ²	30 (58)
140 mg/m ²	18 (34)
100 mg/m ²	4 (08)

Of the 52 total patients, 13 proceeded directly to ASCT after diagnosis without induction, whereas 33 received a bortezomib-based induction regimen (increased from 12 in our previous study, reflecting our institutional commitment to change of practice), and 6 received a non-bortezomib based form of induction treatment. All patients in the newer cohort (i.e., treated from 2013 to 2017) received bortezomib induction. In total, 18 patients received CyBorD, 15 patients received VD, and 9 patients received RVD.

Patients initially transplant ineligible due to advanced cardiac involvement or poor performance status

At the time of diagnosis, pre bortezomib induction, 4 subjects were Mayo clinic cardiac stage III at diagnosis, and improved to stage II, 2 subjects were NYHA stage III (2) improved to stage I (1)

and II (2) and a further 3 subjects had an ECOG PS of 3 at diagnosis, improved to 2 (2) and 1 (1) rendering them transplant eligible. Overall 9 out of 33 subjects, deemed transplant ineligible prior to bortezomib induction (%) became eligible for transplant due to improvement in these factors.

Hematologic and Organ Responses

The overall hematologic (ORR) and organ response rates (OR) at 1-year post-ASCT in the entire cohort of 52 patients were 85% and 67%, respectively (Table 2). Forty percent of patients achieved a CR, 27% VGPR, 15% PR, 6% stable disease (SD), and 8% progressive disease (PD). While all patients in the newer cohort received bortezomib-containing induction regimens, response rates in the early patient cohort (2005-2012) were largely comparable to those managed more recently (2013-2017).

Table 2. Hematologic (ORR) and organ response (OR) rates. Not shown are 6 patients who received non-bortezomib-based induction. CR = complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; PD = progressive disease

	Total Cohort, n (%)	Bortezomib Induction, n (%)	No-Induction, n (%)	P-Value
2005–2012 Cohort	N = 32	N = 13	N = 13	
ORR	25 (78)	12 (92)	9 (69)	
CR	14 (44)	5 (38)	6 (46)	
VGPR	6 (19)	4 (31)	2 (15)	
PR	5 (16)	3 (23)	1 (08)	
SD	2 (06)	1 (08)	0	
PD	4 (13)	0	3 (23)	
Unknown	1	0	1	
2013–2017 Cohort	N = 20	N = 20		
ORR	19 (95)	19 (95)	n/a	
CR	7 (35)	7 (35)	n/a	
VGPR	9 (45)	9 (45)	n/a	
PR	3 (15)	3 (15)	n/a	
SD	1 (05)	1 (05)	n/a	
PD	0	0	n/a	
Total Cohort	N = 52	N = 33	N = 13	
ORR	44 (85)	31 (94)	9 (69)	0.04

CR	21 (40)	12 (36)	6 (46)	
VGPR	14 (27)	13 (39)	2 (15)	
PR	8 (15)	6 (18)	1 (08)	
SD	3 (06)	2 (06)	0	
PD	4 (08)	0	3 (23)	
OR	33/49 (67)	23/30 (77)	7/13 (54)	0.16
Cardiac	13/21 (62)	10/14 (71)	3/7 (43)	0.24
Renal	18/27 (67)	13/18 (72)	5/9 (56)	0.68

ORR at 1-year post-ASCT was 94% and 69%, respectively ($p=0.04$ in patients who received bortezomib induction vs. no induction). In the 33 patients who received bortezomib-containing induction, ORR was 85% prior to ASCT, and increased to 94% post-ASCT. The median time to maximum hematologic response post -ASCT was significantly shorter with bortezomib induction compared to no induction (3 months vs. 14 months). Twenty-five (76%) patients receiving bortezomib induction had a response of VGPR or CR post-transplant compared to 8 (62%) patients receiving no-induction ($p=0.46$).

In the entire cohort, organ-specific responses included 13 cardiac, 18 renal, 4 gastrointestinal, 4 hepatic, and 3 neurologic. OR was 77% in the group that received bortezomib induction compared to 54% in those with no induction ($p=0.16$). The cardiac response rate for the entire cohort was 62.0%, with a rate of 71% in those pre-treated with bortezomib versus 43% in those who did not receive induction therapy ($p=0.24$). Renal response rates were 72% and 56% in those receiving bortezomib induction vs. no induction, respectively ($p=0.68$).

Early (Day 100) Mortality

Two patients died within 100 days after ASCT (3.8% of the overall study population), all occurring in the 2005-2012 cohort in those who received no induction. One patient died early post-ASCT due to exsanguination secondary to spontaneous rupture of an AL-involved spleen. The second patient, who had cardiac involvement, died due to complications of congestive heart failure. No mortalities occurred during stem cell mobilization.

Survival

With a median follow-up of 2.92 years, 5-year PFS and OS in the entire cohort were 50% and 73%, respectively (Figure 1). In those with cardiac involvement, these rates were 59% and 83%, respectively. The median PFS time for the entire study population was 5.8 years, whereas the median OS has not yet been reached.

Figure 1. Overall survival (OS) and progression-free survival (PFS) in the total study population (n=52).

One-, 5-, and 10-year OS for the bortezomib group were 96.9%, 85.9%, and 85.9% respectively (Figure 2), compared to 76.9% ($p=0.03$ compared to bortezomib at 1-year), 59.8% ($p=0.11$), and 59.8% ($p=0.11$), respectively. Comparing bortezomib-based induction versus no induction (Figure 3), PFS at 1-year was 87.0% and 69.2%, respectively ($p=0.06$), and at both 5-years and 10-years was 58.8% and 43.3%, respectively ($p=0.57\%$). In those with cardiac involvement, 5-year OS in the bortezomib-induction group was 86% compared to 50% in those who received no induction ($p=0.17$, Figure 4); 5-year PFS was 50.6% compared to 37.5%, respectively ($p=0.61$, Figure 5). For all survival outcomes assessed, 5-year survival rates (and therefore p-values) were identical to those at the 10-year timepoint.

Figure 2. Overall survival (OS) in those receiving bortezomib induction compared to no induction.

Figure 3. Progression-free survival (PFS) in those receiving bortezomib induction compared to no induction.

Figure 4. Overall survival (OS) in those with cardiac involvement comparing bortezomib induction to no induction.

Figure 5. Progression-free survival (PFS) in those with cardiac involvement comparing bortezomib induction to no induction

Two patients died late (greater than 6-months post-ASCT); attribution of cause of death were end stage heart failure and progressive nephrotic syndrome and renal failure.

Discussion:

Routine use of induction therapy prior to ASCT for patients with AL was still relatively rare at the time of our preliminary analysis, with a retrospective study of a single institution reporting 77% of patients not receiving induction.¹⁸ Having shown efficacy in multiple myeloma,^{19, 20} bortezomib-based treatment for AL was receiving consideration for induction, consolidation, and as stand-alone therapy for those ineligible for transplant or with relapsed disease. Specifically, small retrospective analyses of single-agent bortezomib and CyBorD, as well as a prospective analysis of VD induction had shown rapid and high rates of hematologic response.^{14, 21, 22} Our initial single-institution analysis of 31 patients showed that bortezomib-based induction was well-tolerated and associated with higher hematologic and organ responses compared to no-induction (though comparative analyses for statistical significance were not performed given the small sample size).¹¹

Recently, there has been an increasing awareness of the value of bortezomib-based induction for the treatment of systemic AL amyloidosis. However, likely attributed to the rarity of disease and inherent limitations in sample size, data continues to be largely limited to small retrospective and prospective case series. These series have generally yielded favorable results in the setting of planned induction prior to transplant, in patients deemed ineligible for transplant, and in relapsed disease.^{10, 13, 23-28}

Additionally, several comparative studies have also reported favorable outcomes with bortezomib-based induction. A 2014 matched case-control study of 174 newly diagnosed patients (many with advanced cardiac involvement) comparing frontline bortezomib/melphalan/dexamethasone (BMDex) with melphalan/dexamethasone (MDex) showed higher rate of CR with BMDex. There was no difference in overall survival between the groups in the overall population, however there was a survival advantage with BMDex in patients with lower-risk cardiac involvement.²⁹ Another 2014 matched case-control study by Venner et al comparing 69 patients treated with frontline CyBorD with 69 patients treated with cyclophosphamide/thalidomide/dexamethasone (CTD) showed higher rate of CR and more prolonged PFS with CyBorD, but no difference in 1-year OS, even when stratifying by degree of cardiac involvement.³⁰ Sidana et al assessed transplant-ineligible patients and showed higher hematologic response rates (with higher rates of early VGPR at 3 and 6 months) with bortezomib-based induction compared with no-induction, with faster cardiac response and lower relapse rate, but no difference in overall survival.³¹ Most recently, in 2016, Kastiris et al presented the preliminary results of the first phase III randomized trial of 110 patients with untreated AL ineligible for transplant comparing bortezomib/melphalan/dexamethasone (BMDex) vs. melphalan/dexamethasone alone; BMDex showed a more frequent and deeper hematologic response rate, with equivalent renal and cardiac response, but no difference in survival.³²

Our current analysis continues to support bortezomib-based induction in patients with AL, with significantly higher hematologic response rate and shorter times to maximum hematologic response compared to no induction prior to ASCT. Importantly, with bortezomib pre-ASCT treatment, several patients initially ineligible for transplant ultimately became ASCT-eligible, further supporting the benefits of this therapy in this population, particularly given the excellent long-term survival benefit associated with ASCT alone.^{2, 33} A limitation of our study is that it does not include those that initiated bortezomib and did not reach ASCT. An intent-to treat prospective analysis would undoubtedly result in more balanced results, and less biased data. In our subjects, bortezomib induction was well-tolerated, with all cases of early mortality (before day 100 of ASCT) occurring in transplant patients with high disease burden who did not receive pre-transplant disease burden reduction. This benefit was seen despite 43% having cardiac involvement and over 25% of our population having amyloid involvement of 3 or more organs, both of which are considered by some to be a contraindication to ASCT. No cases of early mortality were observed in our recent cohort, which may be attributed to improvements in peri-transplant care in recent years, but also may reflect the improved performance status achieved and the debulking therapy administered.¹

Although hematologic response rates were more favorable with bortezomib-based induction, the depth of hematologic response, organ response, cardiac and renal response, PFS, and OS did not reach statistical significance, but these results are likely limited by sample size. However as the population matures and responses are sustained, these favorable rates could evolve to statistical significance. Nonetheless, previous studies have shown that attaining hematologic response (even partial response) is associated with high organ response rates and improved survival.³⁴⁻³⁶ Therefore, a primary goal of therapy is to reach hematologic response (an outcome improved with bortezomib-based induction in this study), as the elimination of pathologic monoclonal protein and plasma cell clone may facilitate reversal of organ damage and dysfunction.

Despite the limitations of our small retrospective analysis, our results appear comparable to other transplant center reports, showing that bortezomib-based induction is well-tolerated and associated with frequent and rapid hematologic responses. These findings therefore continue to support the emerging roles for bortezomib-based induction regimens for the purposes of improving response and even increasing eligibility for patients to safely undergo HDM + ASCT. Larger scale analyses in the form of prospective multi-center trials would be beneficial to further study these roles.

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Conflict of interest:

The authors have no conflicts of interest.

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