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Toxicities and Long Term Survival After Autologous Hematopoietic Stem Cell Transplantation for Older Patients with Relapsed/Refractory Hodgkin Lymphoma

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Abstract

High Dose Therapy (HDT) with autologous Hematopoietic Stem Cell Transplant (HCT) is the standard of care for younger patients with relapsed or refractory classical Hodgkin Lymphoma (HL). The safety and efficacy of HDT-HCT in older HL patients is not well studied. We present the outcomes of 42 patients over age 50 at the time of HCT treated between 1995-2013 who had a median age-adjusted Hematopoietic Transplant Comorbidity Index (HCT-CI) of 3 (range, 1-9). Grade ≥2 toxicities through day 100 after HCT were assessed by chart abstraction and graded according to CTCAE version 4. Event Free Survival (EFS) and Overall Survival (OS) were calculated from the time of transplant. Gastrointestinal side effects were the most-common non-hematologic toxicity and were seen in 98% (81% grade ≥3). Neutrophil engraftment occurred at a median of 10 days (range 7-12). Median length of stay was 24 days (17-38). There was one non-relapse death by 100 days after HCT. With a median follow-up among survivors of 7.4 years, median EFS and OS were not reached, and the 5-year EFS and OS were 66% and 70%, respectively. These results suggest that the HDT-HCT is tolerable and efficacious in older HL patients and should therefore be considered in the appropriate clinical setting.

Introduction

Hodgkin Lymphoma (HL) has a distinctive bimodal distribution with patients over age 60 accounting for approximately 20% of cases annually [1]. Prognosis for these patients has been shown to be disproportionately worse than their younger counterparts [2-4]. At diagnosis, older patients often present with more adverse prognostic factors such as B-symptoms and lower performance status, and they are more likely to experience toxicities during first-line chemotherapy that require dose reduction or early treatment discontinuation [2-6]. Modern studies have found cumulative 5-year Overall Survival (OS) rates of 58-80% depending on stage, with

51% of deaths due to HL in patents over the age of 65, [2-8].

Regardless of age, up to 90% of patients will achieve a complete remission to first line treatment with current treatment strategies, but approximately 20% will have primary refractory disease or relapse after a disease-free interval [9]. For the younger patients who respond to salvage therapy, high-dose therapy with autologous Hematopoietic Stem Cell Transplant (HDT-HCT) has been studied extensively and is the standard of care, with a 3-year Event Free Survival (EFS) of approximately 50% [9-11]. On the other hand, the prognosis of older patients with primary refractory or relapsed disease is poor, with a median survival of less than a year when treated with chemotherapy alone [4].

Despite this inferior outcome, there is no consensus on the treatment of relapsed/refractory disease in the older patient population, and there are reservations about more aggressive therapy due to comorbidities and the risk of toxicities. One study evaluating HCT in 15 patients over age 60 found a similar Progression Free (PFS) and OS when compared to younger patients [12], but more extensive data are not available to guide decision making. We therefore aimed to systematically evaluate toxicities and outcomes in patients over the age of 50 treated with HCT at our center over the past 20 years.

Patients and Methods

Consecutive patients ≥age 50 treated with HCT between January 1, 1995 and August 1, 2013 at Memorial Sloan Kettering Cancer Center (MSKCC) were identified from the institutional database. The majority of patients had biopsy-proven relapsed or refractory disease. Patients were included regardless of initial therapy, which included Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD), Stanford V, or radiotherapy alone for localized disease. Salvage therapy during this time was primarily Ifosfamide, Carboplatin, and Etoposide (ICE)-based; partial responses were routinely further debulked prior to consolidation gemcitabine-based therapy. Patients who failed to have at least a partial response to salvage chemotherapy were not offered consolidation, and are therefore not included in this study. Conditioning prior to transplant also varied during this time period. For patients who were previously irradiated or with advanced-stage disease at relapse, chemotherapy-only condition regimens (either Cyclophosphamide, Carmustine, and Etoposide (CBV) Or Carmustine, Etoposide, Cytarabine, And Melphalan (BEAM)) were the most common regimens. Previously unirradiated patients with nodal disease routinely received combined-modality conditioning regimens (either total lymphoid irradiation and high-dose cyclophosphamide and etoposide or pre-transplant involved Field Radiotherapy (IFRT) plus CBV or BEAM). A waiver of authorization to carry out this analysis was approved by our Institutional Review Board.

The age-adjusted Hematopoietic Cell Transplantation-Comorbidity Index (aaHCT-CI) was calculated for all patients 13. A retrospective chart review was conducted to collect grade ≥2 toxicities through day 100 after HCT according to the CTCAE 4.0. These were then grouped into organ systems for descriptive purposes. Neutrophil engraftment was defined as first day of three consecutive days of an absolute neutrophil count over 500 x10^6/Liter. Disease response was determined by the criteria in use at the time of treatment and abstracted from the medical chart. Data-cut off for follow-up was December 1, 2016.

Statistical Methods

Toxicities through day 100 were analyzed using descriptive statistics. EFS was defined as the time from transplant to disease progression, death, or last follow-up, while OS was the time from transplant to death or last follow-up. EFS and OS were estimated by the Kaplan-Meier method with median, 1-, 3-, and 5-year survival estimates and 95% confidence intervals compared by the log rank test. One-hundred-day Non-Relapse Mortality (NRM) after HCT was calculated using cumulative incidence functions where relapse was treated as a competing event. EFS, OS, and NRM were also compared between patients with aaHCT-CI 1-2 versus ≥3.

Results

Patient Characteristics and Pre-Transplant Therapy

Patient characteristics for the 42 patients over age 50 who underwent HCT for relapsed or refractory classical Hodgkin lymphoma between 1995-2013 are described in (Table 1). The median age was 55 (range 50-66), with 10 patients (24%) over age 60. The most common histological subtype was nodular sclerosis classical HL (69%). The majority of patients received front-line ABVD chemotherapy (69%) with a median response duration of 8.5 months. Thirty-eight percent had primary refractory disease. At the time of confirmation of relapse or refractory disease, the majority had early stage disease without B-symptoms.

All patients received salvage chemotherapy and had chemosensitive disease prior to proceeding with HCT. Most patients (79%) received ICE-based therapy, while 2 patients received single agent brentuximab. Six patients required third-line therapy with gemcitabine-based chemotherapy prior to consolidation. Complete Responses (CR) were seen in 32 patients (67%), with the rest achieving a Partial Response (PR), prior to transplant.

CBV was used as conditioning for 18 patients (43%), and 6 (14%) received BEAM. The remaining 16 patients (38%) were treated with TLI, cyclophosphamide and etoposide. IFRT was incorporated into 55% of patients' treatment and was given in addition to TLI in cases of localized disease. A median of 6 x10^6 CD34+ cells/kg were re-infused (range 1.9-13.3).

Patient Characteristics	# Pts (%)
Age, median (range)	55 (50-66)
Gender	
Female	21 (50)
Histology	
Nodular Sclerosis	29 (69)
Mixed Cellularity	4 (10)
Other, NOS	9 (21)
First-Line Therapy	
ABVD	29 (69)
Other Chemo	9 (21)
RT alone	4 (10)
Chemo-RT	13 (31)
First Line Response Duration	
<6 months	16 (38)
6-12 months	9 (21)
>12 months	17 (41)
Reason for Salvage Therapy	
Primary Refractory	16 (38)
Relapsed	26 (62)
Stage at Salvage	
I-II	24 (57)
III-IV	18 (43)
B-Symptoms at Salvage	
Present	11 (26)
Pre-HCT Salvage Treatment	
ICE	33 (79)
ICE + Additional Salvage Chemo	6 (14)
Other Therapy	3 (7)
Conditioning Regimen	
CBV	18 (43)
CV + TLI	17 (40)
Other	7 (17)

HCT, autologous Hematopoietic Stem Cell Transplant; RT, Radiation Therapy; ICE, Ifosfamide, Carboplatin, Etoposide; CBV, Cytarabine, Carmustine, Etoposide; CV, Cytarabine, Etoposide; TLI, Total Lymphoid Irradiation.

Table 1: Pre-HCT Patient Characteristics.

Post-Transplant Course

The median length of stay (LOS) during the HCT admission was 24 days (range, 17-38). Four patients required intensive care unit (ICU) transfers for median of 13 days (range, 4-18). The median time to neutrophil engraftment was 10 days (range, 7-12), while median time to platelet count >50,000/Liter was 18 days (range, 10-182). Nine patients (22%) had delayed platelet engraftment, with platelet counts continuing below 50,000/Liter at day 30. Patients required a median of 3 (range, 0-14) packed red blood cell and 8 (range, 1-31) platelet transfusions during the HCT admission. Nine patients (22%) required readmission within 100 days of transplant with a median LOS of 5 days (range, 1-24).

Toxicities

A summary of the ≥ grade 2 toxicities through day 100 is presented in (Table 2). Gastrointestinal toxicities were the most frequent, with 41 patients (98%) experiencing at least moderate mucositis, nausea, vomiting, and/or diarrhea. Patient Controlled Anesthesia (PCA) was required for 33 patients (79%). Grade 3 liver function test abnormalities were seen in 14%, and 2 patients (5%) had small bowel obstruction. Infections requiring intravenous (IV) antibiotic treatment occurred in 40 patients (95%) and were primarily bacteremias and pneumonias, though 14 patients had febrile neutropenia without an identified source. Grade ≥2 pulmonary toxicities were found in 40% of patients, with grade ≥3 toxicities including chemotherapy and radiation therapy-related dysfunction requiring oxygen supplementation (9.5%), hypoxia requiring intubation (7%), and pulmonary embolism (7%). Grade ≥2 cardiac issues included symptomatic atrial fibrillation (10%), pericardial effusions (5%), and systolic heart failure (2%). Hematologic toxicities (primarily cytopenias) were as expected after HCT, with 39 patients (93%) experiencing grade 3 anemia with hemoglobin <8 g/deciliter. Five (12%) patients experienced ≥grade 4 toxicities including intubation, renal failure (5%), and neurologic complications (2%).

Toxicities	≥Grade 2 N (%)	Grade 3 N (%)	Grade ≥4 N (%)
Gastrointestinal	41 (98)		
Mucositis requiring PCA	33 (79)	33 (79)	0
Abnormal LFTs	15 (36)	6 (14)	0
Diarrhea	27 (64)	6 (14)	0
Nausea/Vomiting	21 (50)	2 (5)	0
Colitis	4 (10)	4 (10)	0
Bowel Obstruction	2 (5)	2 (5)	
Cardiac	10 (24)	2 (5)	1 (2)
Pulmonary	17 (40)		
Chemo/XRT induced	5 (12)	2 (5)	0
Dyspnea/Wheezing needing O2	4 (10)	4 (10)	
Hypoxia Requiring Intubation	3 (7)	0	3 (7)
Inflammation Requiring Bronchoscopy/Thoroscopy	4 (10)	0	0
Pulmonary Embolism	3 (7)	3 (7)	0
Renal	5 (12)		
Renal Insufficiency/Failure	4 (10)	1 (2)	2 (5)
Neurologic	8 (19)	2 (5)	1 (2)
Dermatologic	5 (12)		
Treatment-Related Rash	4 (10)	1 (2)	0
Hematologic	39 (93)	39 (93)	0
Infectious Disease	18 (43)		
Bacteremia	16 (38)	11 (26)	2 (5)
Pneumonia treated w/IV Antibiotics	6 (14)	5 (12)	1 (2)
PCA, patient controlled analgesia; LFTs, liver function tests; IV, intravenous.			

Table 2: Post-HCT toxicities up to day 100.

Outcomes

With a median follow-up among survivors of 7.4 years, median EFS and OS were not reached (Figure 1). The majorities of relapses occurred within the first year after HCT, making the 1-,3-, and 5-year EFS rates 74% (95% CI, 62-88%), 74% (95% CI, 62-88%), and 66% (95% CI, 53-82%), respectively. Furthermore, the 1-, 3-, and 5-year OS rates were 88% (95% CI, 79-98%), 76% (95% CI, 64-90%), and 70% (57-86%), respectively. One patient died of an embolic stroke and multi-organ failure prior to day 100, making the 100-day NRM 8%. Thirteen additional patients died during the follow-up period with causes of death including progression of disease (5), second primary malignancy [non-Hodgkin lymphoma (2), myelodysplastic syndrome (1), and metastatic lung cancer (1)], pulmonary fibrosis/interstitial lung disease (2), progressive multifocal leukoencephalopathy (1), and complications of a subsequent allogeneic transplant (1).

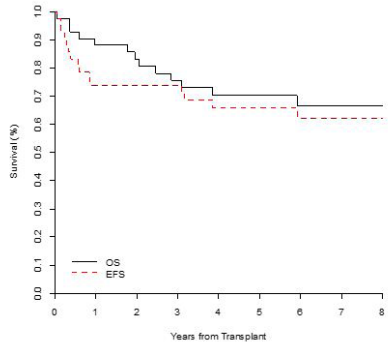
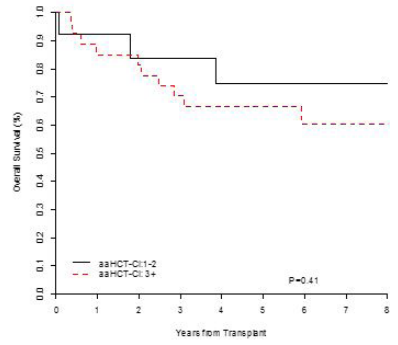
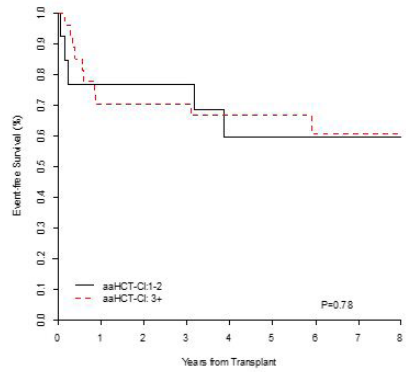


Figure 1: Overall and Event-Free Survival After HCT.

To analyze the impact of comorbidities on outcome, the aaHCT-CI was calculated for each patient prior to transplant. The median HCT-CI was 3 (range, 1-9). Patients were therefore divided into those with a score ≤2 versus ≥3. There was no difference in EFS, OS, or NRM by aaHCT-CI (p=0.78, 0.41, and 0.65, respectively, Figure 2). In the aaHCT-CI low group, the 1-, 3-, and 5- year EFS was 77% (95% CI, 57-99%), 77% (95% CI, 57-99%), 60% (95% CI, 38-95%), and OS was 92% (95% CI, 79-99%), 84% (66-99%), and 75% (53-99%), respectively. Similarly, in the aaHCT-CI high group, the 1-, 3-, and 5- year EFS was 70% (95% CI, 55-90%), 70% (55-90%), and 67% (51-87%) and OS 85% (73-99%), 70% (55-90%), and 67% (51-87%), respectively.





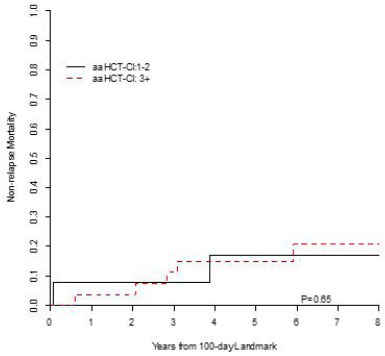


Figure 2: (a) OS (b) EFS (c) NRM by aaHCT-CI.

Discussion

The standard of care for patients with primary refractory or relapsed classical HL is HDT followed by HCT [14]. This approach has been shown to achieve long-term survival in 50% of patients, but is primarily used in younger patients where the safety of such therapy has already been well established. As the population ages, there will continue to be a growing need to improve outcomes for older HL patients, who have a worse prognosis than their younger counterparts. Recent studies have proposed and reviewed the safety and efficacy of HCT in older patients with NHL, but there remains a paucity of data in HL [12-32]. We therefore examined our experience with HDT-HCT for HL patients over age 50 and show that it is both feasible and effective.

The most common toxicities in our study were, as expected, gastrointestinal, infectious, hematologic, and pulmonary, likely secondary to the conditioning regimen. Five patients experienced ≥ grade 4 toxicities; four recovered and the fifth passed away before day 100. Mucositis requiring a PCA was seen in 79% of patients and febrile neutropenia in 95%. The use of TLI and pre-transplant IFRT in the conditioning regimens may be related to the high rates of mucositis, gastrointestinal toxicity, and pulmonary toxicity [18]. However, Puig, et al. reported in their experience with 15 HL patients over age 60 treated with HCT-the only other currently published study evaluating this population-comparable toxicities [12]. Similar to our study, 81% of patients had febrile neutropenia, with a median duration of IV antibiotic therapy of 4 days. Furthermore, the median LOS following stem cell infusion was 14 (range, 11-24). Comparisons of the common conditioning regimens BEAM and CBV in younger patients show differential side effect profiles and impacts on mortality [19-20]. It is therefore possible that a novel conditioning regimen, which limits toxicities while maintaining efficacy, may be able to reduce toxicity in an older patient population.

In terms of outcomes, with a median follow-up of 2.5 years, Puig, et al. report a 3-year PFS and OS of 73% and 88%, respectively [12]. They had no transplant related deaths. With a longer median follow-up, we found an excellent comparable 3-year PFS

and OS of 74 and 76%, respectively, and one treatment related death. On the other hand, a study of elderly relapsed/refractory HL patients from the German Hodgkin Study Group (GHSG) presented in abstract form noted better outcomes in those patients receiving conventional dose therapies compared to HDT-HCT [17]. However, patient characteristics on the two groups were not provided, and so the etiology of this discrepancy is difficult to analyze. Historical data from a study of relapsed or refractory HL patients under 60 who were treated with ICE followed by HDCT and ASCT between 1994 and 1998 at our institution showed an EFS of 68% after a median follow-up of 43 months [21]. Martinez, et al. also show in the patients over age 50 reported to HL Sub-committee of the Spanish Group of Lymphoma and Bone Marrow Transplantation the 5-year PFS and OS were 55% and 64%, respectively, with no difference in those above or below age 60, but with those having an HCT-CI >1 having increased toxicity [32]. This study is consistent with our data, but we present a cohort with longer term follow-up and higher comorbidity scores. Finally, the AETHERA study evaluated maintenance brentuximab after HCT and the control arm showed a 3-year PFS of about 50%. In addition, patients above and below age 45 had prolonged PFS with maintenance therapy with the oldest patient on the brentuximab arm being 71 [22]. Taken in this context, our results support an approach of offering consolidative HDT-HCT to otherwise transplant-eligible patients over age 50. Given the potential for more toxicity during the transplant course, centers should be mindful of enlisting multidisciplinary support both prior to and following admission.

For a more complete look at the experiences of older patients compared to younger patients undergoing HDT-HCT, a recent review tabulated the outcomes in both NHL and HL patients in which early Treatment Related Mortality (TRM) ranges between 0-20% [16]. Some studies have found higher rates of toxicities and NRM in the older patients compared to their younger population [23-26]. For example, a large nation-wide study from Finland found an 11% versus 3% TRM within 100 days of autologous transplant for their >60 and <60-year-old populations, respectively [24]. Others studies, however, have found that increased age was not directly correlated with a higher NRM rate [15, 26-28]. Davison, et al. report no difference in 4-year OS or EFS when comparing patients above and below the age of 60 in an analysis of the randomized phase III Canadian Cancer Trials Group LY.12 study evaluating the optimum salvage chemotherapy regimen before HCT for patients with relapsed or refractory aggressive lymphomas, though the 100-day mortality was 8% in the older patients [29]. Overall, these studies point to comorbidities rather than age as most predictive of post-transplant TRM [27]. In our analysis, only one patient died prior to day 100.

The HCT-CI is a validated tool predicting for NRM and survival based on pre-existing comorbidities in both the autologous and allogeneic transplant settings [30]. Elstrom, et al. report that a high HCT-CI score was associated with worse OS and higher TRM in lymphoma patients over age 69 undergoing HDT-HCT [31], while Hosing, et al. report no correlation with OS, but higher scores relating to more grade 3-5 toxicities in Non-Hodgkin Lymphoma (NHL) patients [28]. In our present study, as well as a prior study evaluating elderly patients with NHL at MSKCC15, we did not find differences in OS, EFS, or NRM based on the HCT-CI. Therefore, the utility of this tool in the older population remains under investigation and alternative assessments may be needed to identify patients at high risk for increased toxicities or adverse outcomes.

There were several limitations to our study. The retrospective nature limits both the sample size and the data available to that contained within the electronic medical record. Retrospective grading of toxicities likely captures major toxicities, but will miss those that are not documented. Furthermore, our study incorporated only those patients who underwent transplant and therefore does not describe an intent-to-treat analysis of older patients with relapsed or refractory classical HL, but who did not undergo transplant due to age, comorbidity, toxicity, or disease progression. No patients in the study are above age 66, and thus we cannot draw conclusions regarding the safety and effectiveness of HDT-HCT in patients beyond this age.

Using these results, future research will focus on ways to decrease toxicity and symptom burden for older patients undergoing HCT. One such option is the use of consolidation volume radiation therapy which limits post-salvage radiation therapy to sites of residual disease over 1.5 centimeter. By doing this, radiation is often limited to the neck and upper esophagus and may help decrease the amount of mucosal toxicity. In addition, the use of different conditioning chemotherapy to abrogate toxicity while maintaining or improving outcomes would be worthwhile. Patient reported outcomes to better quantify and alter the post transplantation experience will also be important to capture alongside upcoming investigations.

In summary, we describe the toxicities and outcomes of a cohort of older HL patients undergoing HDT-HCT with extended follow-up and show that it is feasible and effective in this population. We found acceptably low levels of severe toxicities and similar survival when compared to younger patients with limited impact of pre-transplant comorbidities suggesting that HCT should be considered for older HL patients who have responded to salvage therapy. Additional screening with the aaHCT-CI, geriatric assessments, or newer tools may help to risk stratify these patients. Moving forward, strategies to mitigate toxicity, including supportive treatments and alternative conditioning regimens, and prevent post-transplant relapse with maintenance therapy should be studied and will likely increase the benefit of HDT-HCT and improve the overall prognosis for these patients.

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COI: The authors declare no relevant conflicts of interest.

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