

High-dose therapy and autologous hematopoietic progenitor cells transplantation for relapsed or refractory hodgkin lymphoma: a follow up analysis of king hussein cancer center, results and prognostic variables

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Abstract

Introduction: High dose chemotherapy and autologous stem cell transplantation is a standard of care for patients with relapsed refractory Hodgkin's Lymphoma. Several factors including number of chemotherapy lines received before conditioning, time of relapse and remission status before transplantation can predict overall survival (OS) and progression free survival (PFS) in patients undergoing autologous stem cell transplantation. Abdel-Rahman et al reported on 63 patients, who underwent high dose chemotherapy followed by autologous stem cell transplantation at KHCC from 2003 to 2008. Herein, we report on the outcome of 86 patients, who underwent high dose chemotherapy and autologous HCT at single institution.

Patients and methods: Patients with relapsed and/or refractory Hodgkin's Lymphoma, Jan, 2009-Dec, 2016, who underwent high dose chemotherapy and autologous stem cell transplantation were retrospectively analyzed. The primary end points were complete remission (CR) at day 100, progression free survival (PFS), overall survival (OS) and the impact of the following variables on overall survival and progression free survival: (a) disease status at the time of transplant, (b) number of chemotherapy lines prior to conditioning, (c) time of relapse <12 or > 12 months, (d) age group was also investigated. Secondary end points are day 100 nonrelapse mortality (NRM) and incidence of grade 3-4 mucositis.

Results: 50% of patients were in complete remission at the time of transplantation and 69.2% achieved complete remission at day 100. Median overall survival was not reached and an estimated 5-year overall survival $68.8\% \pm 5.9\%$, (95% confidence interval [CI], 55.6, 78.8%). Median PFS 10.6 months and an estimated 5-year progression free survival rate $51.1\% \pm 6.58\%$ (95% confidence interval [CI], 37.6, 63%). None of the variables studied was significant for survival outcomes. There is a trend toward improved event free survival in those, who received 2 or less lines of chemotherapy. Unexpectedly, male gender was the only significant factor for improved overall survival, progression free survival and event free survival. TRM is 2.7% and mucositis occurred in 53% of patients.

Conclusion: The outcome of relapsed refractory HL is favorable and comparable with worldwide reported outcomes. None of the variables studied was significant for survival outcomes. Two or less salvage chemotherapy lines showed a trend toward improved progression free survival.

Introduction

Hodgkin's lymphoma (HL) is a potentially curable disease with standard chemotherapy combinations. Among patients with early-stage Hodgkin's Lymphoma (HL) the rate of relapse ranges from 10-15% [1] and in patients with advanced stage HL, the relapse rate ranges from 30-40% [2-6]. In addition, approximately 10-15% of patients experience progression of disease after an initial partial response. Although no overall survival (OS) benefit has ever been demonstrated in a prospective, randomized clinical trial, salvage chemotherapy followed by high-dose chemotherapy and autologous hematopoietic cell transplantation (HDT-ASCT) is the treatment of choice for patients with chemosensitive refractory or relapsed HL and currently considered the standard of care [7-19].

Several factors can predict survival outcomes after high dose chemotherapy and autologous transplant, including the number of chemotherapy lines received prior to transplant, time to relapse, disease status at the time of transplant, which predicts the risk of relapse in previous studies with superior outcomes in patients transplanted,

while in complete remission (CR) and the time to initial relapse (TTR) <12 months versus >12 months, which is measured from the date of diagnosis to that of proven relapse have also been shown to influence the outcome [20-22].

There was a significant research in the last few years has focused on maximizing outcomes with HDT-ASCT focusing on identification of prognostic factors at relapse, the incorporation of functional imaging (FI) and biomarkers to improve patient selection and timing of HDT-ASCT, the development of novel salvage chemotherapy and conditioning regimens prior to autologous hematopoietic cell

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transplantation, and the first trial tested maintenance therapy after autologous HCT had been published [23-26].

At King Hussein Cancer Center (KHCC) bone marrow transplantation program,we previously reported on 63 patients, who were transplanted between 2003-2008 .Here in ,we report on the outcomes of 86 patients with HL ,who were transplanted between 2009-2016 .Since our program is combined of adult and pediatric patients, we included the comparison between the two age groups in treatment outcomes.To our knowledge there is no data available on the impact of age on transplantation outcome of Hodgkin's Lymphoma except published report by our group (Adult patients at our center are defined as 18 years or older).

Patients and methods

We retrospectively analyzed the outcome 86 consecutive subjects with chemo-sensitive relapsed or refractory Hodgkin's lymphoma received an autotransplant in the Department of Hematology and Oncology, King Hussein Cancer Center (KHCC), January, 2009-January, 2016. Written informed consent and IRB-approval were obtained. Diagnosis was confirmed by pathology review. Subject-, disease- and transplant-related variables are shown in the Table 1. Disease evaluation was carried out on day 30 and day 100 post-transplant using PETCT and/or CAT scans using RECIST response criteria [27,28].

Treatment

Prior to conditioning regimen, 43% received two lines of salvage chemotherapy. Chemotherapy and GCSF mobilization followed by stem cell collection was used in 94%, while GCSF alone was used only in 6% of patients.Peripheral blood was the graft source in all patients.94% received BEAM (BCNU, Etoposide, Ara-c and Melphalan) conditioning,4.6% received TEAM (Thiotepa, Etoposide, Ara-C, andMelphalan) and 1.4% received BEA (BCNU, Etoposide, Arac). Median CD34 positive cell dose delivered was $5.1 \pm 1.6 \text{ E} + 6$ (SD). All patients received antiviral, antifungal and antibacterial prophylaxis.

Statistical analysis

The primary end points were the rate of complete remission (CR) on day 100,overall survival ,progression free survival (PFS) and Overall survival (OS), progression free survival (RFS) according to disease status at the time of transplant, number of chemotherapy

lines, age group and time to tumor progression (TTR). Secondary end points were transplant-related mortality at day 100 (TRM) and grade III-IV mucositis.Outcomes comparison between groups categorized by disease status at the end of treatment, number of chemotherapy lines received and age group was carried out. Kaplan- Meier method was used to present survival curves. Comparison between groups in survival was carried out using Log Rank test.

Results

All subjects had rapid bone marrow recovery. Median follow-up of survivors was 37.4 months (range: 1.12, 98.7mo). Complete remission at day 100 was 69.2%.Median survival was not reached and an estimated 5-year survival was $68.8\% \pm 5.9\%$, (95% confidence interval [CI], 55.6, 78.8%), Figure 1. PFS was 10.5 months. and 5-year progression free survival was $51.1\% \pm 6.58\%$ (95% confidence interval [CI], 37.6, 63%). At last encounter, 50 (58.1%) patients continue to be relapse free and 36 (41.9%) relapsed.Only 2 patients died in the first 100 days post transplant, representing 2.7% of our cohort. Causes of death were sepsis and respiratory failure-ARDS. This is comparable with international Figures of 3-5 % as for mucositis, it is occurrence reached 53%.

Discussion

High dose chemotherapy with autologous hematopoietic cell transplantation is an established potentially curative therapy for relapsed/refractory Hodgkin's Lymphoma. Of 86 patients received high-dose chemotherapy and autologous HCT in the study period, 50% were in complete remission compared with 25% reported previously with comparable 100 day complete remission rates in both study periods 69.2%, 57% respectively. This supports the notion that complete remission is not prerequisite to proceed to HCT and having a chemo-sensitive disease is a relevant factor.

The median survival for the whole group was not reached with estimated 5-year survival of $68.8\% \pm 5.9\%$ compared to median survival of 40.6 months and projected 3-year overall survival of 64.6%.Median PFS 10.6 months with 5-year progression free survival of $51.1\% \pm 6.58\%$ compared to 20 months and projected 3-year PFS of 42.3% in those reported previously.Also, these survival outcomes were comparable with the results published in a study by Engelhardt, et al. [15] .There was no statistically significant difference in neither overall survival nor progression free survival (PFS) in regard to number of chemotherapy lines received before conditioning, remission status, time to relapse (TTR), age, conditioning regimen (Figure 2). There is only a trend toward improved EFS in those who received less than two lines of salvage chemotherapy before conditioning. Unexpectedly, male gender was the only significant factor for improved survival outcomes,which can be related to small sample size (Figure 3). This concurs with study published by Engelhardt, *et al.* [15] and contradicts most of previously published series [20-22].

Historically, the outcome is better for patients with chemo-sensitive relapse which concur with our study and those whose duration of first remission has been relatively long that contradicts our findings. This is probably related to small sample size. Also, we transplanted all patients with chemo-sensitive disease and having complete remission is not prerequisite to transplant. This supports the hypothesis that the tumor biology is the most important predictor for OS, with tumors that were sensitive to the first line salvage chemotherapy having a better outcome than those, who were not, even if the latter responded to further salvage chemotherapy. The correlation of male gender with improved survival

Table 1. Subject-, disease- and transplant-related variables

Gender	M	46(53.2%)
	F	42(48.8%)
Age	Adult	74(86.0%)
	Pediatric	12(14%)
N. of Chem. cycles	<2	36(42.0%)
	>2	50(58.0%)
Disease status at ABMT	CR	43(50.0%)
	PR	43(50.0%)
TTR	<12 months	46(53.5%)
	>12 months	40(46.5%)
Mobilization regimen	Chem+GCSF	81(94%)
	GCSF	5(6%)
Stem cell source	Peripheral	100%
Stem cell dose	median	$5.1 \pm 1.6 \text{ E}06/\text{kg}$
	BEAM	84(92.0%)
Conditioning	TEAM	6(6.8%)
	BEA	1(1.2%)

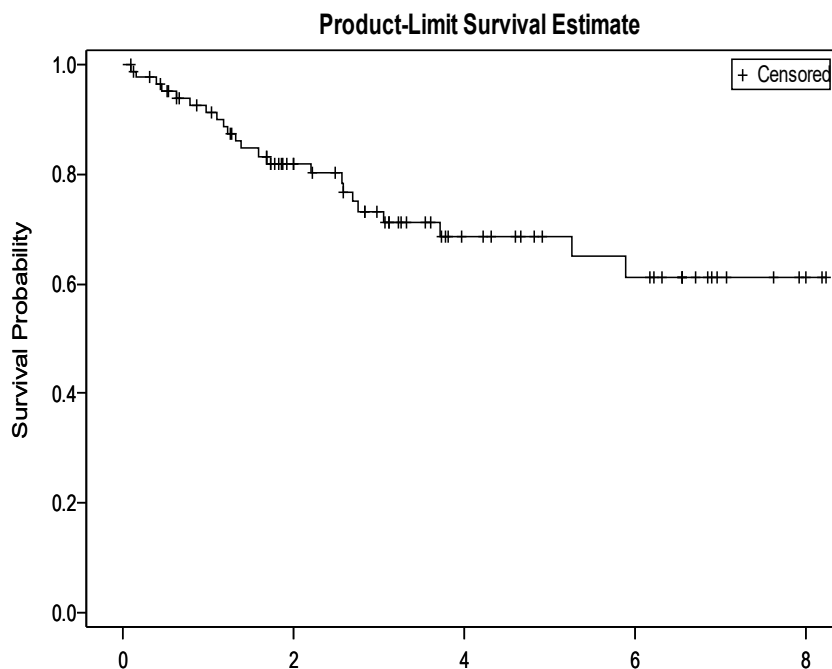


Figure 1. Overall survival of 86 patients received autologous transplantation for HL

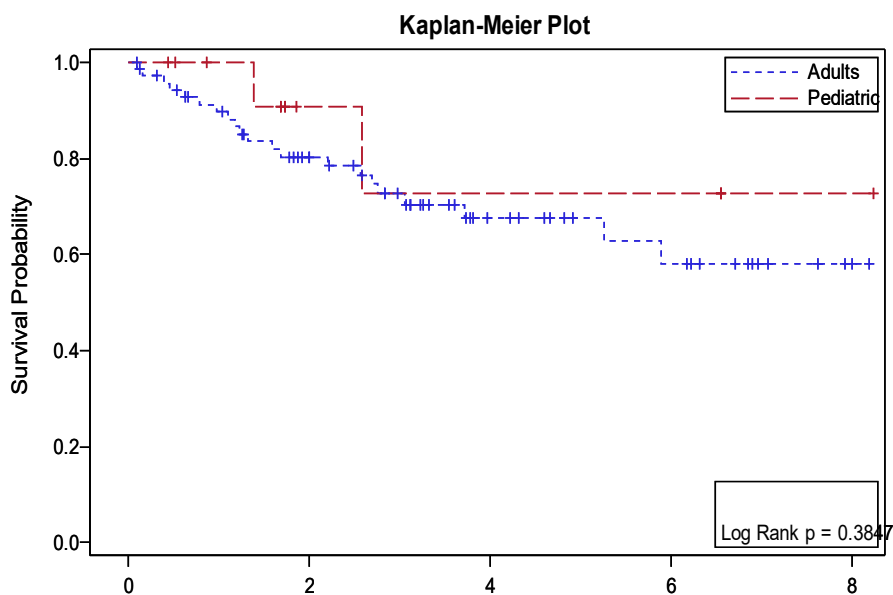


Figure 2. Overall survival according to age group

outcomes cannot be explained in our series and we think this might be related to sampling bias. Relapse after autologous hematopoietic cell transplant for Hodgkin's Lymphoma remains a significant problem with 41.9% of patients relapsed as projected from our study. Large studies have suggested that early relapse, chemotherapy-refractory disease, and the presence of extranodal disease are all clinical factors associated with a high risk for relapse after autologous HCT. It is important to focus on treatment strategies after relapse. There is a potential durable response with reduced intensity allogeneic transplant for HL patients relapsed after autologous transplant as shown in study of Peggs, et al. [23]. Also the use of novel agents like Brentuximab

vedotin and PD-1 inhibitors, which were tested in phase III trials have shown promising results showing high response rate reaching 75% in relapsed/refractory HL and being used as bridging to reduced-intensity allogeneic hematopoietic cell transplantation and proved to be of benefit as maintenance post high dose and autologous HCT for high risk HL patients with residual disease as shown in Aethera trial by Seureda, et al. [23-26,29-31].

Conclusion

We can therefore conclude from our study that the outcome of relapsed refractory HL is favorable and none of the variables studied was

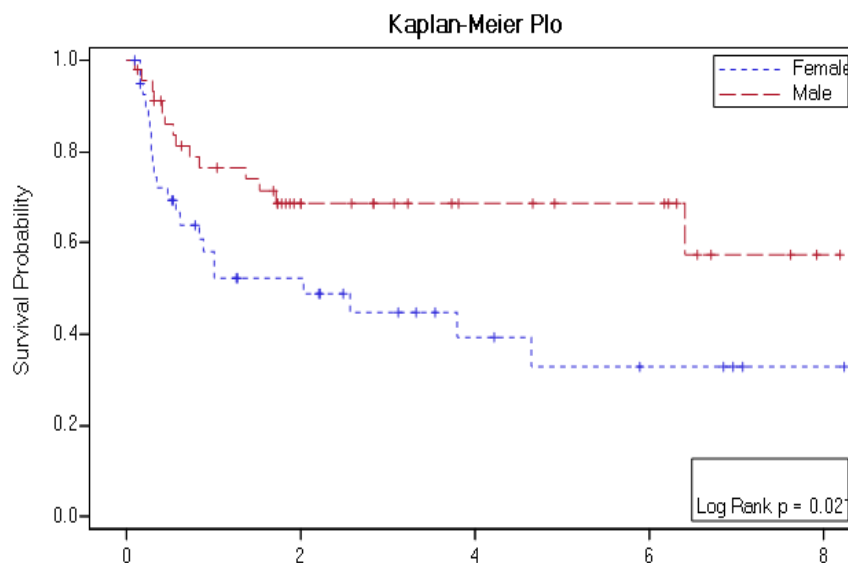


Figure 3. RFS according to gender

significant for survival outcomes, with only a trend toward improved EFS in those who received two or less salvage chemotherapy lines. Our results are comparable with what reported in the literature.

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