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The outcome of relapsed/refractory hodgkin's lymphoma patients post autologous bone marrow transplantation in a Baghdad Medical City Complex Center

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Abstract:

BACKGROUND: Early autologous hemopoietic stem cell transplant is the best option for treatment of relapsed or refractory Hodgkin lymphoma (HL), which is the standard of care at the time being. The aim of this study was to evaluate the outcome of patients with relapsed/refractory (R/R) HL who received autologous hemopoietic stem cell transplant.

METHODS: This is a cohort study with data obtained from the patient's sheets and then with follow-up from January/2014 to May/2017. Analysis involved 48 patients with R/R HL. Those patients received high-dose chemotherapy followed by autologous hemopoietic stem cell transplantation (ASCT). Disease status before ASCT, chemo-mobilization protocols, and stem cell collection and ASCT procedure were recorded. The posttransplantation complications and 30-day mortality were also recorded. Re-evaluation of disease status was done at day 100 post transplantation and the patients were followed up for any evidence of relapse or progression till the end of the study. Comparison of various predictors affecting overall survival (OS) and progression-free survival (PFS) was also performed.

RESULTS: The 3-year PFS and OS for the patients with R/R Hodgkin disease who received ASCT were 80% and 70.2%, respectively, with various predictors affecting them. Patients with disease status before ASCT as partial remission and resistant have shorter mean OS and PFS that are not statistically significant (P = 0.325 for OS and 0.45 for PFS). Patients with the number of pretransplant treatment regimens more than 2 have a statistically significant shorter mean PFS and statistically nonsignificant OS (P = 0.4 for OS and 0.06 for PFS). The first 30-day posttransplantation mortality (procedure-related death) was 6.3% due to sepsis.

CONCLUSION: The mean PFS was inversely affected by the number of treatment lines received prior to ASCT.

Keywords:

Bone marrow transplantation, medical city complex, outcome, relapsed Hodgkin lymphoma

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Introduction

Hodgkin lymphoma (HL) is a clonal lymphoid disorder of mononuclear Hodgkin cells and multinucleated Reed–Sternberg cells, which are considered to be derived from germinal center B cells.[1] In 2013, it was estimated that there would be 9290 new cases of HL in the United States and that 1180 people would die with this diagnosis.[2] The most common HL symptom is painless lymphadenopathy. Patients may have systemic or "B" symptoms consisting

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of unexplained fevers, night sweats, or weight loss. Pruritus may be seen and precede the diagnosis of HL for months. Approximately 70% of patients with nodular lymphocyte predominant-Hodgkin's lymphoma are males in the age range of 30–50 years. Patients often have localized disease and may have an indolent disease course. The most common subtype of classical HL is nodular sclerosis, which is more likely to be present in patients with limited-stage disease.[3] More than 50% of HL patients, including those with advanced disease, can be cured with a wide variety of chemotherapy regimens; this accomplishment is one of the greatest achievements of modern medicine. There has been a dramatic decline in HL mortality and the 5-year survival rate is now approximately 85.[3-5] The poor results of conventional-dose salvage therapy for relapsed and refractory HL have led to the use of high-dose therapy followed by autologous bone marrow transplantation (BMT) and peripheral blood hematopoietic cell transplantation for these patients. This approach is based on the steep dose–response curves exhibited by several drugs, and also radiation therapy, and the fact that dose-limiting toxicities are often related to myelosuppression.[6] A number of factors have been identified that are associated with adverse outcomes for patients who undergo AHSCT for HL. Several prognostic models have been developed that use these factors to predict outcomes following transplantation. The Vancouver group examined patients undergoing AHSCT for HL in the first relapse.[7] The most important risk factors associated with adverse outcome following AHSCT for HL are bulky or "nonminimal" disease at transplant, extensive therapy before transplant, poor performance status, short initial remission, extranodal disease at relapse or at transplant, systemic symptoms at relapse, and chemotherapy resistance.[8,9] The aim of the study was to evaluate the outcome for patients with HL who received autologous hemopoietic stem cell transplant in the BMT center in Baghdad medical city complex.

Methods

This is a cohort study with data obtained from the patient's sheets and then with follow-up from January/2014 to May/2017. In a single institution (BMT center in Baghdad Medical City complex), patients were followed up until November 2017.

Disease status before AHSCT: The imaging studies that were used to assess the disease status before transplantation were chest X-ray, ultrasound, computerized tomography (CT) with intravenous contrast, and positron-emission tomography-CT when available. The patient's status before transplantation was categorized into:[10] complete remission (CR), uncertain CR, partial remission, and primary resistance. Pre transplantation, the chemomobilization was achieved by four types of protocols according to the previous lines that they were received and as the following: Gemcitabine, Dexamethasone, and Cisplatin (GDP): 23 patients, (Ifosfamide, gemcitabine, and vinorelbine)IGEV: 6 patients, Dexamethasone,High-dose Ara-C cytarabine, Platinol (DHAP): 2 patients, ifosfamide, carboplatin, and etoposide: 14 patients, and granulocyte colony-stimulating factor: 3 patients). Peripheral blood CD_{34} cells were assessed by using a stem cell enumeration kit and via fluorescence-activated cell sorting flow cytometry (BD canto II). For autologous BMT, we used two types of conditioning chemotherapy protocols according to the availability of the drugs in our center. BEAM consisted of BCNU (carmustine): 300 mg/m2 (total dose) intravenous (IV) on day 6 before transplant, etoposide: 800 g/m2 (total dose) IV divided over 4 days from day 5 to 2 before tansplantation, Ara-C (cytarabine): 1600 mg/m2 (total dose) I.V twice daily from 5 to 2 before tansplantation, and melphalan: 140 g/m2 (total dose) IV on day 1 before transplatation.[11] LEAM is consisted of CCNU (lomustine): 200 mg/m2 (total dose) intravenous (IV) on day 6 before transplant, etoposide: 800 g/m2 (total dose) IV divided over 4 days from day 5 to 2 before tansplantation, Ara-C (cytarabine): 1600 mg/m2 (total dose) I.V twice daily from 5 to 2 before tansplantation, and melphalan: 140 g/m2 (total dose) IV on day 1 before transplatation then to be followed by periphral blood stem infusion on day zero (day of transplantation) on both protocols.[11] Posttransplantation complications and 30-day posttransplantation mortality were recorded. Re-evaluation of disease status was done at day 100 by clinical examination, chest X-ray, ultrasound, and CT with intravenous contrast. In addition to above measures, the patients are kept on regular follow up for any evidence of relapse or progression until the end of the study.

Statistical analysis

Anderson-Darling test was used to assess continuous variables if these variables follow normal distribution, so mean and standard deviation used to present data, but if not, the normal distribution uses median and interquartile range (25%–75% percentile range) to present data. Hazard ratio was calculated using Cox proportional hazard regression analysis to find the time-dependent association of the model and then calculate the 95% confidence interval, a value less than 1.0 indicates decreased risk and more than 1.0 indicates increased risk (if both were statistically significant). Overall survival (OS) was measured from date of transplant to death from any cause. Progression-free survival (PFS) measured from date of transplant to death any cause or relapse. SPSS 20.0 Armonk, NY: IBM Corp., Minitab 17.1.0 by Pennsylvania State University USA, MedCalc 14.8.1 by,

Ostend, Belgium, and GraphPad Prism 7.0 software San Diego, California USA were used for statistical analysis, P value considered significant if <0.05.

Results

A total of 48 patients were included in this study, the median age was 24.4 ± 8.5 years ranging from 7 to 42 years, 29 patients were male and 19 patients were female (male to female ratio was 1.53:1), and 6.3% of patients died, with mean time 12 ± 6.2 days. The number of treatment regimens and the initial status are illustrated in Table 1. The overall survival for pateint post ASCT was 80% as shown in Figure 1 while the progression free survival was around 70% as in Figure 2. The details of conditioning protocols done for patient who underwent ASCT are shown in Table 2.

In addition to that Table 3 demonstrate the some predictor factors in ASCT in which no significant association was observed between the 3-year OS and predictors in the study Figure 2.

Table 1: Patients' characteristics before autologous hemopoietic stem cell transplantation (*n*=48)

Variables	Value, *n* (%)
Age (years), median±SD (range)	24.4±8.5 (7-42)
<20	14 (29.2)
20-29	22 (45.8)
≥30	12 (25.0)
Gender (male:female ratio)	1.5:1
Male	29 (60.4)
Female	19 (39.6)
Number of treatment regimens	
2 regimen	21 (43.8)
>2 regimen	23 (47.9)
Unrecorded	4 (8.3)
Status before autologous SCT	
UCR+CR	18 (37.5)
PR+primary resistance	30 (62.5)
Death	3 (6.3)
Time to death (days), mean±SD (range)	12±6.2 (7-19)
Neutropenia fever	47 (97.9)

SD=Standard deviation, UCR=Uncertain complete remission, CR=Complete remission, PR=Partial remission, SCT=Stem cell transplantation

Table 2: Parameters of conditioning protocols in patients underwent ASCT

Variables	Value, *n* (%)
Duration between mobilization and transplantation (days)	
Mean±SD	71.2±49.6
Median (IQR)	54 (42-87.8)
Range	19-299
ABMT conditioning protocol	
LEAM	36 (75)
BEAM	12 (25)
Day of engraftment, mean±SD	10.92±1.20
Laboratory assessment of engraftment	
WBC, median (IQR)	1.2 (0.9-1.65)
ANC, median (IQR)	0.7 (0.53-0.98)
Platelet, median (IQR)	21 (15.3-30.8)
Hemoglobin, median (IQR)	8.85 (8.0-9.28)
Blood transfusion	22 (45.8)
Platelet transfusion	44 (91.7)

IQR=Interquartile range, SD=Standard deviation, WBC=White blood cell, ANC=Absolute neutrophils count, ABMT=Allogeneic bone marrow transplantation, LEAM=Lomustine, etoposide, Ara-C cytarabine, melphalan, BEAM=Bis-chlorethylnitrosourea(BCNU), etoposide, Ara-C cytarabine, melphalan

Discussion

HL patients achieve a high rate of remission status reaching about 80%;[12-14] however, in those who relapse after first-line treatment or have primary resistance to the first-line treatment, the outcome if treated with chemotherapy alone is poor with remission rate 10%–35%.[15-17] The standard of care at the time being is high-dose chemotherapy (HDCT) with autologous stem cell transplant (ASCT); still, only half of these patients will achieve sustainable cure.[18] In the current study, a total of 48 patients with R/R HL were studied (four patients had primary resistance), the median age was 24.4 ± 8.5 years (ranging from 7 to 42 years) with a male-to-female ratio was 1.53:1. In Longley and Johnson's study which involved 44 patients with resistant/recurrent HL, the median age was 31 years (13–61 years) with a male-to-female ratio of 1.59:1,[19] also in Tsang *et al*.'s study which included 144 patients, 61 patients offered BEAM with HSCT and 56 patients offered Dexa-BEAM, median age for patients offered BEAM-HSCT was 32 years (16–59 years), with a male-to-female ratio was 1.8:1,[17] so comparison with our patients' characteristics, their patients were older with similar male-to-female ratio, and patients >50 years of age were transplanted in these two studies. Chiappella *et al*.'s study was in agreement with the current study age and male: female ratio in which it was randomized clinical trial involving a total of 40 patients with a male-to-female ratio of 1.5:1, 20 patients received BEAM and 20 patients mini-BEAM with a median age of 26 years (18–40 years).[16] The age

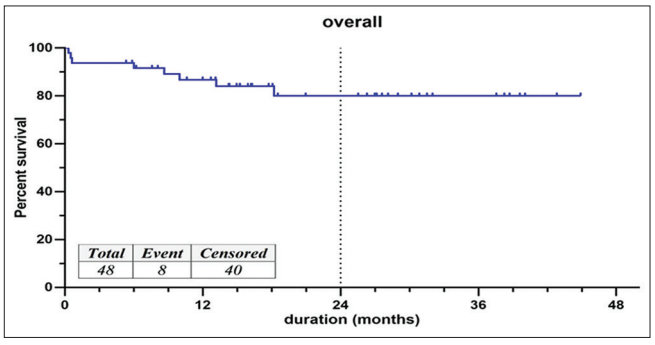

Figure 1: Three-year overall survival in months

Table 3: Survival analysis of various predictors

Predictors	3-year survival (%)	PFS (95% CI)	*P*
Overall	70.2	34.5 (29.4-39.6)	
Gender			
Female	83.5	36.8 (30.5-43.1)	0.198
Male	67.2	31.7 (24.6-38.8)	
Initial status			
CR+UCR	80.8	38.0 (30.8-45.1)	0.316
PR+resistance	62.8	31.1 (24.6-37.5)	
ASBMT protocol			
LEAM	71.6	28.8 (23.7-33.8)	0.493
BEAM	83.3	38.2 (29.8-46.7)	
Number of pretransplant treatment			
2 regimens	90.5	41.0 (35.8-46.1)	0.047
>2 regimens	63.3	25.7 (19.0-32.3)	
Predictors	**3 years OS (%)**	**Mean OS, months (95% CI)**	***P***
Overall	80.0	37.6 (33.1-42.2)	
Gender			
Female (19)	89.5	38.7 (33.2-44.1)	0.320
Male (29)	73.2	35.5 (28.9-42.0)	
Status before autologous SCT			
UCR+CR (18)	85.9	39.7 (33.0-46.4)	0.448
PR+primary resistance (30)	75.5	34.5 (28.6-40.4)	
Number of regimens			
2 regimens (21)	89.6	41.0 (35.9-46.1)	0.41
>2 regimens (23)	75.5	30.9 (24.9-36.8)	
Conditioning protocols			
LEAM (36)	75.0	Not reached	0.127
BEAM (12)	100	Not reached	
100 days disease			
Status CR (43)	89.1	41.0 (37.5-44.6)	0.140
Relapse (2)	Not reached	18.2 (18.2-18.2)	

P<0.05 (significant). OS=Overall survival, PFS=Progression free survival, CR=Complete remission, CI=Confidence interval, UCR=Uncertain complete remission, PR=Partial remission, ASBMT=American Society for Blood and Marrow Transplantation, LEAM=Lomustine, etoposide, Ara-C cytarabine, melphalan, BEAM=Bis-chlorethylnitrosourea(BCNU), etoposide, Ara-C cytarabine, melphalan

and gender distribution of the current study was similar to the above studies, which reflect the age and gender distribution of HL. In the current study, 3-year OS was 80.0% and 3-year PFS was 70.2%; in total, eight patients died, three of them died within the first 30 days of the transplantation procedure (procedure-related death), and nine patients had relapsed, five of them died. The expected cumulative survival (estimated by Kaplan Meir methods) of the current study was higher than that reported by Moskowitz *et al.'s* study which showed a 3-year PFS of 53% for the 20 patients receiving BEAM and ASCT, there were two procedure-related deaths in the BEAM group and three from disease progression,[20] this differences in outcome can be attributed to small sample size for Moskowitz *et al*. and the current study. In the current study, gender did not affect both OS and PFS significantly (despite females had slightly higher OS and PFS), in Longley and Johnson's study in multivariate analysis, the gender did not affect the OS and PFS[19] which was in agreement with the findings of the current study. In the current study, two regimens

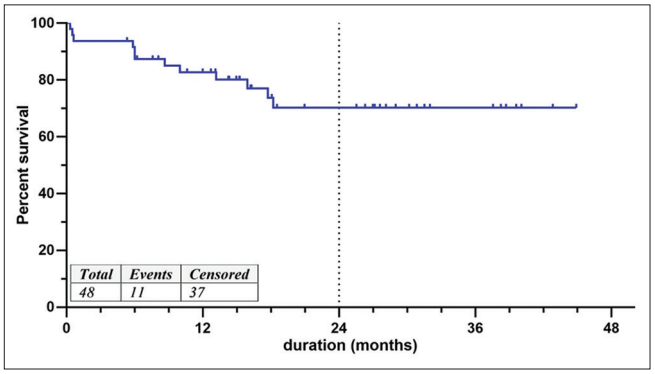

Figure 2: Three-year progression-free survival

were used, the standard approach regimen was BEAM for 12 patients (25%) and LEAM for 36 patients (75%), in which lomustine was introduced instead of carmustine because of unavailability of the latter. Despite there was no statistically significant difference in OS (P = 0.127), and in PFS (P = 0.493), but in terms of 3-year-OS, BEAM had a more favorable result compared to LEAM, despite

the similarity of lomustine to carmustine in terms of mechanism of action. Ramzi *et al*. studied 45 patients with R/R HL, they used LEAM as the conditioning regimen, the median follow-up was 27 months, median OS was 27 months and median PFS was 27 months, and the 2-year OS was 84% and PFS was 77%,[21] which were slightly higher than the findings in the current study. HDCT and AHSCT for lymphomas utilize several drug combinations and in the absence of randomized comparative data, BEAM remains the regimen, the regimen most widely used and accepted because of its apparent tolerability and established efficacy. Shortage of old drugs is a worldwide problem, and while alternative regimens do follow the principles of combination chemotherapy. CCNU (lomustine) is another nitrosourea that is available for oral administration and it seemed to be the most logical substitute. The modified regimen (LEAM) use was reported by other authors;[21,22] in addition, the modified LEAM protocol offered a reduction in the BCNU pulmonary toxicity since CCNU is less toxic in that regard.[23]

Conclusion

The mean PFS was negatively affected by more than two lines of treatment before referring to ASCT.

The most common cause of mortality post-ASCT was found to be sepsis.

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Conflicts of interest
There are no conflicts of interest.

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