Original Article

Comparison of Survival between Hodgkin and Non-Hodgkin Lymphoma after Autologous Stem Cell Transplantation

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Abstract

Background: Autologous stem cell transplantation (ASCT) is a treatment modality for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) patients with increasingly usage worldwide. **Materials and Methods:** One hundred and forty-one patients (96 patients with HL and 45 patients with NHL) who underwent ASCT were followed. We used 3-year overall survival (OS) and 3-year progression-free survival (PFS) to evaluate the survival rates. **Results:** Comparison of 3-year OS and PFS between HL and NHL had no statistically significant difference (OS: 82% vs. 70.2%, $P = 0.07$ and PFS: 72.8% vs. 59.6%, $P = 0.46$). 3-year OS in HL with CR was, however, statistically better than NHL (91% vs. 70.4%, $P = 0.007$) and 3-year OS in males with HL was statistically better than males with NHL (83.2% vs. 66.7%, $P = 0.047$). Moreover, 3-year OS and PFS in HL with three or more chemotherapy lines before transplantation were better than NHL with this condition (3-year OS: 72.8% vs. 44%, $P = 0.01$ and 3-year PFS: 58.1% vs. 33.1%, $P = 0.016$). **Conclusion:** Our purpose was to compare the survival rates in two groups of NHL and HL patients after ASCT. Patients with HL generally showed better OS and PFS after ASCT in comparison to patients with NHL, but statistically significant differences were seen only in few comparisons, requiring more studies to be carried out.

Keywords: *Autologous stem cell transplantation, Hodgkin lymphoma, non-Hodgkin lymphoma, overall survival, progression-free survival*

Introduction

Stem cell transplantation (SCT) is used increasingly as a treatment modality worldwide for different diseases, including leukemia, lymphoma, solid tumors, and nonmalignant disorders.[1] Hematologic disorders such as Hodgkin lymphoma (HL) and non-HL (NHL) are results of dysregulation of hematopoietic stem cells, ineffective erythropoiesis, and dysfunction of immune cells with immunomodulatory role in cancer.[2,3] The prevalence increases in the second and sixth decades of life, and viral infections (specially Epstein–Barr Virus) and familial history are among risk factors of HL disease.[4,5] NHL prevalence increases with age and not only infiltrates hematopoietic and lymph tissues but also infiltrates other organs and accounts for almost 4% of new cancer diagnoses in the USA.[6,7] In HL, after high-dose chemotherapy, autologous SCT (ASCT) was the treatment of choice for those relapsed or refractory to chemotherapy but had chemosensitive disease.[8-11] High-dose chemotherapy (HDCT) followed by ASCT is also an accepted treatment for many NHLs including high-grade and intermediate-grade NHL in patients who relapsed after first complete remission (CR) with conventional chemotherapy regimen but had chemosensitive disease.[12-17] The role of allogeneic SCT in the treatment of relapsed NHL in comparison to ASCT is uncertain because at the expense of lower relapse rate, there will be a higher procedure-related mortality rate.[16,18,19] In NHL patients who relapsed after HDCT-ASCT, allogeneic SCT is an accepted option.[19,20] In the last two decades, mobilized peripheral blood stem cell (PBSC) has been used as an alternative to stem cells from bone marrow, which was a more comfortable procedure and reduced the time of platelet and neutrophil recovery after transplantation.[21] Iran is in Eastern Mediterranean subdivision of the Worldwide Network for Blood and Marrow Transplantation.[1] Cancer is rapidly becoming one of the leading causes of death in most of the developed countries including Iran.[22,23] Unfortunately, there is

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no extensive data about distribution of lymphoma in Iran. However, limited data are available and indicating that lymphoma is among major types of cancers in Iranian population, for instance, Global Burden of Disease Cancer Collaboration studied data of 195 countries between 1990 and 2015 and has shown that NHL is one of the top ten in terms of incidence in Iran.[24] One study reported that the incidence rate of lymphoma in Iranian children is 3–23 and 3–9 per million in girls and boys, respectively.[25] Most of the studies including Mozaheb *et al.*'s study in Mashhad city, located in north-east of Iran, indicate that NHL is the most common form of lymphoma in the studied population and mature B cell forms of NHL such as small lymphocytic lymphoma, mantle cell lymphoma, and diffused large B cell are more prevalent.[26] In this study, we aim at reporting our experience in transplantation of refractory and relapsed chemosensitive Hodgkin and NHL in the BMT ward of Taleghani Hospital affiliated with Shahid Beheshti University of Medical Sciences in Tehran, Iran. HDCT-ASCT in relapsed and refractory Hodgkin and NHL is our policy in this center because of the advantage of this modality in such patients in Western countries. In this study, we want to evaluate our results. The aim of this study is to compare overall survival (OS) and progression-free survival (PFS) in HL and NHL patients. Furthermore, the study aims at comparing the obtained results from OS and PFS to those of other BMT centers in an attempt to find factors which probably affect the results.

Materials and Methods

Ethics

All the procedures performed in the studies involving human participants were in accordance with the Ethical Committee of Shahid Beheshti University of Medical Sciences (No. 91–270) as well as Helsinki declaration.

Selection of participants

In this study, 141 patients (96 patients had HL and 45 patients had NHL) who had eligible criteria for transplantation were evaluated from July 2007 to July 2013. All of them had refractory disease with conventional chemotherapy or had relapsed disease and received ASCT. At first, the referred patients were introduced to a committee for decision-making. Before admission, they were referred for heart, respiratory, psychiatric, and odontology consultation. For all of our patients, stem cells were collected from PBSCs. These stem cells were mobilized with administration of 12–16 g/kg granulocyte colony-stimulating factor (G-CSF), and the cells were collected by leukapheresis procedure. The cells were then stored in temperature between 4°C and 8°C. Before transfusion, conditioning regimen (BEAM protocol) was prescribed for the patients. All the data in this study were collected from hospital record files and transplantation clinic files. The data regarding the survival of patients were collected in July 2014 by phone contacts. Six patients at that time did not respond to phone calls and were censored from the last time that we had information about. Therefore, none of them were eliminated from this study.

Statistics

This study was carried out in 6 years. We used 3-year OS and PFS rates for evaluating our patients. OS was the duration from transplantation to death and PFS was the time interval from transplantation to disease progression or relapse. The survival analysis was done by Kaplan–Meier methods and all the comparisons between different groups were made with the log-rank test. For the multivariable analysis, Cox regression method was used to evaluate hazard ratio (HR) in OS and PFS for all variables. The variables were gender, age, duration of disease before transplantation, CR or partial remission (PR), and the number of chemotherapy lines before transplantation. In all the tests, the level of significance was set at $P < 0.05$. Statistical analysis was performed using SPSS Statistics for Windows, Version 17.0 (Chicago, USA: SPSS Inc.).

Results

One hundred and forty-one patients were studied in this study. 45 (32%) patients had NHL and 96 (68%) patients had HL. Demographic characteristics of all patients at transplantation time are shown in Table 1. In this study, we compared the results of OS and PFS between NHL and HL patients. Gender distribution in the HL group was equal, but in NHL, males were more than females. This was, of course, predictable because NHL is more common in males.[27] The mean age at transplantation time in NHL was 10 years more than HL. While the mean duration time of disease before transplantation in NHL was 2.2 years, it was 3.39 years in HL. 76 (53.5%) patients had CR at transplantation time and 65 (46.5%) patients had PR at that time. The results of 3-year OS and PFS for NHL and HL are represented in Table 2. The 3-year OS rates for NHL and HL were 70.2% and 91%, respectively. The 3-year PFS rates were 59.6% and 71.5% for NHL and HL, respectively. The 3-year OS rate in the HL group was better than the NHL group with borderline P value ($P = 0.07$), but the 3-year PFS was not statistically different between the two groups [Figure 1]. Table 2 shows 3 years of OS and PFS for different variables. A comparison between HL and NHL is also illustrated in Table 2 for all variables with P value. 3-year OS for HL is significantly better than NHL when

Table 1: Demographic characteristics of patients

Patients	Variables, *n* (%)		
	NHL	HL	Total patients
Total patients	45 (32)	96 (68)	141 (100)
Gender: Female	14 (31.1)	49 (51)	63 (44.7)
Male	31 (68.9)	47 (49)	78 (55.3)
Remission status: CR	27 (60)	49 (51)	76 (53.5)
PR	18 (40)	47 (49)	65 (46.5)
The number of chemotherapy lines ≤2 Line	32 (71)	53 (55.2)	85 (60.3)
The number of chemotherapy lines >2 line	13 (29)	43 (44.8)	56 (39.7)
Mean age at transplantation time (years)	37.6±12.8	27.9±8.3	30.99±10.89
Mean duration time of disease before transplantation (months)	26.5±23.9	40.7±30.8	36.2±29.5

HL: Hodgkin Lymphoma, NHL: Non-HL, CR: Complete remission, PR: Partial remission

patients had CR at the time of transplantation (P = 0.007), and in groups who received two or more chemotherapy lines before transplantation, 3 years of OS and PFS in HL were significantly better than NHL (P = 0.01 and P = 0.016). In male patients, 3-year OS in HL and NHL was 83.2% and 66.7%, respectively (P = 0.47), which means that the 3-year OS was better in males with HL and there was, however, no difference between women [Figure 1]. In the HL group, 3 years of OS and PFS [Table 2] for patients who had CR at the time of transplantation were significantly better than others with PR at the time of transplantation (3 years OS 91% vs. 72.6% with P = 0.024 and 3 years PFS 71.5% vs. 53.1% with P = 0.05). In all the patients, 3 years of OS and PFS had advantage in groups with two or fewer chemotherapy lines in comparison to those who received more chemotherapy lines. The 3-year OS in NHL with 2 or less than 2 chemotherapy lines was 80.6% and with more than 2 lines was 44% (P = 0.004). The 3-year PFS for the same groups of patients was 74.6% and 33.1%, respectively (P = 0.001). In HL with 2 or less than 2 chemotherapy lines, 3-year OS was 89.2% and for more than 2 chemotherapy lines, it was 72.8% (P = 0.034). In this study, comparison between HL and NHL in groups with fewer chemotherapy lines (2 or <2 lines) showed no significant differences. However, in patients with more than two lines of chemotherapy before transplantation, 3 years of OS and PFS were better in HL in comparison to NHL (3-year OS 72.8% vs. 44%, P = 0.01 and 3-year PFS 58.1% vs. 33.1%, P = 0.016). The patients' disease status three months after transplantation was evaluated as a criterion for response to this treatment modality [Table 3].

Table 2: Comparison of 3 years overall survival and progression-free survival between Hodgkin lymphoma and non-Hodgkin lymphoma

	HL (%)	NHL (%)	*P*
3 years OS	82	70.20	0.07
3 years PFS	72.80	59.60	0.46
3 years OS with CR	91	70.40	0.007
3 years OS with PR	72.60	68.10	0.949
3 years PFS with CR	71.50	59.30	0.101
3 years PFS with PR	53.10	59.60	0.626
3 years OS in ≤2 chemotherapy lines	89.20	80.60	0.253
3 years OS in <2 chemotherapy lines	72.80	44	0.01
3 years PFS in ≤2 chemotherapy lines	65.60	74.60	0.667
3 years PFS in <2 chemotherapy lines	58.10	33.10	0.016
3 years OS in males	83.20	66.70	0.047
3 years OS in females	81	77.90	0.877
3 years PFS In males	60	54.60	0.288
3 years PFS in females	64.10	70.70	0.657

OS: Overall survival, PFS: Progression-free survival, HL: Hodgkin Lymphoma, NHL: Non-HL, CR: Complete remission, PR: Partial remission

Table 3: Disease evaluation three months after transplantation

	CR, *n* (%)	PR, *n* (%)	Stable disease, *n* (%)	Expired, *n* (%)
HL	73 (76)	9 (9.4)	10 (10.4)	4 (4.2)
NHL	37 (82.2)	4 (8.8)	1 (2.3)	3 (6.7)

HL: Hodgkin lymphoma, NHL: Non-HL, CR: Complete remission, PR: Partial remission

The COX regression was used for multivariate analysis for variables including sex, age, duration of disease, kind of disease (HL vs. NHL), disease status at transplantation time (CR or PR), and the number of chemotherapy lines in both groups (NHL and HL). For all variables, HR with 95% confidence interval (CI) and P value for OS and PFS was calculated [Tables 4 and 5]. As shown in Table 4, increased HR for OS in variables such as age and number of chemotherapy lines had a statistically significant effect (P < 0.05). HR for OS in NHL versus HL, male versus female, and PR versus CR showed an increased but not statistically significant difference. With each single-line increase in chemotherapy lines, the risk of death or disease progression increased significantly [Table 4].

Discussion

In this study, 141 patients who were diagnosed with lymphoma (45 NHL and 96 HL) and underwent ASCT were followed from July 2007 to July 2013 and their OS and PFS rates were then compared. Comparisons

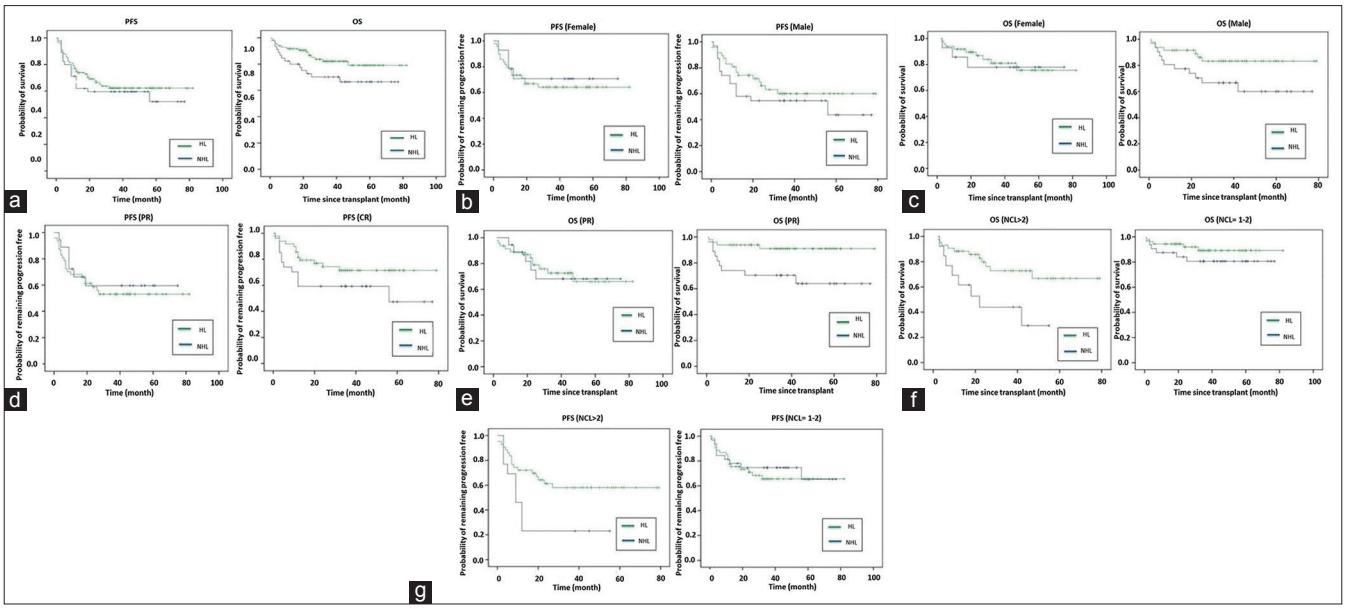

Figure 1: Comparison of OS and PFS between HL and NHL (a); comparison of PFS (b) and OS (c) between HL and NHL in male and female patients; comparison of PFS (d) and OS (e) between HL and NHL with CR and with PR; comparison of OS (f) and PFS (g) between HL and NHL with ≤2 and >2 chemotherapy lines. HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, OS: Overall survival, PFS: Progression-free survival, CR: Complete remission, PR: Partial remission

Table 4: Multivariable analysis of overall survival in all patients

	HR	95% CI	*P*
Male versus female	1.12	0.52-2.4	0.77
Each year increased in pts' age	1.06	1.02-1.10	0.001
NHL versus HL	1.32	0.53-3.27	0.56
Each months increased in dis duration time	0.99	0.98-1.01	0.86
PR versus CR	1.96	0.81-4.46	0.13
Each line increased in chemotherapy lines	1.72	1.16-2.55	0.007

HR: Hazard ratio, CI: Confidence interval, HL: Hodgkin lymphoma, NHL: Non-HL, CR: Complete remission, PR: Partial remission

Table 5: Multivariable analysis of progression-free survival in all patients

	HR	95% CI	*P*
Male versus female	1.24	0.70-2.18	0.46
Each 5 years increased in pts age	1.11	0.99-1.05	0.19
NHL versus HL	1.14	0.59-2.20	0.7
Each months increased in dis duration time	0.99	0.99-1.00	0.81
PR versus CR	1.36	0.75-2.50	0.3
Each line increased in chemotherapy lines	1.44	1.05-1.98	0.02

HR: Hazard ratio, CI: Confidence interval, HL: Hodgkin lymphoma, NHL: Non-HL, CR: Complete remission, PR: Partial remission

of OS and PFS between two types of lymphoma were done with regard to some variables such as gender, age, remission condition at the time of transplantation, and the number of chemotherapy lines before transplantation. Transplantation-related mortality (TRM) in this study was 6.4%, which was comparable to other TRM reports.[19,28] Studies which directly compare OS and PFS between NHL and HL after transplantation were not found in the literature review. In this study, 3 years of OS in NHL and HL were found to be 70.2% and 82%, respectively, which are comparable to other studies and even slightly better.[10,29-37] There is no statistical difference between 3 years of OS in NHL and HL. The comparison of 3 years of PFS between NHL and HL shows no meaningful difference (3 years PFS 59.6% vs. 72.8%). Therefore, the results of this study illustrate that the type of lymphoma (NHL vs. HL) does not probably have any effect on transplantation survival [Table 2]. Comparison of the results of 3 years of OS and PFS regarding remission condition (CR vs. PR) on survival before transplantation showed that OS in CR between NHL and HL was 70.4% versus 91%, so the results of transplantation in HL patients with CR was better than NHL with CR. However, this comparison for 3 years of OS between NHL and HL with PR showed no significant statistical difference ($P = 0.09$) [Table 2 and Figure 1]. In previous studies, it has been mentioned that CR versus PR before transplantation is an independent prognostic factor that influences the survival.[17,10] Our study, however, showed that this difference is prominent for HL in comparison to NHL [Figure 1]. Our result suggests that the number of chemotherapy lines before transplantation affects the transplantation survival of lymphoma patients, meaning that better survival is seen with fewer chemotherapy lines. However, when comparisons between NHL and HL were done, 3 years of OS and PFS in HL with two or fewer lines of chemotherapy were not significantly different from NHL with the same condition [Figure 1]. On the other hand, when patients received three or more chemotherapy lines, their 3-year OS and PFS rates were significantly better in the HL group in comparison to NHL (3 years of OS

72% vs. 44%, $P = 0.01$; 3 years of PFS 58.1% vs. 33.1%, $P = 0.016$) [Figure 1]. In this study, patients with HL, despite contact to many chemotherapy drugs with more duration time, had a better survival after transplantation in comparison to NHL with the same conditions. Based on our findings, gender of patients has no significant effect on survival: Only 3 years of OS in male with HL had better outcomes in comparison to males with NHL, 3 years of OS in males with HL and NHL were 83.2% versus 66.7%, respectively. Since the number of female patients in the NHL group in this study was very low, the assessment of female gender is not reliable. In general, the comparison between NHL and HL in view of 3 years of OS and PFS in this study had statistical significance in these conditions: first, 3 years of OS in HL with CR were better than NHL with CR; second, 3 years of OS and PFS in HL with three or more chemotherapy lines were better than NHL with three or more chemotherapy lines; and third, 3 years of OS in HL male patients were better than NHL male patients. To eliminate the confounding factors, we used the Cox regression method, which is a multivariate analysis method. In this method, the HR for OS and PFS was calculated [Tables 4 and 5]. The most noticeable results were HR for post-transplantation OS between NHL and HL did not show any statistically meaningful difference, but it was better for HL (HR = 1.32, 95% CI = [0.53–3.27], $P = 0.56$). Therefore, when all the variables were omitted, OS was not found to be different between the two kinds of lymphoma. HR for OS significantly increased with increasing in age and increasing of chemotherapy lines before transplantation with meaningful P value, but HR for OS with regard to the kind of lymphoma, the duration of disease, the remission condition, and the gender had no meaningful P value. HR for PFS with these variables increased only for those patients who received more chemotherapy lines (with meaningful P value). HR for PFS with each increased line in chemotherapy was 1.44, 95% CI = 1.05–1.98, $P = 0.02$. However, in comparison to other variables such as gender, kind of lymphoma, remission condition, age at transplantation time, and duration of disease, HR did not show any significant difference. In general, when all variables are simultaneously considered, in this method, increasing chemotherapy lines before transplantation had the most adverse effect on OS and PFS.

Conclusion

Based on our results, HL patients tolerated the side effects of chemotherapy drugs on bone marrow better than NHL and showed better outcomes after transplantation even with more chemotherapy lines. Moreover, CR was an independent prognostic factor for OS in HL in comparison to NHL. Therefore, more chemotherapy lines to achieve CR were found to be a probably good choice in the HL group for better outcomes after transplantation. For NHL patients, if the chemotherapy will not result in CR after two chemotherapy lines, it is suggested that ASCT be done as soon as possible in order to achieve better survival after this procedure.

Research involving human participants and/or animals

All the procedures performed in the study involving human participants were in accordance with ethical standards of the Ethical Committee of Shahid Beheshti University of Medical Sciences as well as 1964 Helsinki declaration.

Informed consent

All patients signed the consent form.

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Conflicts of interest

There are no conflicts of interest.

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