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The autologous hematopoietic stem cell transplantation in adult patients with lymphoma: Turkish Bone Marrow Transplantation Registry results

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ABSTRACT

Turkish Bone Marrow Transplantation Registry (TBMTR) was established in 1995. Since 1992, data of adult lymphoma patients from fifteen national transplantation centers were collected and analyzed by TBMTR. A total of 437 adult lymphoma patients (185 Hodgkin's and 252 non-Hodgkin's lymphoma) undergoing autologous hematopoietic stem cell transplantation (HSCT) were registered in TBMTR from 1992 to 2002. Peripheral blood as stem cell source was used in 94% of the transplantations. Non-TBI (total body irradiation) conditioning regimens were administered in 88% of the cases. The 100-day transplantation-related mortality (TRM) was 11% in relapsed and 11% in primary refractory Hodgkin's lymphoma patients whilst TRM was found to be 9% and 30% in non-Hodgkin's lymphoma patients in first remission and in primary refractory cases, respectively. Infection was the most common cause of TRM. 10-year and 5-year survival rates were 50% and 49% in relapsed cases and primary refractory cases with Hodgkin's lymphoma, respectively; while in non-Hodgkin's lymphoma patients 10-year survival rate was 65% in cases in first remission, 7-year survival rate was 50% in sensitive relapse, 2-year survival rate was 0% in resistant relapse and 3-year survival was 24% in primary refractory cases. In conclusion, TBMTR results are comparable to EBMT and IBMTR results. Therefore, autologous HSCT may provide long-term survival in patients with Hodgkin's lymphoma as well as in patients with non-Hodgkin lymphoma in first remission and in sensitive relapse. [Turk J Cancer 2007;37(2):45-53]

KEY WORDS:

Registry, lymphoma, autologous stem cell transplantation, Turkish Oncology Group

INTRODUCTION

Bone marrow or peripheral blood stem cell transplantation (PBSCT) may provide long-term remission and cure for a proportion of patients with Hodgkin's and non-Hodgkin's lymphoma.

First Turkish allogeneic bone marrow transplantation for lymphomas was commenced in 1987, whereas autologous bone marrow transplantation in 1992 and PBSCT in 1993. The Turkish Bone Marrow Transplantation Registry (TBMTR) was founded in 1995 and nationwide data accumulation for hematopoietic stem cell transplantation (HSCT) has been done since then. A total of 15 centers participate actively in bone marrow and PBSC transplantation activities and report their results regularly to the registry.

This is the first published report for long-term results of HSCT activity and outcomes in Turkey. Here, we evaluate retrospectively the results of patients with Hodgkin's and non-Hodgkin's lymphoma who underwent autologous transplantation from 1992 until 2002 in Turkish bone marrow transplantation (BMT) centers.

MATERIALS AND METHODS

Patients

A total of 511 adult (over 15-years of old) lymphoma patients (185 Hodgkin's and 252 non-Hodgkin's lymphoma) undergoing HSCT were registered in TBMTR between 1992 and 2002; while of these 511 patients, 74 were excluded due to insufficient data records. Histopathologic subclassification was done according to REAL classification and no patient has received rituximab before transplantation.

Disease status of the patients before the transplantation were relapse and primary refractory disease for Hodgkin's lymphoma and sensitive relapse, resistant relapse, first complete or partial remission (CR1/PR1) and primary refractory disease for non-Hodgkin's lymphoma patients.

Data collection

Each transplantation center in Turkey has been requested to contribute data to the Registry and data of 15 transplantation centers registered in TBMTR were analyzed retrospectively beginning from 1992 to 2002. A standard Med-A form was completed at each center and sent to registry center for each transplantation. The presence or absence of relapse and the disease status of the patient and cause of death was requested to each center in annual basis.

The date of autologous HSCT was noted as day 0 and follow-up date was the date of the last medical examination.

Statistical analysis

Probabilities of 100-day mortality (death from any cause in the first 100 days after transplantation) and overall survival were calculated using SPSS 9.0 statistical software by the method of Kaplan-Meier (SPSS Inc, Chicago, IL, USA). Overall survival was measured from the date of transplantation (stem cell infusion) to the date of death from any cause or the last follow-up evaluation.

Table 1
Characteristics of patients with Hodgkin's lymphoma

Total number (n)	185
Disease status at transplantation	
Relapsed	159
Primary refractory	26
Median age (year)	23 (15-64)
Sex (M/F) (%)	68/32
Median Dx-Tx time (days)	884 (112-5874)
Histopathologic subclassification	%
Mixed cellularity	48
Nodular sclerosing	25
Lymphocyte predominant	13
Lymphocyte depleted	7
Pathology unknown	7
Relapsed patients	
Total number (n)	159
Median age	23 (20-55)
Sex (M/F) (%)	71/29
TTT*(days)	944 (112-5874)
Primary refractory patients	
Total number (n)	159
Median age	23 (15-64)
Sex (M/F) (%)	73/27
TTT(days)	498 (226-566)

TTT: Time to transplantation

RESULTS

During the 10 years from 1992 to 2002, a total of 511 adult patients with diagnosis of lymphoma were transplanted in Turkey, 437 of whom were eligible for registry.

Hodgkin's lymphoma

Patient characteristics for the entire group are shown in table 1. One-hundred and eighty-five patients were Hodgkin's lymphoma with a male to female ratio of 125/60. The median age of the patients was 23 years (range: 15-64). One-hundred and fifty-nine patients out of 185 were relapse cases and 26 out of 185 were primary refractory disease at the time of transplantation. Histopathologic subclassification were mixed cellular (48%), nodular sclerosing (25%), lymphocyte-predominant (13%), lymphocyte-depleted (7%) and pathology unknown (7%).

Non-Hodgkin's lymphoma

Patients' characteristics are given in table 2. Two-hundred and fifty-two patients were non-Hodgkin's lymphoma. The median age of the patients was 36 years (range: 15-65) with 189 male and 63 female. The histopathologic subtype of the disease was diffuse large B cell (47%), precursor T lymphoblastic (18.8%), mantle cell (6.92%), peripheral T cell (6.92%), anaplastic large cell (5.42%), follicular (4.74%), immunoblastic (4.34%), Burkitt's (3.25%), nodal marginal zone B cell (1.62%), mycosis fungoides (1.08%).

Hematopoietic stem cell sources and conditioning regimens

Bone marrow (3%), bone marrow with peripheral blood (<1%), peripheral blood with CD34+ selection (3%) and peripheral blood (94%) were used as sources of hematopoietic stem cells.

Non-TBI (total body irradiation) conditioning regimens were used in 88% of the transplantations [BEAM (BCNU, etoposide, cytarabine and melphalan) vs. CBV (cyclophosphamide, BCNU, etoposide)], whereas 12% of the patients underwent TBI containing conditioning regimens for lymphoma.

Outcome

100-day transplantation-related mortality rate was 11% in all Hodgkin's lymphomas including relapsed and

Table 2
Characteristics of patients with non-Hodgkin's lymphoma

Total number (n)	252
Disease status at transplantation	
Sensitive relapse	112
Resistant relapse	23
CR1/PR1*	72
Primary refractory	45
Median age (year)	36 (15-65)
Sex (M/F) (%)	75/25
Median Dx-Tx time (days)	422 (55-5139)
Histopathologic subclassification	%
Diffuse large B cell	47
Precursor T lymphoblastic	18.8
Mantle cell	6.92
Peripheral T cell	6.92
Anaplastic large cell	5.42
Follicular lymphoma	4.74
Immunoblastic	4.34
Burkitt's lymphoma	3.25
Nodal marginal zone B cell	1.62
Mycosis fungoides	1.08
Sensitive relapse	
Total number (n)	112
Median age	40 (18-63)
Sex (M/F) (%)	72/28
Median Dx-Tx time (days)	651 (304-5139)
Resistant relapse	
Total number (n)	23
Median age	41 (15-65)
Sex (M/F) (%)	79/21
Median Dx-Tx time (days)	407 (174-2041)
CR1/PR1	
Total number (n)	72
Median age	32 (17-62)
Sex (M/F) (%)	78/22
Median Dx-Tx time (days)	274 (111-390)
Primary refractory	
Total number (n)	45
Median age	32 (15-57)
Sex (M/F) (%)	74/26
Median Dx-Tx time (days)	370 (55-448)

*CR1/PR1: first complete remission/partial remission

Table 3
Transplant-related mortality (TRM) in patients with Hodgkin's and non-Hodgkin's lymphoma

	TRM (%)
Hodgkin's lymphoma	
All cases	11
Relapsed	11
Primary refractory	11
Non-Hodgkin's lymphoma	
All cases	15
Sensitive relapse	13
Resistant relapse	30
CR1/PR1*	9
Primary refractory	22

*CR1/PR1: first complete remission/partial remission

primary refractory cases; whereas the rate was 15% in all non-Hodgkin's lymphomas (9% in CR1/PR1, 13% in sensitive relapse, 22% in primary refractory cases and 3% in resistant relapse) (Table 3).

The main cause of death in all patients was the relapse of the primary disease (86%) in addition to transplantation-related mortality (14%).

The overall survival rate was 50% in all patients with Hodgkin's lymphoma at 10-year follow-up (Figure 1),

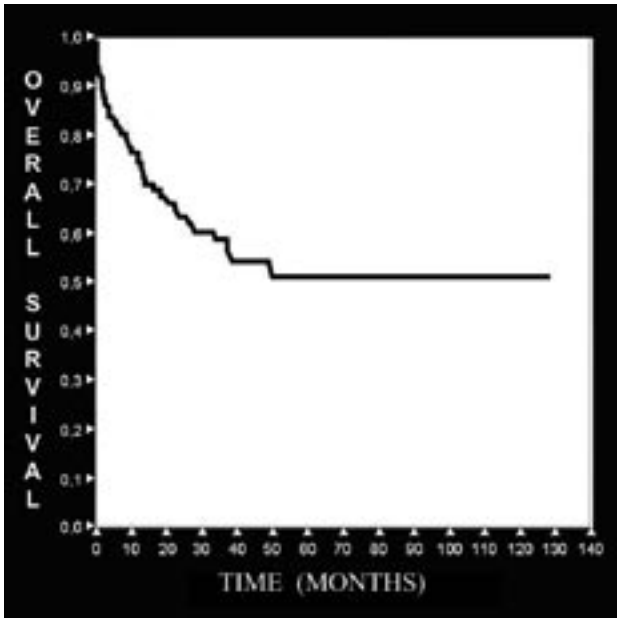

Fig 1. Survival of all patients with Hodgkin's lymphoma

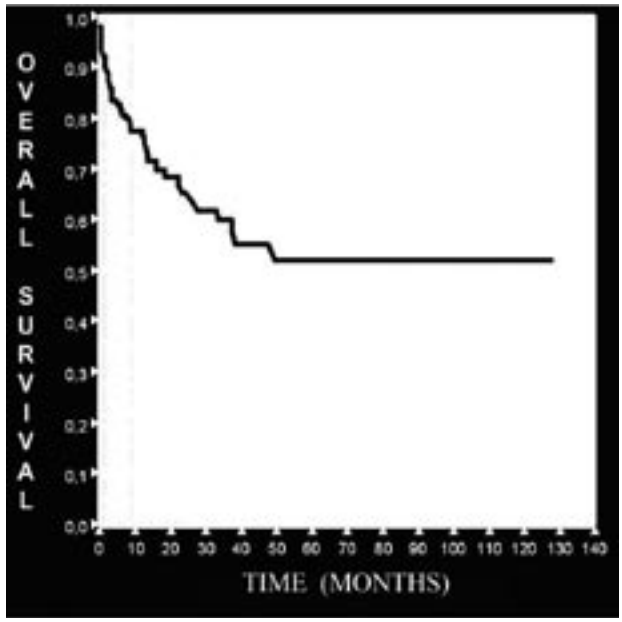

Fig 2. Survival of patients with Hodgkin's lymphoma with relapse

50% in relapsed cases at 10th year (Figure 2) and 49% in primary refractory cases at 5th year (Figure 3); whereas, in patients with non-Hodgkin's lymphoma the overall survival rate at 10th year was 45% in all cases (Figure 4), 65% at 10th year for CR1/PR1 (first complete/partial remission) (Figure 5), 50% at 7th year for sensitive relapse (Figure 6), 24% at 3rd year for primary refractory disease (Figure 7) and 0% at 2nd year for resistant relapse (Figure 8).

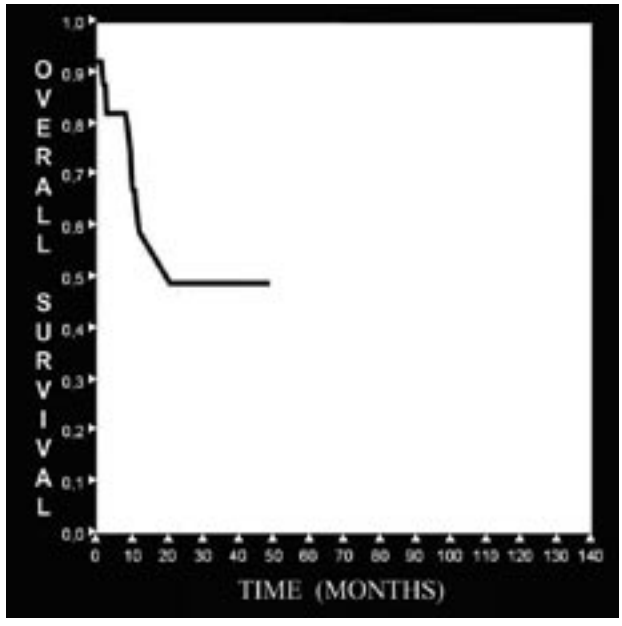

Fig 3. Survival of patients with Hodgkin's lymphoma with primary refractory disease

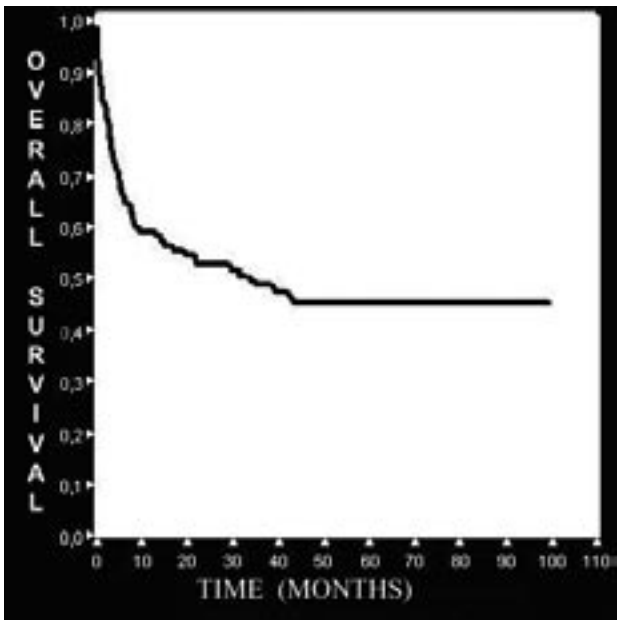

Fig 4. Survival of all patients with non-Hodgkin's lymphoma

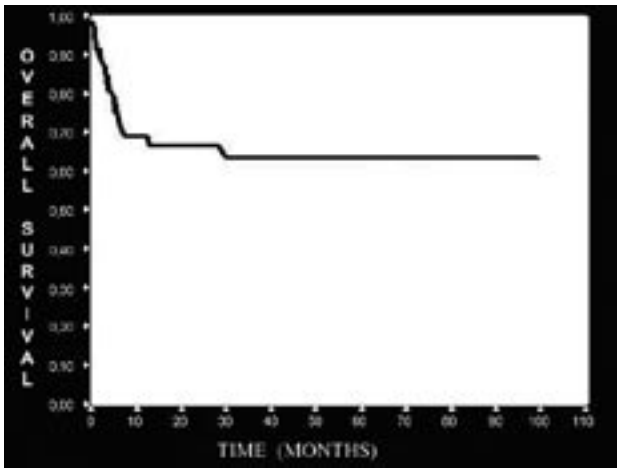

Fig 5. Survival of patients with non-Hodgkin's lymphoma with CR1/PR1

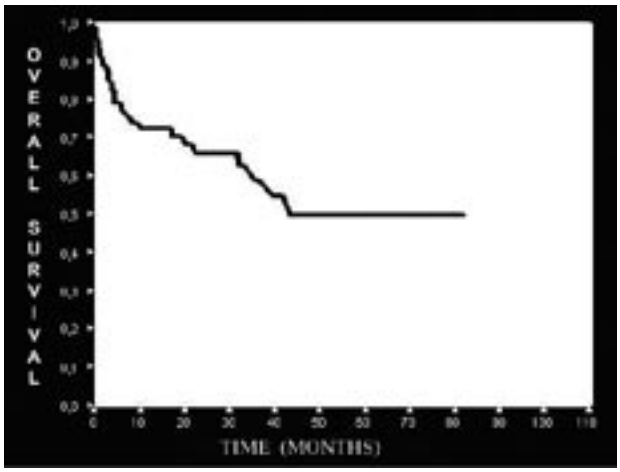

Fig 6. Survival of patients with non-Hodgkin's lymphoma with sensitive relapse

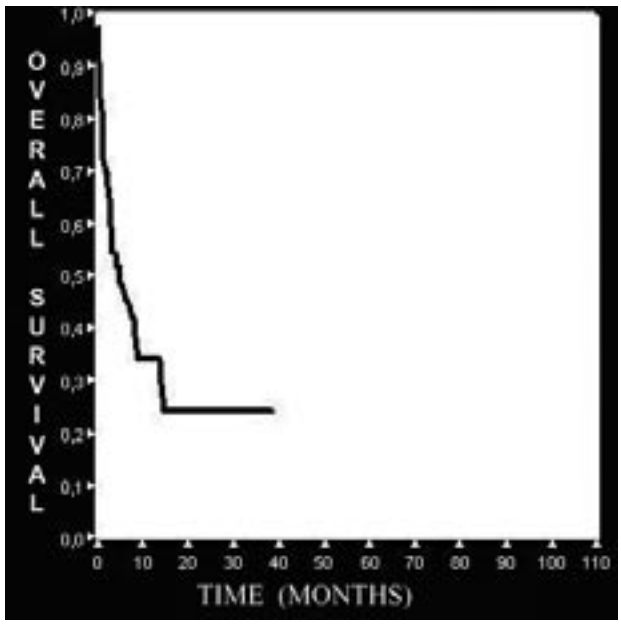

Fig 7. Survival of patients with non-Hodgkin's lymphoma with primary refractory disease

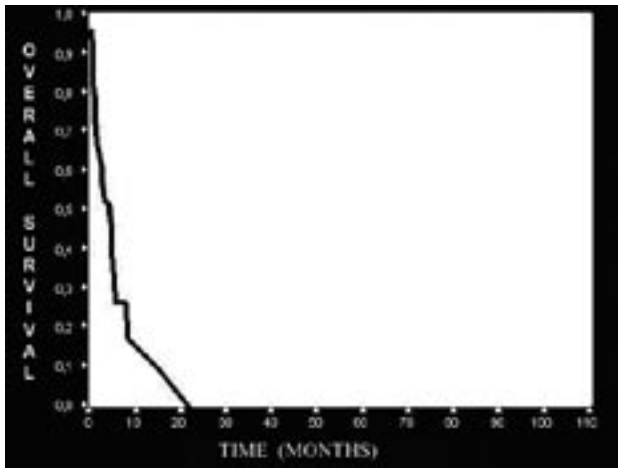

Fig 8. Survival of patients with non-Hodgkin's lymphoma with resistant relapse

DISCUSSION

The number of HSCT in Turkey increased rapidly beginning from early 1990 hitherto. The number of transplantations in Hodgkin's lymphoma reached around 43 transplantations per year, whereas 63 transplantations per year were done for non-Hodgkin's lymphoma. After year 2000, the activity of the transplantation has been accelerated (Turkish Transplantation Registry, oral communication).

It is well known that the majority of patients with advanced Hodgkin's lymphoma can be effectively treated with standard chemotherapy (1). Unfortunately, patients with primary resistant or relapsed disease have a relatively low chance of cure.

There are no randomized trials comparing conventional salvage chemotherapy to autologous transplantation in patients with Hodgkin's disease who have not achieved a complete remission with initial therapy. There are only two relatively small randomized clinical trials comparing high-dose with standard-dose chemotherapy in high-risk Hodgkin's lymphoma showing a 4-year event-free survival rate of 50% (2-4). Some reports have also suggested that patients with Hodgkin's lymphoma with primary refractory disease do less well than those patients who achieved an initial remission to front-line therapy (5).

In fact, autologous HSCT seems to be the best curative option for patients with relapsed and primary refractory Hodgkin's lymphoma (2,6,7). Recently, encouraging reports on high-dose chemotherapy in primary refractory Hodgkin's disease have been published worldwide (5, 8-11). Reported 5-year overall survival probability is 35-60% in patients with primary resistant disease and 50-65% in patients who have relapsed after standard therapy (8-12). Moskowitz et al. (13) found a marked survival advantage with HSCT for patients who have chemosensitive Hodgkin's disease; however overall survival was similar for patients with relapsed or primary refractory disease.

Our study findings indicate that autologous HSCT can lead to durable remissions in 50% of patients with primary refractory or relapsed Hodgkin's lymphoma patients which is consistent with other study results, as well as with those of ABMTR (8,14,15).

Anthracycline-based induction chemotherapy produces complete remission rates of 50% to 70% and long-term disease-free survival in approximately 40% of patients with aggressive non-Hodgkin's lymphoma (16, 17). However, in all series, 30% to 50% of patients fail to achieve complete remission with standard induction therapy and require salvage therapy. Increasingly, salvage therapy strategies include autologous HSCT.

The benefit of autologous HSCT in patients without complete remission by their initial induction chemotherapy is not well defined. GEL/TAMO trial (18) demonstrated a 5-year survival response of 43% in patients who failed to achieve complete remission with front-line conventional chemotherapy. Whereas, the Parma trial (19) is the first study which randomized patients with chemotherapy-sensitive relapsed disease to either standard salvage chemotherapy or autologous HSCT, and demonstrated improved progression-free survival and overall survival in the transplantation group. SWOG phase-II study (20) showed similarly that autologous bone marrow transplantation prolongs survival in relapsed non-Hodgkin's lymphomas. Mills et al. (21) reported a progression-free survival rate of 32% in patients with chemotherapy-sensitive relapsed disease. Many other studies containing small numbers of patients demonstrated progression-free survival rates of 30% to 40% (18,22,23). Another study from ABMT showed a better outcome in chemotherapy-sensitive disease with a survival rate of 44% at 3-year (24). Our survival outcome was 50% at 85 month follow-up for patients with sensitive relapse and is comparable to these studies.

Sensitivity to chemotherapy in relapsed non-Hodgkin's lymphoma is of prognostic significance. Relapse-free survival rate after autologous transplantation was 0-15% in the primary refractory group and 15-30% in the sensitive relapsed group (25). Philip et al. (26) reported an event-free survival of 10-15%, which is similar to that observed with standard-dose salvage regimens in patients with refractory relapsed non-Hodgkin's lymphoma. Many subsequent studies of transplantation excluded such truly primary refractory patients from transplantation and better results were observed in chemosensitive patients than chemoresistant primary failures (23). We haven't excluded patients with primary refractory disease from the study and we found a low rate of survival as 24% at 40-month follow-up consistently with these studies.

Despite controversy, some randomized controlled trials showed positive value for autologous HSCT as an initial treatment for high-intermediate and high-risk non-Hodgkin's lymphoma: the GELA (27) and Milan (28) studies, and the Italian study by Santini et al. (29) reported that high-dose therapy with transplantation improves relapse-free survival and overall survival. This was prospectively confirmed by the recent GOELAMS study (30). On the other hand, three other studies from an Italian group (31), the German Lymphoma Group (32), and Martelli et al.'s study (33) found no significant difference with respect to relapse-free survival and overall survival. Our results also confirm that early transplantation in the first complete and partial remission may increase the overall survival rate (65%) in aggressive non-Hodgkin's lymphoma.

With better selection of patients, improved supportive care and the introduction of blood stem cells, the early

TRM associated with autologous HSCT has decreased to less than 5% (34,35). According to ABMTR data, TRM rate is around 5-8% in Hodgkin's lymphoma and around 10% in non-Hodgkin's lymphoma. In our study, TRM was 11% in Hodgkin's and 15% in all non-Hodgkin's lymphoma cases. These rates are consistent with the results of international registries.

In summary, autologous HSCT leads to durable remission in the majority of patients with Hodgkin's disease and non-Hodgkin's lymphoma. However, chemoresistant relapsed and primary refractory patients with non-Hodgkin's lymphoma have a poorer survival than chemosensitive patients. Our transplantation results on lymphomas are similar to other single or multicenter study results.

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