Original Article
Middle East Journal of Cancer; April 2023; 14(2): 259-269

Outcomes of Autologous Stem Cell Transplantation for Non-Hodgkin Lymphoma Patients at a Tertiary Referral Centre

Ajay Prakash*♦, FRACP, Hugh Goodman, FRACP**

*Division of Oncology, Saskatchewan Cancer Agency, College of Medicine, University of Saskatchewan, Regina, Canada
**Department of Hematology, Waikato Hospital, Hamilton, New Zealand

Please cite this article as: Prakash A, Goodman H. Outcomes of autologous stem cell transplantation for non-Hodgkin lymphoma patients at a tertiary referral centre. Middle East J Cancer. 2023;14(2):259-69. doi: 10.30476/mejc.2022.93676.1703.

Abstract

Background: Autologous stem cell transplant (ASCT) has been used as a consolidative treatment modality in non-Hodgkin's lymphoma (NHL), but its role in NHL management is still evolving. The study aimed to evaluate the patient outcomes based on age, NHL subtypes, and conditioning regimen.

Method: We performed a retrospective analysis of NHL patients who received ASCT (n = 140) in our centre from 1992-2015. Data were gathered for this investigation using electronic records and case notes. Refractory illness, relapse, progressive disease, or death were all considered progression events. Time from ASCT to the last follow-up or progression event was used to define progression-free survival (PFS), and time from ASCT to death or the final follow-up was used to define overall survival (OS).

Results: Median age at ASCT was 55 years (16-68). Amongst patients ≤60 years (n = 109) and >60 years (n = 31), there was no significant difference in PFS (*P* = 0.756), OS (*P* = 0.711), neutrophil (12.5 vs. 11 days) and platelet (12 vs. 14 days) engraftment times. Amongst follicular lymphoma patients (n = 54) who received BEAM (carmustine, etoposide, cytarabine, melphalan) (n = 30) or Cy/TBI (cyclophosphamide/total body irradiation) (n=24) conditioning, there was no significant difference between PFS (*P* = 0.111) and OS (*P* = 0.667). There was no significant difference (*P* = 0.46) in the incidence of second malignancies in the patient receiving BEAM or TBI-based conditioning.

Conclusion: ASCT can be safely performed for NHL in patients >60 years with outcomes similar to those ≤60 years. TBI based conditioning appear safe with similar outcomes to BEAM in follicular lymphoma patients. Prospective studies are needed to confirm these findings.

Keywords: Non-Hodgkin lymphoma, Stem cell transplant, Autologous, Total body irradiation, Transplantation conditioning

♦Corresponding Author:
Ajay Prakash, FRACP
Division of Oncology, Saskatchewan Cancer Agency, College of Medicine, University of Saskatchewan, Regina, Canada
Tel: +1 306-625-2016
Fax: +1 855-809-3067
Email: babloo_doc@hotmail.com
Ajay.prakash@saskcancer.ca

Middle East Journal of Cancer

Received: November 30, 2021; Accepted: July 20, 2022

Introduction

Autologous haematopoietic stem cell transplant (ASCT) was successfully used as a consolidative treatment modality in non-Hodgkin's lymphomas (NHL) for many years, but its role to manage NHLs continues to evolve.

Results of therapies for many indolent lymphoma subtypes have improved dramatically over the last several years using the monoclonal antibodies like rituximab[1,2] and radio-immuno-conjugates[3] and in turn, resulted in redefining the use of ASCT in first complete remission for these subtypes. However, recent studies have further verified the effectiveness of ASCT in primary central nervous system (CNS) lymphoma and further supported that ASCT continues to be a significant consolidative therapeutic strategy for many forms of NHL in relapse/refractory context.[4]

Data from different centres differ in terms of the outcomes, toxicity and overall survival (OS) with various conditioning regimens and disease subtypes.[5] It is reflected, for example, in the differences in conditioning regimens. There are conflicting reports about negative outcomes in patients over the age of 60 years undergoing ASCT.[6,7] The increased incidence of secondary myelodysplastic syndrome/acute myeloid

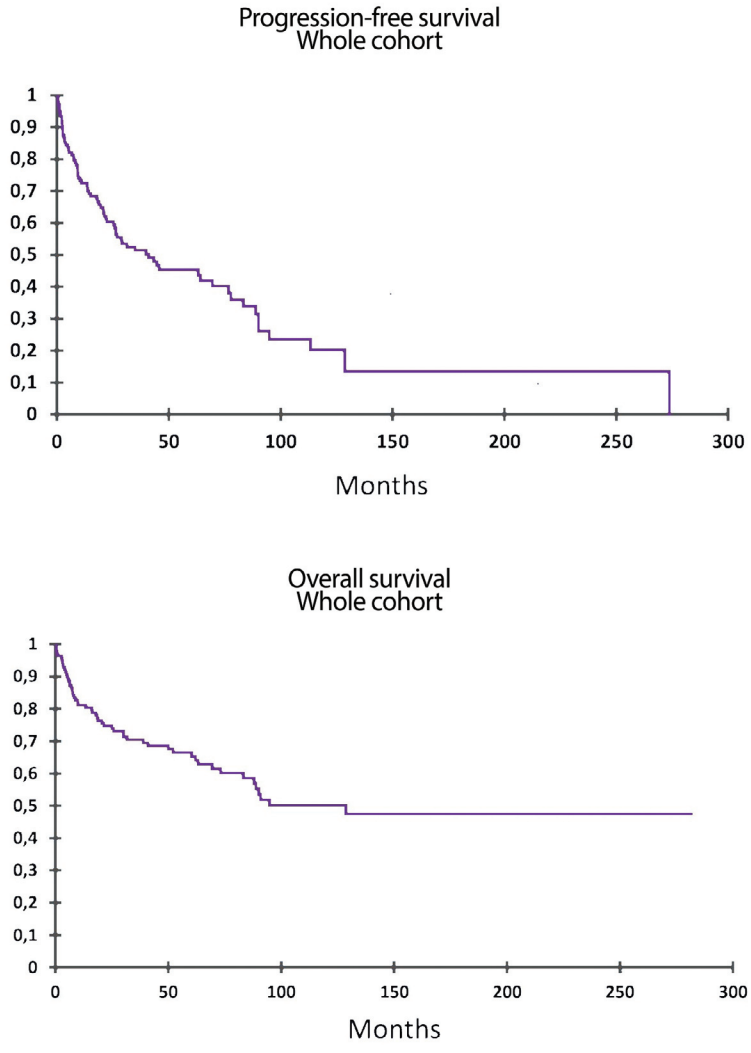

Figure 1. This figure shows the progression-free survival and the overall survival for whole cohort.

leukaemia (sMDS/sAML) following ASCT is well documented.[8,9] Factors reported to be associated with an increased risk of sMDS/sAML after ASCT include older patient age,[7,8] multiple lines of chemotherapy particularly with alkylating agents,[10] etoposide[11] or fludarabine,[8] and using total body irradiation (TBI) with transplant conditioning[12] and so on.

We report retrospective data of 140 NHL patients who received ASCT at Waikato Hospital, Hamilton, New Zealand over a period of 23 years with the purpose of adding to the data on these difficulties (1992-2015). Based on age, NHL subtypes, and exercise routine, we assess patient outcomes and sequelae as well as potential confounding variables.

Patients and Methods

All patients (n = 140) who underwent their first ASCT for NHL between 1992 and 2015 at Waikato Hospital, Hamilton, New Zealand were included in this retrospective study. Patients were found using a prospective ASCT database, and information was gathered from both digital and analog clinical records. The study was approved by the Department of Haematology of Waikato Hospital, New Zealand, and by Health and Disability Ethics Committees of New Zealand

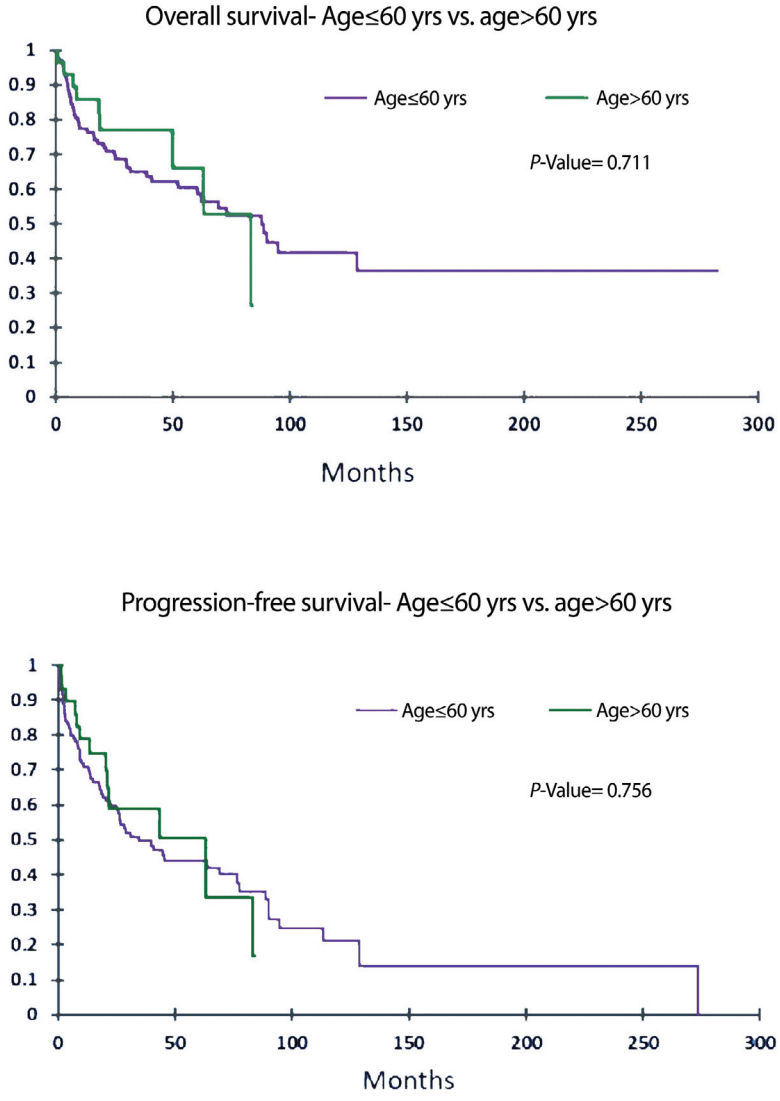

Figure 2. This figure shows the progression-free survival and the overall survival for the patients aged ≤ 60 and > 60 years.

under the study project to evaluate outcomes of patients managed in New Zealand blood and cancer centers (ethics code: 16/STH/251).

Age alone was not employed as a decisive criterion to determine ASCT eligibility as a departmental policy, and the entire clinical state, together with additional comorbidities, was used to assess transplant eligibility in an individual patient. The transplant physician made the decision on the regimen, namely between cyclophosphamid/TBI (Cy/TBI) and BEAM. However, in recent years, there has been a broad tendency among clinicians to use BEAM as a conditioning program. Transplant outcome parameters included neutrophil engraftment (defined as first day of recovery to >0.5 × 109/L), platelet engraftment (first day of spontaneous recovery to >20 × 109/L) and admission duration. Transplant related mortality (TRM) was defined as death during the hospital admission for ASCT or any time within 100 days of ASCT unless due to progressive disease.

Disease response, relapse, and progression were assessed by the International Working Group response criteria.[13] In brief, these are:

a) Relapse was defined as disease recurrence after remaining in complete remission for at least 90 days from end of treatment.

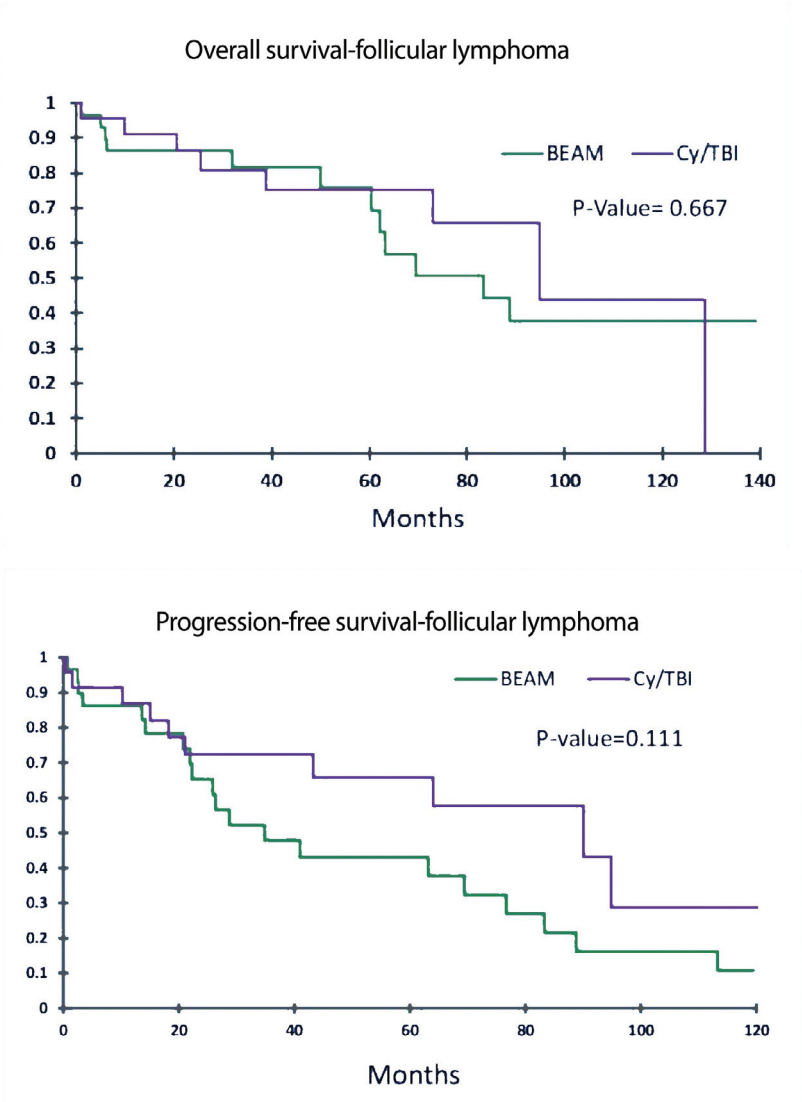

Figure 3. This figure shows the progression-free survival and the overall survival for follicular lymphoma patients as per conditioning.
TBI: Total body irradiation; Cy: Cyclophosphamide; BEAM: carmustine, etoposide, cytarabine, melphalan

Table 1. Data as per age group

	Age ≤60 years	Age > 60 years
Total	109	31
Sex distribution	Female= 39, Male= 70	Female= 9, Male= 22
Conditioning	BEAM=78, Cy/TBI= 22, Etoposide/TBI=4, Thiotepa/BCNU= 5	BEAM= 22, Cy/TBI= 7, Thiotepa/BCNU= 2
Diagnosis	DLBCL-28, FL-41, Burkitt's -3, Burkitt's Like-3 Lymphoblastic - 6, Mantle-6, Marginal Zone-1, NHL NOS- 2, NK/T Cell-2, PTCL-9, PMBC-2, Primary CNS-4, Secondary CNS-1 Plasmablastic -1	DLBCL-8, FL- 13, Double HIT-3 Burkittís Like-1, Mantle-2, Marginal- 1, PTCL- 1, Primary CNS-1 Secondary CNS-1
Median age at transplant, years (range)	50 (16-60)	64 (61-68)
Median neutrophil recovery, days (range)	12.5 (8-20)	11 (9-41)
Median platelet recovery, days (range)	12 (8-50)	14 (8-78)
Median days in hospital (range)	21 (16-47)	20 (16-35)
TRM	2	0
Relapse/Refractory	57	13
Death	46	9
Follow-up, months (range)	30.6 (0.2-282.7)	21.4 (0.4-84)
Median PFS, months (range)	23.8 (0.2-273.7)	13.7 (0.6-87.4)
Median OS, months (range)	31.1 (0.2-282.7)	28.3 (0.6-141.2)
2 year PFS (%)	49.5	45.22
Year OS (%)	57.8	51.6

FL: Follicular lymphoma; DLBCL: Diffuse large B cell lymphoma; CNS: Central nervous system; PMBC: Primary mediastinal B cell lymphoma; PTCL: Peripheral T cell lymphoma; NK: Natural killer cell; NOS: Not otherwise specified; TBI: Total body irradiation; Cy: Cyclophosphamide; BEAM: Carmustine, etoposide, cytarabine, melphalan, TRM: Transplant related mortality; BCNU= Carmustine; PFS: Progression-free survival; OS: Overall survival

b) Refractory disease was defined as response <partial remission (PR), or disease recurrence within 90 days of ASCT.

c) Disease progression was defined as new site/s of disease or > 50% increase in previously involved sites as measured clinically or by radiological scans after achieving PR and stable disease for at least 90 days.

Relapse, refractory disease, progressive disease, or death were all considered progression events. PFS was defined as the time from transplant to a progression event, or if no progression event occurred, the time from transplant to the date of final follow-up. OS was defined as time from transplant till death, or if no death, then time from transplant till date of last follow-up.

XLSTAT v2016.03 (Addinsoft) was used for statistical analysis. Kaplan Meier method was used to calculate PFS and OS, and differences were assessed by log-rank technique.

Results

140 patients were identified, 89 (64%) male / 51 (36%) female with a median age of 53 years (16-68).

The transplanted diseases are listed in table 1.

The vast majority of patients (100, 71%) had conditioning with BEAM (BCNU/carmustine, etoposide, ara-C/cytarabine, melphalan), 29 had Cy/TBI, 7 had thiotepa/BCNU and 4 had etoposide/TBI as conditioning regimen (Table 1).

The median period of follow-up was 29.1 months (0.2-282.6). The median PFS and OS for the whole cohort were 20.9 months (0.2-273.7) and 48.8 months (0.2-281.5), respectively (Figure 1).

The median age at transplant was 53 years (16-68). 109 patients were ≤60 years with a median age at transplant of 50 years; and total 31 patients were >60 years with a median age at transplant of 64 years (Table 1). Age did not affect transplant outcome. Median time to neutrophil recovery, platelet recovery, and inpatient days

Table 2. Follicular lymphoma data as per conditioning

	FL (BEAM)	FL (Cy/TBI)
Total	30	24
Median age at transplant, years (range)	51 (35-67)	57 (34-67)
TRM	0	0
Median neutrophil recovery (days)	11 (8-19)	10 (9-18)
Median platelet recovery (days)	12 (8-29)	11 (8-20)
Median days in hospital	21 (17-38)	19 (16-23)
Relapse/refractory	16	9
Death (total/ relapse related)	12/8	8/6
Median follow-up, months (range)	44.5 (0.5- 139.1)	44.1 (0.4-129)
Median PFS, months (range)	24.2 (0.5-119.4)	37.8 (0.4-129)
Median OS, months (range)	44.5 (0.5-139.1)	44.1 (0.4-129)
2-year OS (%)	63.3	66.8
2-year PFS (%)	50	54.2

FL: Follicular lymphoma; TBI: Total body irradiation; Cy: cyclophosphamide; BEAM: Carmustine, etoposide, cytarabine, melphalan; TRM: Transplant related mortality; PFS: Progression-free survival; OS: Overall survival

were 12.5, 12, and 21 days for age ≤ 60 years and 11, 14, and 20 days for age >60 years, respectively. By a median follow-up of 30.6 months (0.2-282.7) and 21.4 months (0.4-84) for patients aged ≤ 60 years and >60 years, respectively; there was no difference in PFS (P = 0.756) or OS (P = 0.711) (Figure 2).

54 patients with follicular lymphoma (FL) underwent conditioning treatments: 30 got BEAM (FL-BEAM) and 24 received Cy/TBI (FL-Cy/TBI) (Table 2). The median time to neutrophil recovery, platelet recovery, and inpatient days were quite close to one another at days 11, 12, 21 and days 10, 11, 19, respectively. There was no TRM in either of the groups. By a median follow-up of 44.5 months (0.5- 139.1) and 44.1 months (0.4- 128.6) for patients in FL-BEAM and FL-Cy/TBI groups respectively, the differences in PFS (P = 0.111) and OS (P = 0.667) were not statistically significant (Figure 3). Long-term adverse effects were also similar. Secondary MDS/AML developed in two patients in each group. Cataract as side-effect was exclusively seen in Cy/TBI group. Persistent cytopenias were more common in FL-cy/TBI group than FL-BEAM group (4 vs. 1, respectively).

There were 36 DLBCL patients (excluding primary mediastinal B-cell [PMBC], CNS lymphoma and double hit lymphoma) who had an ASCT during this period with a median age of 55 years (28-68) (Table 3). The majority of patients were treated during their second remission. The BEAM conditioning protocol was administered to all DLBCL patients. The median time to recover neutrophils, platelets, and hospital days was 11, 14, and 22 days, respectively. There was one TRM, with the patient dying of Staphylococcus aureus sepsis on day +7. By a median follow-up of 17.81 months (0.2- 282.7), the median PFS was 13.6 months and median OS was 17.8 months. Two year PFS and OS were 36.1% and 44.4%, respectively.

Cy/TBI conditioning was used in 29 patients, the majority (24) was for FL (Lymphoblastic lymphoma-2, Burkitt's-like-2 and marginal zone lymphoma-1).

100 patients received BEAM conditioning. The majority (36) had DLBCL or FL (30). The median age at transplantation was 52 (23-68). The median time to recover neutrophils, platelets, and hospital days was 11, 13, and 21 days, respectively. There were 2 TRM, both due to sepsis. By a median follow-up of 25.8 months (0.2-282.7), the median PFS and OS were 18.20 months (range 0.2-273.7) and 21.57 months (range 0.2-282.7), respectively. The 2-year PFS and OS was 40% and 49%, respectively. The most common complication was prolonged cytopenia (10 patients), followed by *Clostridium difficile* infection, paroxysmal atrial fibrillation and cardiomyopathy developing in 3 patients each.

The total numbers of other NHL subtypes were low. The combined data to remain B-cell NHL (including Mantle cell, Marginal zone, Primary

Table 3. Data as per NHL subtype

NHL type	FL	DLBCL	Other B cell †	T, Nk cell ‡
Number	54	36	32	18
Follow-up months (range)	45.1(0.4-140.9)	17.8 (0.2- 282.7)	16.4(0.4-143.1)	39.6(5.3-185.8)
Median age,years (range)	54(34-67)	55 (28-68)	53(31-65)	37 (16-64)
Remission status	CR1=2, CR2=31, CR3=6, CR4=2, PR1=3, PR2=8, PR3=2	CR1=2, CR2=22, PR1- 5, PR2- 6, PR3- 1	CR1=20, CR2=4, CR3=1CR4=1, PR1=1, PR2=5	CR1=9, CR2=6, PR1=1, PR2=2
Conditioning	BEAM30, CyTBI-24	BEAM (All)	BEAM-22, Thiotepa/BCNU- 7, CyTBI-3	BEAM-12, Etoposide/TBI-4, CyTBI-2
Median PFS months (range)	26.3(0.4-128.6)	13.6(0.2-273.7)	12.5(0.4-87.4)	38.5(1.2-183.3)
Median OS months (range)	44.5(0.4-139.1)	17.8(0.2-282.7)	19.5(0.4-259)	46(5.2-264.6)

† Burkitt's-3, Burkitt's Like-4, PMBC-2, Plasmablastic-1, Mantle cell-8, Marginal zone-2, Primary CNS-5, Secondary CNS-2, Double Hit-3, NOS-2
‡ PTCL-10, NK/T Cell-2, T Lymphoblastic-6
FL: Follicular lymphoma; DLBCL: Diffuse large B cell lymphoma; CNS: Central nervous system; PMBC: Primary mediastinal B cell lymphoma; PTCL: Peripheral T cell Lymphoma; NK: Natural killer cell; NOS: Not otherwise specified; TBI: Total body irradiation; Cy: Cyclophosphamide; BEAM: Carmustine, etoposide, cytarabine, melphalan; BCNU: Carmustine; CR: Complete remission; PR: Partial remission; PFS: Progression-free survival; OS: Overall survival

CNS, Secondary CNS, Double Hit, Burkitt's, Burkitt's like, Primary mediastinal B cell, Plasmablastic) and T cell NHL (including peripheral T cell lymphoma, NK/T Cell, T lymphoblastic lymphoma) are presented in table 3. The outcomes for these individual NHL subtypes were difficult to interpret due to low numbers.

The adverse impacts were examined. Only 2/140 early non-disease related fatalities, both from sepsis, indicated low TRM. Two patients had secondary MDS after BEAM, while four patients experienced sAML after BEAM and two after Cy/TBI. The median time from ASCT to sAML was 65.5 months (48-83). Non-haematological second malignancies developed in five patients with a mix of NHL types and conditioning regimens. Amongst these five patients, two developed bowel carcinoma and one developed both right renal transitional cell carcinoma and metastatic squamous cell lung carcinoma. Out of remaining two, one developed lung carcinoma and other had right medial canthus basal cell carcinoma.

In total, 5/100 (5%) patients receiving BEAM conditioning developed secondary malignancy (haematological and non-haematological) in comparison to 3 out of 33 (9%) patients who received TBI-based conditioning regimen. This difference was not statistically significant (P = 0.46).

Discussion

ASCT is still a very important consolidative treatment for many types of NHL. The goal of this retrospective study of ASCT-treated NHL patients at our facility was to assess patient outcomes depending on age, NHL subtypes, and conditioning regimens. Based on these criteria, we also tried to assess the side-effect profiles. The typical limitations of a retrospective research were present in our analysis. However, it offered some distinct results that were in line with certain other research that had already been published.

Older NHL patients have been historically considered to be having increased risk of therapy-related toxicity, including TRM and sMDS/AML.[8] It is believed to be because of age-related physiological changes and frequent comorbidities. Age is one of the factors included in hematopoietic cell transplantation-comorbidity index (HCT-CI).[14,15] Other publications; however, suggest that the patient's overall clinical condition rather than age alone should guide eligibility for ASCT in elderly patients. This conclusion is supported by our investigation, which identified no differences in second malignancies, TRM, neutrophil or platelet engraftment times, or survival outcomes between individuals older or younger than 60.

Nevertheless, the oldest patient in our series was 68, reflecting persisting caution amongst clinicians. French Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)[16] recently reported a retrospective analysis of 81

NHL patients over 70 years (median 72.3) who received ASCT. Engraftment and toxicity were satisfactory and the main cause of death was relapse rather than adverse effects. This study concluded that ASCT appears acceptable in NHL patients over 70 years, if clinical condition is adequate. Similar conclusions were drawn by Dahi et al. in a retrospective analysis of 202 NHL patients aged ≤60 years that had ASCT.[17] With a median age of 65 years (60-74), the OS, PFS and TRM were similar to historic controls of younger patients. There are some data to the contrary, with Jantunen et al. reporting a high TRM of 11% for ASCT in NHL patients >60 years[6] and another group reporting age at ASCT as a principal factor for developing second malignancy ($P = 0.0002$).[7]

Internationally and across centers, several conditioning programs are used for ASCT. Our facility has performed several FL ASCTs with Cy/TBI due to FL's radiosensitivity. After TBI-based conditioning, there is considerable worry regarding the potential of hematologic and other subsequent cancers.[7,12,18]

Our data did not show any significant difference among the outcomes of FL patients treated with BEAM or Cy/TBI based regimen in terms of PFS, OS, TRM, secondary malignancies or neutrophil/platelet engraftment times. Results from earlier investigations have shown contradictory results. Data from 605 individuals who had ASCT for B-cell NHL and received Cy/TBI conditioning before receiving purged autologous stem cells were published by Brown et al. This study reported a 10-year incidence of second malignancy as 21%. A 2007 EBMT registry study[18] reported ASCT outcomes of 693 FL patients; the 58% who received TBI-based conditioning had a shorter OS ($P = 0.004$), higher NRM ($P = 0.04$), and a higher incidence of sMDS/AML. In total, 39 patients developed sMDS/AML, out of which 34 cases received TBI as conditioning regimen. This study concluded that TBI-containing regimens are associated with a negative impact on survival. The same study showed that older age was associated with shorter OS ($P < 0.001$) and higher NRM ($P < 0.001$).

On the contrary, El-Najjar et al. for the EBMT Lymphoma Working Party[19] reported in 2014 that in the patients with FL who received TBI-based ASCT after 1995, there was no statistically significant difference in the incidence of non-relapse mortality (NRM) and sMDS/AML, when compared to BEAM, while disease control was at least equivalent.

Furthermore, a 2003 retrospective case-control study showed no significant increase in incidence of sMDS/AML in the patient receiving TBI dose of 12 Gy or less in conditioning regimen.[10]

We are aware that many patients who had transplants in the early stages of the cohort in our analysis did not have access to information on the histologic grade of FL. Further subgroup analysis to compare ASCT results between low-grade and high-grade FL patient groups would have benefited from this information. It would have been fascinating to see how the different conditioning regimens (BEAM vs. Cy/TBI) affected these subgroups.

We acknowledge that the lack of difference in PFS and OS between younger and older groups, as well as FL patients receiving BEAM vs. Cy/TBI could be in terms of small numbers and the heterogeneity of diseases included.

DLBCL continues to be a significant indication for ASCT in many relapsed/refractory patients as consolidative therapy and in certain chosen individuals as upfront therapy. There are many factors which were shown to affect ASCT outcomes in DLBCL, including disease status at ASCT, age, and international prognostic index (IPI) risk category.[20]

In total, there were 36 DLBCL patients who had ASCT during this period in our centre. Unfortunately, further subgrouping of DLBCL patients based on IPI score could not be done in terms of the non-availability of this information in many patients transplanted in 1990s. Most of our patients 29/36 (80.6%) did not have upfront ASCT in line with the mostly negative data for upfront ASCT.[21]

The relatively poor PFS and OS outcomes in our DLBCL patients[22] could be multifactorial and because of a significant percentage 12/36 (33.3%) of them being in PR at time of ASCT.

Non-availability of follow-up data for some patients transplanted in 90s could affect survival outcomes.

It was clearly unable to do the molecular categorization of DLBCL (GCB (germinal center B cell) vs. non-GCB), which is known to affect treatment results in DLBCL patients,[23] since these entities were essentially non-existent for a significant beginning portion of our research period.

Various factors were implicated in development of secondary malignancies in the setting of ASCT, including conditioning regimen, age, previous chemotherapy regimens and time from diagnosis to transplant/number of relapses.[7,11,12,24] Besides, one report found an increased risk of sMDS/AML in patients who required more than 5 days of apheresis, suggesting that a difficult stem cell harvest is a marker of genotoxic damage.[25]

A shorter period of follow-up for some patients in our study could have contributed to relatively low incidence of sAML (4/140), as many studies have reported a higher incidence of sMDS/AML with 5 plus years of follow-up post-transplant.[26]

We believe the study has following strengths and weaknesses:

1. The retrospective nature, single institution data and heterogeneity of the cases presented.
2. Our study did not evaluate the effect of stage/grade of FL or the subtype of DLBCL on the side-effect profile, PFS and OS in patient receiving BEAM and Cy/TBI regimen.
3. Our study has relatively reasonable number of studied patients compared with other published studies.
4. There was a long period of follow-up which could highlight the long-term complications of ASCT, particularly secondary malignancies.

Conclusion

This study of 140 lymphoma ASCT recipients allowed us to examine several factors that remain uncertain in the literature.

Firstly, there was no discernible difference between patients under and over 60 in terms of PFS and OS. This implies that older individuals may undergo ASCT safely with results that are comparable to those of comparatively younger patients, and that age alone should not be a factor used to disqualify people from ASCT. Secondly, there was no significant difference between BEAM and Cy/TBI conditioning in FL patients in terms of toxicity, PFS and OS. Hence, we cannot recommend one over other in FL patients. We recommend that prospective studies are required to further corroborate this as there are no prospective trials contrasting these two conditioning regimens side by side. Our study; however, did not evaluate the effect of grade of FL on the side-effect profile, PFS and OS in patient receiving BEAM and Cy/TBI regimen.

We did not find any significant increase in the incidence of sMDS/sAML in patients who had Cy/TBI conditioning compared to BEAM conditioning. Considering small number of patients developing sMDS / sAML, no particular chemotherapy or conditioning regimen could be implicated in developing sMDS / sAML. Moreover, there was no suggestion towards age being a factor for developing sAML, as 3 out of 4 patients with sAML were less than 60 years.

Our study did not suggest any significant increase in incidence of secondary malignancy (haematological and non- haematological) in any particular conditioning, NHL subtype or age group (greater or less than 60 years).

Only 2 patients out of 140 had TRM suggesting ASCT can be performed safely in most patients regardless of age, NHL subtype or conditioning regimen.

However, all these results need to be confirmed with focused randomised prospective studies.

Acknowledgement

I would like to sincerely thank Dr. Humphrey Pullon, senior haematologist in Waikato Hospital, who has played a leading role to establish the bone marrow transplant program in our centre. I acknowledge the kind support and guidance provided by him throughout this project. His mentoring was immensely helpful and he was always available for help, whenever needed.

Conflict of Interest

None declared.

References

1. Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 2011;377(9759):42-51. doi: 10.1016/S0140-6736(10)62175-7. Erratum in: *Lancet*. 2011;377(9772): 1154.
2. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood.* 2005;106(12):3725-32. doi: 10.1182/blood-2005-01-0016.
3. Morschhauser F, Radford J, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol.* 2008;26(32):5156-64. doi: 10.1200/JCO.2008.17.2015.
4. Cote GM, Hochberg EP, Muzikansky A, Hochberg FH, Drappatz J, McAfee SL, et al. Autologous stem cell transplantation with thiotepa, busulfan, and cyclophosphamide (TBC) conditioning in patients with CNS involvement by non-Hodgkin lymphoma. *Biol Blood Marrow Transplant.* 2012;18(1):76-83. doi: 10.1016/j.bbmt.2011.07.006.
5. Chen YB, Lane AA, Logan B, Zhu X, Akpek G, Aljurf M, et al. Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2015;21(6): 1046-53. doi: 10.1016/j.bbmt.2015.02.005.
6. Jantunen E, Itälä M, Juvonen E, Leppä S, Keskinen L, Vasala K, et al. Autologous stem cell transplantation in elderly (>60 years) patients with non-Hodgkin's lymphoma: a nation-wide analysis. *Bone Marrow Transplant.* 2006;37(4):367-72. doi: 10.1038/sj.bmt.1705266.
7. Brown JR, Yeckes H, Friedberg JW, Neuberg D, Kim H, Nadler LM, et al. Increasing incidence of late second malignancies after conditioning with cyclophosphamide and total-body irradiation and autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol.* 2005;23:2208-14. doi: 10.1200/JCO.2005.05.158.
8. Micallef IN, Lillington DM, Apostolidis J, Amess JA, Neat M, Matthews J, et al. Therapy-related myelodysplasia and secondary acute myelogenous leukemia after high-dose therapy with autologous hematopoietic progenitor-cell support for lymphoid malignancies. *J Clin Oncol.* 2000;18(5):947-55. doi: 10.1200/JCO.2000.18.5.947.
9. Vaxman I, Ram R, Gafter-Gvili A, Vidal L, Yeshurun M, Lahav M, et al. Secondary malignancies following high dose therapy and autologous hematopoietic cell transplantation-systematic review and meta-analysis. *Bone Marrow Transplant.* 2015;50(5):706-14. doi: 10.1038/bmt.2014.325.
10. Metayer C, Curtis RE, Vose J, Sobocinski KA, Horowitz MM, Bhatia S, et al. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multicentre case-control study. *Blood.* 2003;101(5):2015-23. doi: 10.1182/blood-2002-04-1261.
11. van Leeuwen FE. Risk of acute myelogenous leukaemia and myelodysplasia following cancer treatment. *Baillieres Clin Haematol.* 1996;9(1):57-85. doi: 10.1016/s0950-3536(96)80037-0.
12. Rohatiner AZ, Nadler L, Davies AJ, Apostolidis J, Neuberg D, Matthews J, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. *J Clin Oncol*. 2007;25(18):2554-9. doi: 10.1200/JCO.2006.09.8327.
13. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol.* 1999;17(4):1244. doi: 10.1200/JCO.1999.17.4.1244. Erratum in: *J Clin Oncol*. 2000;18(11):2351.
14. Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative regimens for treatment of lymphoma and chronic lymphocytic leukemia. *Blood.* 2008;111(1):446-52.doi: 10.1182/blood-2007-07-098483.
15. Sorror ML, Storb RF, Sandmaier BM, Maziarz RT, Pulsipher MA, Maris MB, et al. Comorbidity-age index: a clinical measure of biological age prior to allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2014;32(29):3249-56. doi: 10.1200/JCO.2013.53.8157.
16. Hermet E, Cabrespine A, Guiéze R, Garnier A, Tempescul A, Lenain P, et al. Autologous hematopoietic stem cell transplantation in elderly patients (≥ 70 years) with non-Hodgkin's lymphoma: A French Society of Bone Marrow Transplantation and Cellular Therapy retrospective study. *J Geriatr Oncol*. 2015;6(5):346-52. doi: 10.1016/j.jgo.2015.04.005.

17. Dahi PB, Tamari R, Devlin SM, Maloy M, Bhatt V, Scordo M, et al. Favourable outcomes in elderly patients undergoing high-dose therapy and autologous stem cell transplantation for non-Hodgkin lymphoma. *Biol Blood Marrow Transplant.* 2014;20(12):2004-9. doi: 10.1016/j.bbmt.2014.08.019.
18. Montoto S, Canals C, Rohatiner AZ, Taghipour G, Sureda A, Schmitz N, et al. Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. *Leukemia.* 2007;21(11):2324-31. doi: 10.1038/sj.leu.2404850.
19. El-Najjar I, Boumendil A, Luan JJ, Bouabdallah R, Thomson K, Mohty M, et al. The impact of total body irradiation on the outcome of patients with follicular lymphoma treated with autologous stem-cell transplantation in the modern era: a retrospective study of the EBMT Lymphoma Working Party. *Ann Oncol.* 2014;25(11):2224-9. doi: 10.1093/annonc/mdu440.
20. Caballero MD, Pérez-Simón JA, Iriondo A, Lahuerta JJ, Sierra J, Marín J, et al. High-dose therapy in diffuse large cell lymphoma: results and prognostic factors in 452 patients from the GEL-TAMO Spanish Cooperative Group. *Ann Oncol.* 2003;14(1):140-51. doi: 10.1093/annonc/mdg008.
21. Oliansky DM, Czuczman M, Fisher RI, Irwin FD, Lazarus HM, Omel J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: update of the 2001 evidence-based review. *Biol Blood Marrow Transplant.* 2011;17(1):20-47. doi: 10.1016/j.bbmt.2010.07.008.
22. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;333(23):1540-5. doi: 10.1056/NEJM199512073332305.
23. Kim YR, Kim SJ, Cheong JW, Yang DH, Lee H, Eom HS, et al. The different roles of molecular classification according to upfront autologous stem cell transplantation in advanced-stage diffuse large B cell lymphoma patients with elevated serum lactate dehydrogenase. *Ann Hematol.* 2016;95(9):1491-501. doi: 10.1007/s00277-016-2729-4.
24. Milligan DW, Ruiz De Elvira MC, Kolb HJ, Goldstone AH, Meloni G, Rohatiner AZ, et al. Secondary leukaemia and myelodysplasia after autografting for lymphoma: results from the EBMT. EBMT Lymphoma and Late Effects Working Parties. European Group for Blood and Marrow Transplantation. *Br J Haematol.* 1999;106(4):1020-6. doi: 10.1046/j.1365-2141.1999.01627.x.
25. Kalaycio M, Rybicki L, Pohlman B, Sobecks R, Andresen S, Kuczkowski E, et al. Risk factors before autologous stem-cell transplantation for lymphoma predict for secondary myelodysplasia and acute myelogenous leukemia. *J Clin Oncol.* 2006;24:3604-10. doi: 10.1200/JCO.2006.06.0673.
26. Hake CR, Graubert TA, Fenske TS. Does autologous transplantation directly increase the risk of secondary leukemia in lymphoma patients? *Bone Marrow Transplant.* 2007;39(2):59-70. doi: 10.1038/sj.bmt.1705547.