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RESEARCH ARTICLE

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High dose chemotherapy and autologous stem cell transplantation in nodular lymphocyte-predominant Hodgkin lymphoma: A retrospective study by the European society for blood and marrow transplantation-lymphoma working party

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Abstract

Whilst autologous stem cell transplantation (auto-SCT) is considered standard of care for relapsed/refractory classical Hodgkin lymphoma, the role of auto-SCT in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is not well defined due to limited data. We report the first study on auto-SCT for NLPHL with a larger cohort. Eligible for this retrospective registry study were patients reported to the EBMT between 2003 and 2013, aged 18 or older with relapsed/refractory NLPHL who underwent first auto-SCT with disease chemosensitive to salvage therapy. NLPHL transformed to diffuse large B cell lymphoma were excluded. Sixty patients (83% male; median age 40 years) met the eligibility criteria. The median time between diagnosis and transplant was 21 months (IQR 13–58), and the median number of prior treatment lines was 2 (range 1–5), including rituximab in 63% of the patients. At auto-SCT, 62% of the patients were in complete remission (CR) and 38% in partial remission. Seventy-two percent of the patients received BEAM as high-dose therapy. With a median follow-up of 56 months (range 3–105), 5-year progression-free and overall survival (OS) were 66% and 87%, respectively. Univariate comparisons considering age, time from diagnosis to transplant, prior chemotherapy lines, and prior rituximab use failed to identify significant predictors for any survival endpoint except for being in CR at the time of auto-SCT (vs PR, $P = .049$) for OS. Auto-SCT in patients with relapsed/refractory NLPHL who are sensitive to salvage therapy gives excellent disease control and long-term survival independent of the time interval between diagnosis and transplant.

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1 | INTRODUCTION

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a relatively uncommon lymphoma accounting for about 5%–6% of all Hodgkin lymphoma (HL). NLPHL is considered as a separate entity by the World Health Organization classification and has unique clinicopathological, morphologic, and immunohistochemical characteristics.[1] Histologically, NLPHL is characterized by atypical "lymphocyte predominant cells" (LP cells) in a background of reactive nodular small mature B-lymphocytes. LP cells express CD20 but are negative for CD 15 and CD 30.[1–4] NLPHL peaks between 30 and 50 years of age with a male preponderance.[5–7] Although long-term survival is superior to classical HL, relapses occur over time, and transformation to aggressive non-Hodgkin lymphoma (NHL) may happen.[3,4,7–10] Whilst high-dose chemotherapy with autologous stem cell transplantation (auto-SCT) is considered the standard treatment for relapsed/refractory classical HL, information on auto-SCT in NLPHL is sparse and only a few specific reports with limited patient numbers are available.[11–13] Not only this, emerging nonrandomized data with upfront use of rituximab containing regimens have shown better outcome as compared to historical control in a stage matched fashion.[14] An interesting question in the future will be the management and outcome of those patients who are refractory or relapsing after first line rituximab containing regimens. The aim of the present study was to investigate the outcome of patients who received an auto-SCT for relapsed/refractory NLPHL on a large sample and to identify risk factors for poor outcome after transplant.

2 | PATIENTS AND METHODS

2.1 | Data source

EBMT is a voluntary organization comprising more than 600 transplant centers mainly from Europe. Accreditation as a member center requires submission of minimal essential data (MED-A form) from all consecutive patients including diagnosis of underlying disease and type of transplantation to a central registry. As the name indicates, this primary data is minimal information for reporting purpose. Informed consent for transplantation and data collection were obtained locally according to regulations applicable at the time of transplantation. Since January 1 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT following the Helsinki Declaration 1975.

2.2 | Study design

This was a retrospective EBMT registry-based analysis. Eligible for this study were patients aged 18 or older with relapsed NLPHL who underwent a first auto-SCT between 2003 and 2013 and were reported to the EBMT. Patients with refractory disease (not responding to salvage chemotherapy) at auto-SCT and those with NLPHL transformed to DLBCL were not eligible (in the registry data, these NLPHL patients transformed to DLBCL are captured as DLBCL as the final diagnosis requiring auto-SCT). Baseline patient, disease, and transplant data were collected from EBMT MED-A standard forms. Centers with potentially eligible patients were contacted to provide additional treatment details,

TABLE 1 Patients' characteristics and disease status before and after auto-SCT

Variable		
Total patients	*N*	60
Disease status pre HDC auto-SCT	*N* (%)	
CR		37 (62%)
Partial response		23 (38%)
Types of HDC		
BEAM		43 (72%)
Other HDC		11 (18%)
Rituximab + HDC		6 (10%)
Age at HDC auto-SCT	Median (IQR)	40 (31–50)
Duration from diagnosis to HDC in months	Median (IQR)	21 (13–58)
<12 months		12 (20%)
12–24 months		19 (32%)
24–60 months		15 (25%)
>60 months		14 (23%)
Best disease status at day 100[a]	*N* (%)	
CR		45 (79%)
Partial response		10 (17%)
Progression[b]		2 (3.5%)
Disease status at last FU (52 patients alive at last FU)	*N* (%)	
CR		41 (79%)
Not in CR		7 (12%)
Unknown		4 (8%)

Abbreviation: BEAM, BCNU + etoposite + Ara-C + melphalan.
[a]Three with missing information.
[b]Both were in CR before auto-SCT.

follow-up information, and a copy of the written histopathology report for "central review." As per registry practice, response was accepted as reported without further inquiries related to the criteria used for the response.

2.3 | Statistical analysis

Primary end-point was 5-year progression free survival (PFS) defined as the time from auto-SCT to disease relapse or progression or death from any cause, whichever came first. Secondary endpoints were overall survival (OS), defined as the time from auto-SCT to death from any cause, relapse incidence (RI), and nonrelapse mortality, defined as the time from auto-SCT to death in the absence of prior relapse or progression.

Univariate and multivariate analyses to study the association of patient, disease and transplant variables with outcome were performed. Survival curves for OS and PFS were estimated by the Kaplan Meier method and compared between groups using the log-rank test. The following prognostic factors were considered: age, sex, remission status at auto-SCT (complete remission, CR vs. PR as reported/provided by the participating centers), type of high-dose therapy and use of rituximab prior to transplant. All analyses were done using R version 3.1.1 with the R packages survival version 2.38, cmprsk version 2.2–7 and Hmisc version 3.16-0 (R Core Team. R: a language for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-sided with a P value $<.05$ considered to indicate a statistically significant result.

3 | RESULTS

3.1 | Patients

A total of 374 patients were identified in the EBMT registry meeting the eligibility criteria for this study. These centers were contacted to participate in this study. Additional information upon request was provided for 105 of 374 patients. Of these, 39 patients had to be excluded after histopathology review (17 classical HL, 2 NHL, 20 not informative), and 6 patients were excluded based on disease status at auto-SCT (2 primary induction failure/refractory to chemotherapy, 4 refractory relapses), leaving 60 patients in the final study sample, 50 (83%) of them being male. (Supporting Information 1: CONSORT diagram – patient's selection).

Median age at diagnosis was 35 years (interquartile range IQR: 27–45 years) with 63% of patients presenting with advanced disease (stage III–IV). First-line treatment was anthracycline-based chemotherapy in most patients (92%); 13% had received radiation therapy (XRT), and 23% rituximab as part of first-line therapy. Response to initial treatment was CR (38%), PR (35%), and stable or progressive disease in 17%. Details on patient characteristics at presentation are provided in Supporting Information 2: Patient's characteristics.

3.2 | Outcome

When comparing the outcome of the 60 patients included with that of the 220 patients who were not included because of missing verification of diagnosis and/or baseline data, we found an inferior outcome for

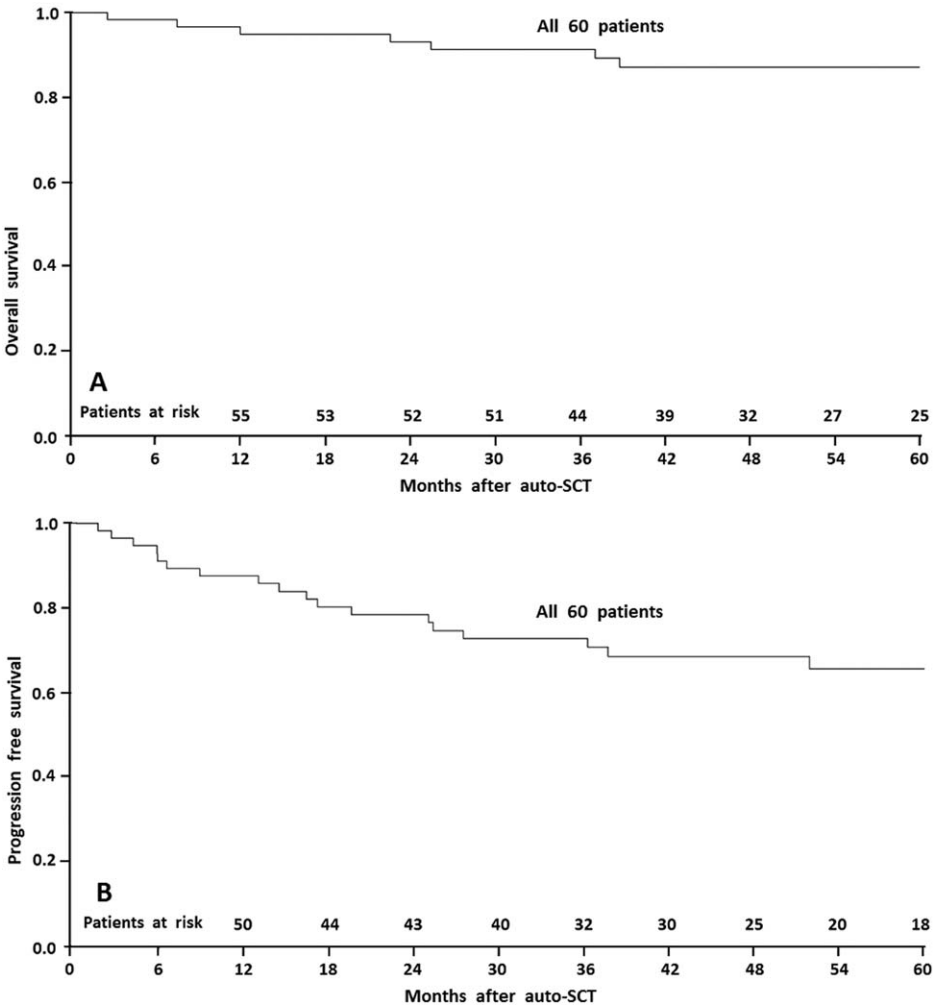

FIGURE 1 Five-year Kaplan-Meier probability of (A) OS and (B) progression-free survival

patients not included in the study for both PFS [5-year 66% (95%CI 54–81) vs. 55% (95%CI 46–66); $P = .11$] and OS [5-year 87% (95%CI 79–97) vs. 71% (95%CI 61–82); $P = .041$], suggesting that the excluded cohort indeed represents a different population of patients including maybe patients with different diagnoses and others with chemorefractory disease. This should be interpreted with caution due to the limitations already stated above.

Response to salvage chemotherapy/disease status prior to auto-SCT and post transplant disease status are shown in Table 1. All patients engrafted. Best disease status at day 100 after auto-SCT was reported in 57 (95%) patients with 45 CR (79%), 10 PR (18%), and 2 progressive diseases (3%). With a median follow-up for survivors of 56 months (range 3–105 months), five-year PFS and OS were 66% (95%CI 54–81), and 87% (95%CI 79–97), respectively (Figure 1). Nineteen patients had disease relapse or progression, resulting in a five-year RI of 34% (95%CI 21–47). There were no transplant-related deaths. Among the 19 relapsed patients, 9 received further treatments: 7 received one line and 2 received two lines after auto-SCT, which contained rituximab in 4/19 patients. One patient received rituximab maintenance. Of the 19 relapsed patients, 8 have died (causes of death were the relapse in 6 patients, CNS hemorrhage in 1 and pulmonary infection-hemorrhage in 1) and 11 were alive at last follow-up (disease status at last follow-up were CR in 4 patients, not in CR in 5 patients and unknown in 2).

3.3 | Prognostic factors

On univariate analysis, patients who underwent auto-SCT in PR had a significantly shorter OS than those patients who were transplanted in CR [hazard ratio (HR) 5.02, 95%CI 1.01–25.01; $P = .049$) although PFS was not significantly reduced (HR 1.59, 95%CI 0.64–3.91; $P = .32$). Age, time from diagnosis to transplant, the number of pretreatment lines, and rituximab at any time prior to auto-SCT had no significant impact on any survival endpoint (Supporting Information 3). Multivariate analyses were not performed because of the small number of events.

4 | DISCUSSION

Auto-SCT is considered the standard treatment in patients with relapsed or refractory classical HL. In contrast, the role of auto-SCT in NLPHL is not well defined. To date, only a few series on NLPHL autografts have been reported, all of them limited by small patient numbers

TABLE 2 Outcome after HDC auto-SCT in relapsed and refractory HL: different studies

Author (Reference) Years published Study period	Total NLPHL Total HL % of NLPHL	Type of failure included	Median age at Dx At auto-SCT (median f/u)	Male:female	OS PFS/DFS/ Dead/total pts	Median prior lines Transformed NLPHL	CR: PR:PD Post HDC (total patients) Total relapsed	- Poor prognostic factors-Comments
Bierman (12) [2006]. 1987–2002 Abstract only	19 229 8.3%	Relapsed, progressed, persistent	NA 33 years (19–52) f/u NA	18:1	56% 5 year OS 40% 5 year PFS 10/19 died (calculated)	13 pts 1–2 and 6 pts ≥3 lines, before SCT NA	NA	- 56% vs. 53% long term survival (NLPHL vs. HL)
Karuturi (12) [2013]. 1990–2008	26 Not provided	Relapsed	NA 35 (13–51) f/u 50 m (2–138)	24:2	76% 5 year OS 69% 5 year EFS 6/26 died	3 18 NLPHL: 8 transformed	22 CR: 4 No CR	- OS for NLPHL 73% vs. transformed 87% at 5 year - Auto-SCT as early as 9 months indicates refractory disease too
Akhtar [2016] 1996–2014	17 306 6.2%	Relapsed, progressed, persistent after first line	22 years 28 yrs (15–58) f/u 63 (6–124 months)	14:3	94% 5 year OS 76% 5year EFS 1/17 died	2 lines 13 NLPHL: 4 transformed	14 CR:1 PR:2 PD	- Separate analysis of patients received rituximab based salvage showed superior EFS but no difference in OS - 94% vs. 67% long term survival (NLPHL vs. HL)
This study [2016] 2003–2013	60 16,303[a] 2.3%[a]	Relapsed, refractory but chemo sensitive to salvage	35 years(18–70) 40 yrs f/u 60	50:10	87% 5 year OS 66% 5year PFS 8/60 died	2 lines Only NLPHL	45 CR: 10 PR: 2 PD	- EBMT registry data. Separate analysis of - patients received rituximab based salvage showed no difference in PFS or OS

Abbreviation: NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; HL, Hodgkin lymphoma; OS, overall survival; PFS, progression free survival; DFS, disease free survival; FFS, failure free survival; EFS, event free survival; NA, not available; EBMT, European Society for Blood and Marrow Transplantation; XRT, radiation therapy.

[a]Total as reported to the EBMT registry.

precluding valid conclusions.[7,11–13,15,16] Here, we report the largest cohort of patients with NLPHL who underwent auto-SCT for relapsed or refractory disease, after responding to salvage therapy. With a 5-year PFS and OS of 66% and 87%, respectively, the long-term outcome appears to be much better than that of auto-SCT in relapsed/refractory classical HL[17–19] and other B-cell lymphomas,[20–22] suggesting an excellent sensitivity of NLPHL to high-dose chemotherapy (Table 2).

In spite of limitations, like the selection bias inevitably associated with a retrospective registry study reporting on patients who have received an auto-SCT, failure to get a response from non-participating centers on large number of patients, diverse managements/salvage chemotherapy, these patients had high-risk features. Although almost all the patients received anthracycline-based primary chemotherapy, half of the patient's disease did not enter into CR, 1/3 of the patients had received 3 or more lines of therapy and 2/3 had received rituximab; in addition, the majority of the patients had advanced disease at diagnosis and 1/3 also had B-symptoms. These poor risk features are not commonly reported in patients with NLPHL. We have not included patients with DLBCL transformed from NLPHL The registry.

Our data are consistent with the results of the two case series on auto-SCT in NLPHL fully published to date. Karuturi et al.[13] observed a 5-year overall and event-free survival of 73% and 61%, respectively, in 18 patients who had HDC auto-SCT for untransformed NLPHL. Akhtar et al. reported 17 patients (including 4 transformed to high-grade lymphoma) with 5-year OS and PFS of 76% and 94%.[11] Another small study on 19 patients with NLPHL, available only in abstract form, reported slightly inferior 5-year estimates (OS 56%, PFS 40%).[12] A few additional very small anecdotal case series have been reported but given the small number of patients per case series, firm conclusions are difficult.[7,15,16] Of note and also in contrast to the experience in classical HL, patients relapsing after auto-SCT had a relatively good prognosis with only 8 deaths in 19 relapsed patients. Similar observations were made by Akhtar et al, where only one out of four patient with NLPHL recurrence after auto-SCT died, contrasting with a 75% mortality rate in 117 patients with classical HL who relapsed after auto-SCT.[11]

In our report, we have observed that patients with NLPHL undergoing auto-SCT with measurable residual disease (PR only after salvage chemotherapy) had a significantly poorer OS than those in CR. Since this was not due to a PFS disadvantage of the same size, it appears that patients not completely responding to salvage therapy prior to transplant are more difficult to rescue in case of disease recurrence post transplant. However, we were not able to detect a significant effect of any other variable on any survival endpoint. This included rituximab pre-exposure, a factor that had shown some beneficial effect on PFS in one of the previous case series[11] and the time between diagnosis and auto-SCT.

The excellent results of auto-SCT in this study are also observed by a recent report of the German Hodgkin Study Group analyzing the outcome of 99 patients with relapsed NLPHL. 28 of these underwent auto-SCT, which resulted in a PFS of 90% after 5 years. Similarly excellent, however, was the outcome of patients who received rituximab with or without chemotherapy-based salvage therapy (5-year PFS 72.4%) or XRT with or without chemotherapy-based salvage therapy (5-year PFS 78.6%). Finding of this study prompted the authors to advocate anti-CD20 antibodies alone or in combination with conventional chemotherapy, XRT alone or conventional chemotherapy followed by XRT for patients with a longer remission after first-line treatment failure and presenting with limited tumor mass at relapse. They recommended auto-SCT as a treatment option for NLPHL relapsing early after primary treatment or extensive disease at relapse including extranodal involvement may require more aggressive treatment.[23] Although definition of early is not clear, a common practice is to consider <12 months failure as an early failure. Our finding of a similar efficacy of auto-SCT in patients with early or late relapse would support this suggestion, bearing in mind the limitations of retrospective registry data and emerging rituximab based treatment.

In conclusion, auto-SCT consolidation of patients with relapsed/refractory NLPHL who are sensitive to salvage therapy gives excellent disease control and long-term survival. Achievement of a deep remission prior to transplant is associated with a significant OS benefit. On the other hand, survival is not affected by a short interval between diagnosis and auto-SCT, suggesting that HDC auto-SCT might be particularly considered in patients with early relapse who otherwise have a relatively poor prognosis. Additional studies are needed for definite assessment of the place of rituximab and auto-SCT in the treatment algorithm of NLPHL.

CONFLICT OF INTEREST

Nothing to report.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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