Outcome predictors of autologous hematopoietic stem cell transplantation in children with relapsed and refractory Hodgkin lymphoma: Single-center experience in a lower-middle-income country

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Abstract
Background: Children and adolescents with HL have excellent long-term survival exceeding 95% after combined modality treatment. However, about 20% will either relapse or have PRF. Salvage HDCT followed by AHSCT is considered to be the preferential treatment.

Objective: To describe the outcome (OS and EFS) and prognostic factors in pediatric patients with relapsed or refractory HL (r/rHL) who underwent AHSCT.

Methods: We retrospectively included 43 pediatric patients with r/rHL who underwent AHSCT from July 1, 2007, till December 31, 2016, at the Children's Cancer Hospital of Egypt. MAC regimen given was CMV.

Results: Of the whole cohort, 88.4% of patients achieved CR, while 11.6% had a positive PET scan prior to transplantation. The 3-year OS and EFS were 85% and 70.6%, respectively. The 3-year OS for patients > 10 years was 94% versus 65.5% for patients 10 years of age or younger (P = 0.046). There is strong tendency toward better 3-year OS...
for patients with negative PET scan as compared to those with positive PET scan before AHSCT, 89.4% vs 60%, respectively ($P = 0.059$). This tendency is also applicable when looking at the 3-year EFS for the two groups, 78.3% vs 40%, respectively ($P = 0.069$).

**Conclusion:** Poor predictors of OS were younger age and positive PET scan before AHSCT. The latter, along with single modality treatment before AHSCT, were poor predictors of EFS.

**KEYWORDS**
auto-transplantation, Hodgkin’s disease, pediatric hematopoietic stem cell

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1 | **INTRODUCTION**

Children and adolescents with HL have excellent long-term survival exceeding 95% after combined modality treatment.\(^1\) However, depending on disease stage, about 20% will either relapse after anthracycline-based first-line chemotherapy or have PRF.\(^2\)-\(^6\)

To induce remission, salvage regimens such as DHAP, mini-BEAM, or ICE have been developed.\(^7\)-\(^9\)

Response rates after using salvage with chemotherapy and/or RT can reach 40%-65%. However, long-term survival is poor, and hence, salvage HDCT followed by AHSCT is considered to be the preferential treatment, especially for patients with a chemosensitive relapse.\(^7\)-\(^10\) Some patients who undergo AHSCT still develop recurrence within 1 year.\(^11\)

Some studies failed to find survival benefit from HDCT over CDCT in relapsing pediatric HL patients. Linch et al compared 20 patients receiving BEAM followed by AHSCT with 20 patients who received mini-BEAM without AHSCT. EFS and PFS were superior and relapse rate was lower for patients in the high-dose therapy group, whereas OS was similar in both groups.\(^12\),\(^13\)

There has been extended research to find the poor prognostic factors at diagnosis and pre- and post-transplant, on the relapse rate and survival of children with HL who undergo AHSCT. Some of these factors included early timing for relapse, advanced stage at relapse, extranodal disease at the time of relapse, mediastinal mass at the time of transplant, PRF, and a positive FDG-PET scan prior to AHSCT.\(^11\),\(^14\),\(^15\)

Regarding these points of concern, we report our experience and the outcome of 43 children and adolescents, who underwent AHSCT for relapsed or refractory HL at the Children’s Cancer Hospital Egypt (CCHE-57357), using one cycle of high-dose CMV, followed by autologous stem cell infusion.

2 | **PATIENTS AND METHODS**

2.1 | **Study design**

After obtaining approval from our institutional research committee, we retrospectively included 43 pediatric patients, aged ≤ 18 years at initial diagnosis, with relapsed/refractory HL who underwent AHSCT consecutively, from July 1, 2007, till December 31, 2016, at the Children’s Cancer Hospital of Egypt. Patients’ guardians gave their informed consent prior to their inclusion in the study. Patient- and treatment-related data as documented in the files were recorded. Patient- and treatment-related factors analyzed were age at AHSCT, sex, B symptoms at presentation, stage at diagnosis, bulky disease at diagnosis (the optimal cutoff for disease bulk was maximal diameter greater than 7 cm measured in either the transverse or coronal plane on pretreatment imaging), interval between first remission and relapse, salvage chemotherapy, single or combined modality of therapy before transplant, disease status at the time of transplant, conditioning regimen, post-transplant RT, and outcome after AHSCT.

2.2 | **Therapy**

ABVD regimen (Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine) was used in all patients as a frontline therapy followed by involved field RT (IFRT) in patients who did not have refractory or PD. Three-dimensional conformal RT (3DCRT) was applied to all involved nodal areas detected at initial presentation up to a dose of 1980 cGy in 11 fractions. Refractory/relapsing patients (pathologically documented) received ICE (ifosfamide, carboplatin, and etoposide) as a salvage second-line therapy. Vinorelbine and gemcitabine were used as a third-line therapy. Following 2nd or 3rd line of therapy, all patients underwent AHSCT. Patients and/or their parents or guardians provided informed consent for therapy and for long-term follow-up.

MAC regimen given was CMV (cyclophosphamide 3 g/m²/d on days −6 to −5, melphalan 100 mg/m² on day −2, and etoposide 150 mg/m²/day on day −6 to −2), followed by autologous stem cell infusion. G-CSF was administered from day + 6 until granulocyte recovery.

cRT post-transplant was administered to all involved areas detected upon relapse. The radiation dose ranged between 1980 and 2520 cGy in 11-14 fractions 3DCRT, even to areas previously irradiated at initial treatment. The dose-volume histogram was calculated for all surrounding normal structures considering the radiation tolerance of each organ.
2.3 | Response definitions

Tumor response at the time of transplant is defined as follows:

Complete response was defined as no evidence of tumor by clinical examination and no more than minimal disease by radiographic and FL, particularly a negative FDG-PET evaluation by 30 days after completion of primary or salvage therapy (ie, second CR, third CR). Patients who did not achieve CR1 following first-line treatment but who did achieve CR1 following multiple treatments prior to AH SCT were considered to be late CR1 responders.\(^\text{15,18}\)

Partial response was defined as persistence of tumor by clinical or radiographic evaluation by 30 days after therapy without further worsening of the disease.\(^\text{15,19}\)

Primary or relapsed refractory disease if they had a response other than CR or PR following first-line treatment or subsequent treatments for newly diagnosed HL (PRF) or if they were treated using salvage treatment modalities following their first relapse (RRF).\(^\text{15}\)

Chemosensitive tumor at the time of AH SCT if they had achieved either CR or PR after relapse.\(^\text{15}\)

Chemorefractory if they had SD or PD prior to their AH SCT.\(^\text{15}\)

2.4 | Time to relapse definitions (after first-line therapy)\(^\text{20}\)

Refractory disease was defined as occurring within 3 months after completion of therapy or during therapy.

Early relapse was defined as disease recurring within 3-12 months.

Late relapse was defined as disease occurring more than 12 months from the end of therapy.

2.5 | Statistical methods

End-points analyzed were OS and EFS calculated from the time of transplantation (day 0). OS was defined from the date of stem cell infusion until the date of death from any cause. EFS was calculated as the time from date of stem cell infusion until the date of an adverse event, including relapse or progression of HL, development of a secondary malignancy, or death from any cause. When patients suffered more than 1 event, the time to the first event was used to determine the EFS. Life tables were constructed using the method of Kaplan and Meier.\(^\text{21}\) Patients not suffering adverse events were censored at the time of last follow-up. TRM was defined as death within 100 days of the date of transplant.

3 | RESULTS

3.1 | Patients and disease characteristics

From July 2007 to January 2017, 43 patients with refractory/re-lapsed HL who underwent HDCT followed by AH SCT rescue were analyzed. The demographic features are presented in Table 1.

The median age at transplantation was 12 years (ranging from 2 to 21 years), and the male/female ratio was 33/10 = 3.3:1. B symptoms at diagnosis were present in 24/43 patients (55.8%). Classical HL was found in 38 patients (18 nodular sclerosis, 16 mixed cellularity, 2 lymphocyte rich, and 2 lymphocyte depleted), while nodular lymphocyte predominance subtype was found in the remaining 5 patients.

Seventeen/43 patients were stage IV at initial diagnosis (39.5%), 13 (30.2%) were stage III, 7 (16.3%) were stage II, while 6 patients (14%) were stage I. Initial bulky disease was found in 5 out of 39 evaluable patients (12.8%). Splenic involvement at initial diagnosis was present in 6 patients (14%).

First-line chemotherapy (ABVD) was given to all patients (12 received 4 cycles, 17 received 6 cycles and 14 received 8 cycles). Radiation therapy as consolidation was given to 16 patients (37.2%). The rest of patients did not receive RT due to diverse causes, like refractory disease just following ABVD, or extensive field of nodal involvement at initial presentation which could preclude the administration of RT due to toxicity.

Time to 1st relapse varied among the 43 patients, ranging from 0 to 72 months (mean: 18.5 months) after ending their first-line therapy (refractory disease was found in 8 patients [18.6%], early relapse in 14 patients [32.5%] while late relapse in 21 patients [48.9%]).

Second-line chemotherapy (ICE) was given to the whole cohort of patients (ranging from 3 to 8 cycles). Of them, 6 patients (who had refractory disease to ICE) received third-line chemotherapy, Vinorelbine/gemcitabine (ranging from 2 to 4 cycles). Of the whole cohort, 38 patients (88.4%) achieved CR, while the remaining 5 patients (11.6%) had a positive PET scan prior to transplantation with a Deauville score of 4.

All patients received MAC regimen in the form of cyclophosphamide/melphalan/etoposide (CMV) followed by stem cell infusion. Stem cells were obtained from peripheral blood in all patients using G-CSF. The median CD34 dose was 3.2 × 10^\text{5} /Kg recipient weight (ranging from 2.1 to 17.0). Radiation therapy post-AH SCT was given to 38 patients (88.4), while 5 patients (11.6%) skipped CRT (4 of them did not receive RT pre- or post-AH SCT due to extensive nodal disease at initial presentation, while 1 patient received RT pre-AH SCT but he did not receive post-AH SCT due to extensive nodal disease at the time of relapse). Two of these 5 patients relapsed at 21.7 and 19.4 months post-AH SCT, respectively.

Nine patients (20.1%) developed relapse post-AH SCT (2 of them did not receive RT post-AH SCT). Median time to relapse was 23.85 months, ranging from 4.47 to 70.3 months.

3.2 | Survival analysis

At the time of the study, 37 of the enrolled 43 patients were alive (86%) [33 were disease-free] and 6 were dead (14%) out of disease progression following AH SCT.

With median duration of follow-up of 25.6 months post-AH SCT (ranging from 3 to 89 months), the 3-year OS and EFS of the
whole study cohort were 85% (95% CI 100‐71) and 70.6% (95% CI 89.9‐55.5), respectively (Figure 1).

The 3‐year OS for patients >10 years at transplantation was 94% as compared to 65.5% for patients 10 years of age or younger with a P‐value of 0.046 (Figure 2).

Patients who received multimodality therapy before AHSCT (chemotherapy and radiation therapy) had better 3‐year EFS than those who received chemotherapy only (91.7% vs 62.9%, respectively) with a P‐value of 0.116 (Figure 3).

There is a strong tendency toward better 3‐year OS for patients with negative PET scan as compared to those with positive PET scan before AHSCT (89.4% vs 60%, respectively) with a P‐value of 0.059. This tendency is also applicable when looking at the 3‐year EFS for the two groups (78.3% vs 40%, respectively) with a P‐value of 0.069 (Figure 4). The impact of other various risk factors on OS or EFS was not of statistical significance (Table 2).

### DISCUSSION

Data describing the use of HDCT followed by AHSCT in pediatric patients with HL who have relapsed or are refractory to frontline therapy have been scarce. No prospective, randomized pediatric trials comparing the effectiveness of AHSCT with that of standard chemotherapy in relapsed children with HL have been conducted. Many investigators reported marked improvement of EFS compared to non‐transplanted patients and reflecting on a better OS.

We describe in this study the outcome and prognostic factors of 43 patients with refractory/relapsed HL who underwent HDCT followed by AHSCT at a single cancer center.

Due to the poor outcome of AHSCT for patients with multiple relapses, we transplanted 37 patients after their 1st salvage therapy.
(ICE) once they showed chemosensitivity (n = 37). Only 6 patients were transplanted after 2nd salvage therapy (vinorelbine/gemcitabine), as their response was not satisfactory to 1st salvage treatment. Numbers are small to show statistical survival significance related to the number of chemotherapy lines given before AHSCT. Similarly, others signify that AHSCT is a good treatment modality for chemosensitive relapsed HL after their first relapse rather than multiple relapses.\(^{23}\)

The 3-year OS and EFS rates for pediatric patients who underwent AHSCT for refractory/relapsed HL in this study were 85% (95% CI 100-71) and 70.6% (95% CI 89.9-55.5), respectively. These results are better than those described by other authors, where 3-year OS and EFS rates were 74.3% (95% CI 59.6-89) and 58.5% (95% CI 42.8-74.2), respectively,\(^{16}\) while the 5-year OS rate described in another study was approximately 60%.\(^{15}\)

All patients included in this study received CMV (cyclophosphamide/melphalan/etoposide) conditioning regimen. Schütz et al\(^{7}\) found that conditioning with CMV in pediatric cases has been shown to be highly effective against lymphomas, with dose-limiting hematological toxicities and associated with 10% TRM in the same range as reported by others using different conditioning regimens.\(^ {24}\)

Garfin et al reported in a pediatric age-group a 5-year survival probability of 71% and 65% for OS and EFS, respectively. In the later study, they investigated different conditioning regimens and OS differed significantly by regimen ($P = 0.007$). CBV was associated with the best outcomes, with a 5-year OS of 75% and EFS of 67%.
and FTCV resulted in the worst 5-year OS of 50% with an EFS of only 33%.  

Radiation therapy remains an integral component of treatment for relapsing/refractory HL. Our standard practice included cRT for all cases, when possible. Five patients skipped cRT after AHSCT, due to extensive nodal disease. Two of them relapsed at 21.7 and 19.4 months post-AHSCT, respectively. Others also consider RT only for limited volume disease in patients with relapsed/refractory HL in their salvage treatment with pros and cons for such approach.  

Notably, there was no statistical survival significance in this study as regards OS and EFS, due to small number of relapsing cases, for patients who received cRT compared to no cRT after AHSCT (P = 0.3 and 0.188, respectively). Our data and multiple other studies support the improved survival with irradiation after transplant, but it remains of great importance to have a randomized pediatric trial to determine the beneficial role of irradiation following AHSCT.

In the current study, factors that were adversely related to 3-year OS included age ≤ 10 years (P = 0.046) and positive PET scan at the time of transplant (P = 0.059). On the other hand, EFS seems to be negatively impacted when patients received chemotherapy alone rather than multimodality treatment (chemotherapy and radiotherapy) before AHSCT (62.9% and 91.7%, respectively, with P = 0.116), as well as a positive PET scan before AHSCT (P = 0.069). It is worth noting that only 5 patients had positive PET scans at the time of transplant, 3 of them did not receive radiation therapy before AHSCT and relapsed following transplant. This highlights the influence of radiation therapy on improvement of remission rate before AHSCT and highlights the prognostic significance of CR before AHSCT on the outcome. Similar observations by others that patients with positive PET scans before AHSCT are at much higher risk of having therapy failure. Our cohort included few patients with positive PET scan (Deauville score of 4) at the time of transplant. This indicates like others that proper selection of candidates for transplant, with complete metabolic remission, is an important predictor for better outcomes after AHSCT.

Two pediatric reviews stated that short time duration of the CR1 and the occurrence of refractory disease at the time of transplantation were poor risk factors for outcome following AHSCT. Strangely, our results did not find survival difference (OS and EFS) as regards to time to relapse after first-line treatment in the univariate analysis with P = 0.520 and 0.831, respectively. Our explanation is that the number of patients with refractory disease was low (only eight patients; 18.6%). Also, all patients had to show chemo sensitivity before proceeding to AHSCT according to our eligibility policies. So, with the negative selection for a group of refractory cases who did not show chemo sensitivity to salvage therapies, we cannot emphasize their poor outcome in relation to other relapsing cases.

Many other factors that are often associated with differences in survival expectancy and are predictors of poor outcome in many studies, including B symptoms, histopathological subtypes, bulky disease, advanced stage and extranodal disease at the time of relapse, did not correlate with survival outcome in the current study.
There were no cases of TRM in our study. This may be attributed to the improved supportive care measures during the early phase post-transplant (100 days), absence of serious comorbidities during first- and second-line salvage regimens and the lower toxicity of the (CMV) conditioning regimen used. The primary cause of transplant failure in this study appears to be relapse with a median time to relapse of 23.85 months post-AHSCT and a relapse rate of approximately 20%.

Others described a cumulative incidence of relapse to be 40% with most of their patients experienced late relapse > 12 months post-AHSCT.16

In conclusion, the results of the current study consolidate the importance of HDCT followed by AHSCT to improve the survival of children with relapsing/refractory HL. The disease status of the patient at the time of transplantation as regards to complete metabolic remission appears to be the strongest predictor of survival in our cohort.
<table>
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<th>EFS at 36 mo (%)</th>
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Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; EFS, event-free survival; OS, overall survival; PET, positron emission tomography.

**TABLE 2** Univariate analysis of prognostic factors associated with OS and EFS

**AUTHOR CONTRIBUTIONS**

Amr Abdalla: Substantially contributed to the conception or design of the work; the acquisition and interpretation of data for the work; drafted the work and revised it critically for important intellectual content; approved the final version of the manuscript; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; Mahmoud Hammad: Substantially contributed to the conception or design of the work; the interpretation of data for the work; drafted the work and revised it critically for important intellectual content; approved the final version of the manuscript; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; Hanafy Hafez: Substantially contributed...
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Hanafy Hafez


