Chapter 13

Current Status of Hematopoietic Stem Cell Transplantation in Patients with Refractory or Relapse Hodgkin Lymphoma

Leylagül Kaynar, Mustafa Çetin, Ali Ünal and Taner Demirer

Additional information is available at the end of the chapter

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1. Introduction

1.1. Current status of hematopoietic stem cell transplantation in patients with refractory or relapse hodgkin lymphoma

Although the high response rates, approximately 10% of patients with early-stage Hodgkin Lymphoma (HL) and 20% with advanced disease will be refractory to initial treatment or relapse after a first complete response [1-3]. The strategy for management of relapsed or refractory disease is to deliver salvage chemotherapy, followed by high-dose chemotherapy and autologous stem-cell transplantation (AutoSCT) in responding patients [4,5].

2. Autologous stem cell transplantation for Hodgkin lymphoma

2.1. Autologous stem cell transplantation at first-line therapy

The use of autoSCT for HL in first remission was wondered. There are only a few prospective randomized clinical trials focusing in this issue. Although historically controlled studies are promising, prospective controlled studies showed different results [6].

The HD01 trial included 163 patients achieving complete remission (CR) or partial remission (PR) with advanced HL after four cycles of ABVD (ABVD; doxorubicin, bleomycin, vinblastine, and dacarbazine) or other doxorubicin-containing regimens who had an unfavorable risk profile (at least two factors: high lactate dehydrogenase level, large mediastinal mass, more

than one extranodal site of disease, low hematocrit, or inguinal involvement). The patients were randomly divided into two groups; AutoSCT and four additional cycles of conventional chemotherapy. There was no significant difference regarding complete remission rates, and the 5-year failure-free survival, overall survival and relapse-free survival rates between the groups [7]. Similarly, the recently published 10-year follow-up results could not demonstrate an advantage of the high dose therapy in terms of failure-free survival, overall survival and relapse-free survival rates between the groups [8]. The HD01 trial suggested that patients responding to an anthracycline- based regimen do not benefit from autoSCT at first line therapy.

In the GOELAMS Group's (Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang) randomized phase 2 study, H97-HR trial, the authors tested 2 intensive chemotherapy regimens in 158 patients with stage IIB - IV HL accompanied by high-risk factors. High-risk were defined by the presence of >5 involved lymphoid areas, and/or a mediastinal mass ratio > 0.45, and/or >2 extra lymph node sites affected by the disease. This study examined an early intensive chemotherapy and ABVD for 4 cycles followed by delayed myeloablative intensification. In one of the arms, patients received 3 courses of combined vindesine, doxorubicin, carmustine, etoposide, and methylprednisolone (VABEM) followed by low-dose lymph node irradiation. In the other arm, patients received 4 cycles of ABVD followed by myeloablative regimen containing carmustine, etoposide, cytarabine, and melphalan and underwent autoSCT. After the completion of treatment, the CR rates for both of arms were similar. The 5-year freedom from treatment failure and 5-year overall survival rates also were similar between the arms. Consequently, the authors recommended that conventional chemotherapy should remain the reference treatment in advanced and high risk HL [9].

In considering all these results, autoSCT for HL does not take place as a part of first line therapy even for high-risk patients.

2.2. Autologous stem cell transplantation for relapsed/refractory HL

Because conventional salvage chemotherapy and/or radiotherapy have poor results in first relapsed or progressive HL, autoSCT was evaluated as a curative approach for patients with relapsed or progressive disease. There were two prospective randomized clinical trials in the last twenty years. Firstly the British National Lymphoma Investigation performed a randomized smaller prospective study in 40 patients. The aim of the study was comparison of high-dose chemotherapy (BEAM = carmustine, etoposide, cytarabine, and melphalan) plus autoSCT (n=20) with the same drugs at lower doses (mini-BEAM) (n=20) in patients with primary refractory disease, early relapse, or prior failure of conventional therapy. All patients have been followed up for at least one year. Although there was no difference in overall survival (OS), both event-free survival and progression-free survival showed statistical significant differences in favour of BEAM plus autoSCT ($p = 0.025$ and $p = 0.005$, respectively) [10]. This study suggested that High-dose chemotherapy with autoSCT could provide better disease-free survival but not overall survival.

The second randomized multicenter trial (HD-R1) was performed by investigators of the German Hodgkin's disease Study Group and the Lymphoma Working Party (LWP) of the

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EBMT to determine the benefit of HDCT in relapsed HL. Patients were randomly assigned to either four cycles of conventional chemotherapy (Dexa-BEAM: dexamethasone and carmustine, etoposide, cytarabine, and melphalan) or two cycles of Dexa-BEAM followed by autoSCT (n=73, n=88). After two cycles Dexa-BEAM chemotherapy, only 117 patients with chemosensitive disease proceeded to further treatment. Median follow-up was 39 months (IQR 3–78). Freedom from treatment failure at 3 years was significantly better for autoSCT patients (55%) than for those on Dexa-BEAM (34%; difference –21%, 95% CI –39 87 to –2 13; p=0 019), although OS was not different [11].

Data from randomized trials established autoSCT as standard therapy in relapsing HL patients responding to salvage therapy [11,12,13]. Moskowitz et al reported retrospective analysis of 75 consecutive patients with primary refractory HD, who were treated with high dose chemoradiotherapy and autoSCT. Median follow-up was 10 years. Only chemosensitivity to second-line chemotherapy predicted for a better survival, thus responding patients had an event-free survival (EFS), progression-free survival (PFS) and OS of 60%, 62% and 66%, respectively, versus 19%, 23% and 17% for patients who had a poor response to second-line chemotherapy ($P < 0.001$). Patients with disease refractory to first-line therapy but chemosensitive to standard-dose second-line therapy might have better outcome after an autoSCT [14]. Primary refractory patients or for patients in chemorefractory relapse, autoSCT has only a small likelihood to induce long-term remission. For these patients, autoSCT can be clinical option [13]. Patients with progressive disease after autoSCT have a poor outcome, and either allogeneic stem cell transplantation or other investigative approaches are necessary [14,15].

Nodular lymphocyte predominant HL (LPNHL) has to be accepted a complete different entity. There is almost no information in the literature about the impact of autoSCT in those groups of patients. Nevertheless, autoSCT can be considered a therapeutic option for LPNHL patients in advanced stages and relapsing after standard treatment [13].

2.3. High dose conditioning regimens for autologous stem cell transplantation

There is no randomized clinical trial comparing different high dose conditioning regimes for autoSCT. In retrospective analyses, the superiority of a specific regimen has not been demonstrated. Total body irradiation (TBI)-based regimens as high dose conditioning regimens were compared to chemotherapy combinations. There was no difference in efficacy and toxicity between the regimens [16,17,18]. German Hodgkin Study Group evaluated the impact of sequential high-dose therapy to increase the intensity of conditioning before autoSCT. Additional high-dose therapy did not improve the prognosis of patients with relapsed HL compared with the standard BEAM regimen and autoSCT, and was associated with increased toxic effects [19]. There was no benefit of increasing the intensity of conditioning regimen. Most of randomized trials of autoSCT in HL used BEAM regimen and this regimen is regarded, by most transplant centers, as the standard high dose-conditioning regimen [20].

2.4. Prognostic factors associated with outcome in relapse and refractor Hodgkin lymphoma before autologous stem cell transplantation

Several trials have identified prognostic factors in patients with RR-HL who have undergone subsequent salvage chemotherapy and autoSCT. These prognostic factors are summarized in table-I. Extra nodal disease, B symptoms at relapse and short remission duration after initial therapy have consistently been demonstrated to be predictors of poor outcome. Chemotherapy resistance prior to autoSCT is generally associated with poor outcome [21].

The depth of response to salvage chemotherapy before autoSCT is important. Detectable disease with functional imaging has predictive value for an unfavorable outcome [21, 22]. Jabbour et al suggested that positive functional pretransplant imaging (either gallium or Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography; FDG-PET scan) can be predictive of poor outcome. The 3-year OS rates for patients with negative functional imaging were 87% but this was 58% in patients with positive functional imaging [22]. Moskowitz et al demonstrated that patients with negative functional imaging (either gallium or FDG-PET scan) had 75% EFS compared to 31% for patients with positive functional imaging [21]. Recently, Moskowitz et al reported a prospective phase 2 study. They used a risk-adapted approach to improve PFS after high-dose radio chemotherapy and autoSCT. First salvage chemotherapies were 2 cycles of ICE (ICE; ifosfamide, carboplatin, etoposide) in a standard or augmented dose, followed by restaging FDG-PET scan. Patients with a negative scan received a transplant. If the FDG-PET scan was still positive, patients received again chemotherapy (GVD; gemcitabine, vinorelbine, and liposomal doxorubicin). Patients without evidence of disease progression proceeded to high-dose chemotherapy (HDT)/ autoSCT. Patients transplanted with negative FDG-PET had an EFS of > 80%, versus 28.6% for patients with a positive scan (P <. 001). In that study, FDG-PET–negative status is a major factor in the determination of outcome. The finding that the outcome for patients receiving GVD and having a FDG-PET–negative result is indistinguishable from patients with ICE-based therapy induced FDG-PET–negative response argues that quality of response is an important determinant of outcome. The authors suggested that the goal of salvage chemotherapy in patients with HL should be a negative FDG-PET scan before HDT/AutoSCT [23].

3. Allogeneic stem cell transplantation

Although allogeneic stem cell transplantation (alloSCT) historically associated with significantly greater treatment-related mortality (TRM) than autologous stem cell transplantation (autoSCT), Because of the potential for graft versus lymphoma (GVHL) effects and the assurance of a tumor-free graft, alloSCT is carrying curative potential especially in patients with Hodgkin lymphoma (HL) who are younger than other lymphoma patients. Nevertheless, comparative studies between myeloablative alloSCT and autoSCT in refractory and relapsed HL patients provided evidence of GVHL effect. The widespread use of alloSCT in HL patients is still a matter of controversy because of the TRM and was quite limited until the advent of reduced intensity conditioning (RIC). Nowadays, increasing numbers of studies have been

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Prognostic factors	Effects of prognostic factories	Reference
B symptoms at relapse, Extranodal disease at relapse, Initial remission duration of < 1 year	3-year PFS: No risk factor: 100%, 1 risk factor: 81%, 2 risk factors: 40% 3 risk factors: 0%	24
>2 prior chemotherapy regimens,	Patients who had received >2 chemotherapy regimens had a poorer DFS	17
Performance status; ECOG: 1-3 >1 chemotherapy regimens failed, The presence of mediastinal disease at AutoSCT	These factors significantly associated with FFS, Patients with >2 failed chemotherapy regimens have an estimated 4 year FFS of 10%.	25
Systemic symptoms at relapse, Disseminated pulmonary or bone marrow disease at relapse, More than minimal disease at AutoSCT	4-year FFP: No risk factor: 85% >1 risk factors: 41%	18
End-of-treatment to relapse interval < 12 months Presence of extranodal disease at relapse	4-year survival: No risk factor: 93%, 1 risk factor: 59%, 2 risk factors: 43%	26
Chemotherapy resistance prior to AutoSCT, Advanced disease stage at diagnosis (stage ≥III)	These factors associated with a higher risk of disease progression after transplantation	27
B symptoms, Extranodal disease, Complete remission duration of less than 1 year	EFS: 0-1 risk factor: 83% 2 risk factors: 27% 3 risk factors: 10%	28
Advanced stage at diagnosis, Radiotherapy before AutoSCT, A short first CR, Detectable disease at AutoSCT	5-year TTF: No risk factor: 71%±4% 3 or more risk factors: 18%±5%	29
Pre-autoSCT positive functional imaging (FDG-PET or gallium scan)	In this trial, the only factor that predicted an unfavorable outcome in the transplanted patients was a pre-HDT/AutoSCT–positive functional imaging	30
Pre-autoSCT, FDG-PET status	Persistent FDG-PET positivity after salvage therapy have a poor outcome with HDT/ AutoSCT	31

EFS: Event-free survival, FFP: Freedom from progression, FFS: Failure-free survival, PFS: Progression-free survival, TTF: Time to treatment failure, FDG-PET: Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography, HDT: High-dose chemotherapy

Table 1. Prognostic factors in relapse and refractory HL

investigating the role of especially RIC-alloSCT in patients with refractory or relapsed HL, most of whom have previously received autoSCT. [32]

3.1. Myeloablative conditioning regimens

Myeloablative Conditioning (MAC) alloSCT derives its benefit from both the high-dose conditioning regimen and the GVHL effect. To determine whether this approach would benefit patients with advanced HL, proof of concept was reported by Appelbaum et al. in Seattle [33]. Eight patients with disseminated HL resistant to MOPP chemotherapy were treated with high-dose chemoradiotherapy and marrow transplantation from an HLA-match sibling donor (MSD). Two patients remain alive in unmaintained complete remission (CR) at 38 and 39 months after transplant. In the other six patients, reasons for failure included relapse of lymphoma (two patients), or death due to complications of the transplant procedure. They suggest that some patients with MOPP-resistant HL can obtain prolonged CR following intensive chemoradiotherapy followed by alloSCT.

In Johns Hopkins Oncology Center, the first prospective study to compare autoSCT with allogeneic marrow transplantation (alloBMT) was done by Jines RJ. et al. [34]. Patients with HL who have failed two or more chemotherapy regimens or who have relapsed after an initial chemotherapy-induced remission of less than 12 months are seldom cured with conventional salvage therapies. They studied the effect of high-dose cytoreductive therapy followed by alloBMT in 50 patients with relapsed HL. Twenty-one patients with HLA-matched donors had alloBMT, one patient received marrow from an identical twin, and 28 patients received autologous grafts. The authors demonstrated that autoSCT and alloSCT yield similar EFS. However, they did see a difference in relapse rates between recipients of alloSCT (17%) and autoSCT recipients with chemosensitive disease (34%), which indicated the possibility of a GVHL effect [34]. In another study Anderson et al. reported from Seattle, between 1970 and 1991, 127 patients (median age, 29 years) with relapsed or refractory HL received high-dose chemotherapy with or without irradiation, followed by autoSCT (n=68), alloSCT (n=53), or syngeneic transplantation (n=6) [35]. The 5-year actuarial probabilities of OS, EFS, relapse, and nonrelapse mortality (NRM) for the entire group were 21%, 18%, 65%, and 49%, respectively. HLA-match allogeneic marrow recipients had a statistically lower relapse rate compared with recipients of autologous marrow, but OS, EFS, and NRM rates were not significantly different. They described that the use of HLA-MSD marrow results in a lower relapse rate and, thus, for some individuals, may be preferable to the use of autologous marrow. The European Group for Blood and Marrow Transplantation (EBMT) directed a retrospective study of 45 patients (median age, 29 years) with refractory or relapsed HL, who received matched sibling allogeneic versus autoSCT [36]. The 4-year actuarial probabilities of OS, PFS, relapse, and NRM were 25%, 15%, 61%, and 48% and 37%, 24%, 61%, and 27% after alloBMT and autoBMT, respectively. The 4-year actuarial probability of survival was 30% after alloBMT and 64% after autoBMT (P =.007). This difference is mainly due to a higher TRM rate after alloBMT (65% v 12%, P =.005). The authors suggested that patients with relapsed or resistant HL derive no benefit from alloSCT over autoSCT. However, lower relapse rate (13%) among patients with acute GVHD, supporting a substantial GVHL effect with alloSCT. The second EBMT registry

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reported by Peniket et al. in 2003, One-hundred-sixty-seven poor-prognosis HL patients who underwent myeloablative transplantation (77% with stage III or IV at diagnosis and 42% with chemoresistant disease) were assessed. [37] These patients received allogeneic transplants as their first transplant procedure. Actuarial OS at 4 years from transplantation was 24.7% years. These outcomes are relatively poor because of the high TRM associated with these procedures in patients with HL (51.7% actuarial procedure-related mortality at 4 years). The authors concluded that the high TRM was probably a reflection of the large percentage of patients with resistant disease. Gajewski et al. reviewed IBMTR data on 100 consecutive patients with HL who received HLA-match sibling BMT between 1982 and 1992. All patients had advanced disease [38]. Eighty-nine of 100 patients were not in remission at the time of transplant. Fifty had pretransplant Karnofsky scores less than 90% and 27 had active infection in the week before transplant. The 3-year probability of relapse and the probability of OS were 65% and 15, respectively. They concluded that the role of HLA-identical sibling BMTs have a limited therapeutic effect in advanced HL. Akpek et al. evaluated the long-term outcome after allogeneic and autologous blood or marrow transplantation in patients with relapsed or refractory HL [39]. They analyzed the outcome of 157 consecutive patients with relapsed or refractory HL, who underwent BMT between 1985 and 1998. There was a trend for probability of relapse in sensitive patients to be less after alloBMT at 34% (range, 8% to 59%) versus 51% (range, 36% to 67%) for the auto patients (HR = 0.51, P =.17). There seems to be a clinical GVHL effect associated with alloBMT. Allogeneic BMT for HL also seems to have a lower risk of secondary AML/MDS than autoBMT. Thus, alloBMT warrants continued study in HL.

Actually, comparisons of MAC versus autologous transplantation are problematic, because MAC regimens are favored in patients with extensive prior therapy or comorbidities. In general, higher NRM has been associated with myeloablative regimens and a greater risk of relapse associated with autologous approaches, leading to similar long-term outcomes for patients treated with each approach. The poor outcomes for allogeneic stem cell transplantation in HL reported by the IBMTR and the EBMT may result from the selection of patients with unfavorable risk for these studies. At that point, however, high rate of the TRM with MAC in Hodgkin lymphoma is considered is rarely pursued [40]. Because of the most of this studies have been reported at least couple decade ago, the effect of myeloablative transplantation in HL may reevaluate with the developed supportive treatment modalities and new drugs.

3.2. Reduced-intensity conditioning

Last decade has seen a radical change in the approach to alloSCT. Previously, MAC regimens were thought to be necessary for preventing graft rejection, making marrow space, and providing antitumor activity. Interest in exploring transplantation with RIC in relapsed or refractory HL arise from evidence of GVHL effect in these studies comparing allogeneic with autologous transplantation. In an attempt to decrease TRM, authors increasingly have been using alloSCT with RIC to patients with HL. Reduced-intensity conditioning could be sufficient to restore allogeneic engraftment, and allow graft versus host reactions could eliminate host hematopoiesis and provide antitumor effects. This has allowed treatment to be

considered in older patients, or patients with co-morbidities, including those with HL for whom prior autoSCT failed.

The EBMT analyzed the first retrospective analysis comparing RIC-alloSCT (n=89) with MAC-alloSCT (n=79) in patients with relapsed or refractory HL [41]. In the RIC group NRM was significantly decreased, OS was better and there was a trend for better PFS. Results demonstrated nearly twice the relapse incidence in the RIC group (57% vs. 30%), but the 5-year OS was significantly higher in the RIC group (28% vs. 22%, P=0.003). They also indicate that the existence of a GVHL effect correlated to the development of GVHD and additional efforts to reduce the high relaps rate seen in both groups of patients. The centers reported the outcomes of 143 patients undergoing unrelated donor reduced-intensity and nonmyeloablative (RIC/NST) SCT for relapsed and refractory HL between 1999 and 2004 reported to the CIBMTR [42]. They analyzed Patients were heavily pretreated, including autoSCT in 89%. With a median follow-up of 25 months, the probability of TRM at day 100 and 2 years was 15% and 33%, respectively. The probabilities of PFS and OS were 30% and 56% at 1 year and 20% and 37% at 2 years. The presence of extranodal disease and the Karnofsky Performance Scale (KPS) <90 were significant risk factors for TRM, PFS, and OS, whereas chemosensitivity at transplantation was not. Dose intensity of the conditioning regimen (RIC versus NST) did not impact outcomes.

Peggs et al. undertook RIC-alloSCT in 49 patients with multiply relapsed HL, 44 (90%) of whom had progression of disease after previous autoSCT, number of previous treatment courses was five [range 3-8], and time from diagnosis 4.8 years [range 0.6-4.8]) [43]. Thirty-one patients had HLA matched donors who were related and 18 had donors who were unrelated. All patients engrafted. Eight of 49 (16%) had grade II-IV acute GVHD and seven (14%) had chronic GVHD before DLIs. Sixteen (33%) patients had DLI from 3 months after transplantation for residual disease or progression. Six (38%) of the 16 developed grade II-IV acute GVHD and five developed chronic GVHD. Nine (56%) showed disease responses after infusion (eight complete, one partial). Non-relapse-related mortality was 16.3% at 730 days (7.2% for patients who had related donors vs. 34.1% for those with unrelated donors, p=0.0206). Projected 4 year OS and PFS was 55.7% and 39.0%, respectively (62.0% and 41.5% for related donors). In this prospectively study, authors showed that the potential for durable responses in patients who have previously had substantial treatment for HL. In another prospective study, Alvarez et al. described the results of RIC-alloSCT in patients with advanced HL. Forty patients with relapsed or refractory HL were homogeneously treated with an RIC protocol (fludarabine 150 mg/m(2) intravenously plus melphalan 140 mg/m(2) intravenously) and cyclosporin A and methotrexate as GVHD prophylaxis [44]. Twenty patients (50%) were allografted in resistant relapse, and 38 patients received hematopoietic cells from an HLA-match sibling. Five patients (12%) died from early TRM (before day +100 after allo-RIC). One-year TRM was 25%. Acute GVHD developed in 18 patients (45%). Chronic GVHD developed in 17 (45%) of the 31 evaluable patients. The response rate 3 months after the allo-RIC was 67% (21 [52%] CRs and 6 [15%] partial remissions). Eleven patients received DLIs for disease relapse. The response rate after DLI was 54% (3 complete remissions and 3 partial remissions). Overall survival and PFS were 48% +/- 10% and 32% +/- 10% at 2 years, respectively. They suggest that RIC-alloSCT

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is feasible in heavily pretreated HL patients and has an acceptable early TRM. Results are better in patients allografted in sensitive disease. Both responses observed after the development of GVHD and DLI may suggest a GVHL effect. Allogeneic RIC has to be considered an effective therapeutic approach for patients who have had treatment failure with previous autoSCT. Anderlini et al. reported that a total of 40 patients with relapsed/refractory HL underwent RIC-alloSCT [45]. Disease status at alloSCT was refractory relapse (n=14) or sensitive relapse (n=26). The conditioning regimens were fludarabine-cyclophosphamide+/-antithymocyte globulin (n=14), a less intensive regimen, and fludarabine-melphalan (FM) (n=26), a more intensive one. The two groups had similar prognostic factors. Day 100 and cumulative TRMs (18-month) were 5 and 22%. Twenty-four patients (60%) are alive (14 in CR or CR-unconfirmed) with a median follow-up of 13 months (4-78). In all, 16 patients expired (TRM n=8, disease progression n=8). FM patients had better OS (73 vs. 39% at 18 months; P=0.03), and a trend towards better PFS (37 vs 21% at 18 months; P=0.2). Reduced intensity alloSCT is feasible in relapsed/refractory HL patients with a low TRM. This group updated the results comparing outcomes of 58 patients with HL underwent RIC-alloSCT from a MRD (n=25) or a MUD (n=33) [46]. Forty-eight (83%) had undergone prior autoSCT. Disease status at transplant was refractory relapse (n=28) or sensitive relapse (n=30). Cumulative day 100 and 2-year TRM rates were 7% and 15%, respectively (day 100 transplant-related mortality MRD vs. MUD 8% vs. 6%, p=ns; 2-year MRD vs. MUD 13% vs. 16%, p=ns). Projected 2-year overall and progression-free survival rates are 64% (49-76%) and 32% (20-45%), with 2-year disease progression/relapse at 55% (43-70%). There was no statistically significant difference in OS, PFS, and disease progression/relapse between MRD and MUD transplants. They also suggested that FM as a preparative regimen for RIC-alloSCT in progression-free survival HL is associated with a significant reduction in TRM, with comparable results in MRD and MUD allograft.

In a recent study, Sarina et al., using RIC as a salvage option, to evaluate the role of alloSCT in patients HL relapsing after autoSCT [47]. In this retrospective study based on the commitment of attending physicians to perform a salvage alloSCT; thus, only HL patients having human leukocyte antigen-typing immediately after the failed autoSCT were included. Of 185 patients, 122 found an identical sibling (55%), a matched unrelated (32%) or a haploidentical sibling (13%) donor; 63 patients did not find any donor. Clinical features of both groups did not differ. Two-year PFS and OS were better in the donor group (39.3% vs 14.2%, and 66% vs 42%, respectively, P <.001) with a median follow-up of 48 months. In multivariable analysis, having a donor was significant for better PFS and OS (P <.001). Patients allografted in complete remission showed a better PFS and OS. They concluded that, that: (1) HL patients relapsing after an autoSCT have a survival advantage if they undergo RIC alloSCT; (2) CR achievement before RIC alloSCT is very important and influences patients' clinical outcome; and (3) NRM after RIC alloSCT is rather low; therefore, this procedure can be considered a feasible option in the clinical setting. Stephen et al. [48] investigated the role of RIC-alloSCT in the management of patients with HL. To further define its role they conducted a retrospective analysis of 285 patients with HL who underwent a RIC-alloSCT in order to identify prognostic factors that predict outcome. Eighty percent of patients had undergone a prior autoSCT and 25% had refractory disease at transplant. Non-relapse mortality was associated with chemorefractory disease, poor performance status, age >45 and transplantation before 2002. For patients with

no risk factors the 3-year non-relapse mortality rate was 12.5% compared to 46.2% for patients with 2 or more risk factors. The use of an unrelated donor had no adverse effect on the non-relapse mortality. Acute GVHD grades II-IV developed in 30% and chronic GVHD in 42%. The development of chronic GVHD was associated with a lower relapse rate. The disease progression rate at one and five years was 41% and 58.7% respectively and was associated with chemorefractory disease and extent of prior therapy. Donor lymphocyte infusions were administered to 64 patients for active disease of whom 32% showed a clinical response. Eight out of 18 patients receiving DLIs alone had clinical responses. Progression-free and OS were both associated with performance status and disease status at transplant. Patients with neither risk factor had a 3- year PFS and OS of 42% and 56% respectively compared to 8% and 25% for patients with one or more risk factors. Relapse within six months of a prior autologous transplant was associated with a higher relapse rate and a lower progression-free. They recommend that for patients deemed to be at high risk of failing an autologous transplant a RIC-alloSCT may represent a more effective therapy and prospective comparative studies in this setting should be considered.

On the basis of current data, some authors recommend RIC-allo for HL only in the context of prospective clinical trials because allo-SCT trials continue to report disappointing relapse rates. However, if clinicians feel strongly about proceeding with this strategy, patients with refractory disease should be excluded and opportunities to exploit the GVHL effect should be used [20].

3.3. The role of functional imaging in response assessment before RIC allo-SCT

Dodero et al. investigated the prognostic value of PET scanning in 80 patients who had chemosensitive disease (34 patients with HG-NHL and 46 patients with HL before undergoing to RIC and followed by alloSCT [49]. Positron emission tomography was used to assess before they underwent alloSCT: 42 patients had negative PET studies, and 38 patients had positive PET studies. Patients underwent allograft from MSD (n = 41) or alternative donors (n = 39). At the time of the last follow-up, 48 patients were alive (60%), and 32 had died. The 3-year cumulative incidence of nonrecurrence mortality and disease recurrence was 17% and 40%, respectively. The cumulative incidence of disease recurrence was significantly lower in the PET-negative patients (25% vs. 56%; P =.007), but there was no significant difference between the patients with or without chronic GVHD (P =.400). The patients who had negative PET studies before undergoing alloSCT also had significantly better outcomes in terms of 3-year OS (76% vs. 33%; P =.001) and 3-year PFS (73% vs. 31%; P =.001). On multivariate analysis, OS was influenced by PET status (hazard ratio [HR], 3.35), performance status (HR, 5.15), and type of donor (HR, 6.26 for haploidentical vs. MSD; HR, 1.94 for MUD vs. MSD)l. The current results indicated that PET scanning appears to be an accurate tool for assessing prognosis in patients who are eligible for RIC allografting.

In summary, autoSCT and alloSCT may be curative therapy options for patients with relapse/refractory HL. AutoSCT is a standard therapy in relapsing HL patients especially responding to salvage therapy. However, there is no place of autoSCT even in high-risk patients with first remission. If patients with refractory disease after first-line treatment respond second line

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standard-dose therapy, these patients can benefit from an autoSCT. BEAM regimen is used as the standard high dose-conditioning regimen. Detectable disease with functional imaging before autoSCT can be an indicator of poor prognosis. Patients with relaps or progressive disease after autoSCT need either alloSCT or other investigative approaches. The review of the literature of alloSCT in HL patients has showed that in the last decade an increasing interest has been raised on this topic. The results that are now available allow the following considerations: (i) Although myeloablative allogeneic SCT has lower relaps rate still has been associated high non relaps mortality; (ii) The effect of myeloablative transplantation in HL may reevaluate with the developed supportive treatment modalities and future studies should be aimed at integrating intensified therapies and/or new drugs into the treatment plan to pursue the best response before allografting; (iii) RIC alloSCT is a feasible option in relapsed/refractory HL patients even if they were heavily pretreated; (iv) 20–30% of the allografted patients can be long-term survivors after RIC alloSCT; (v) Complete response is the most important predictor of a favorable outcome; (vi) PET scanning appears to be an accurate tool for assessing prognosis in patients who are eligible for RIC allografting; thus (vii) Since the relapse risk after RIC-alloSCT is still high maintenance treatment or immunological methods should be explored in prospective clinical trials.

Author details

Leylagül Kaynar[1*], Mustafa Çetin[2], Ali Ünal[3] and Taner Demirer[4]

*Address all correspondence to: drleylagul@gmail.com

1 Erciyes University, Faculty of Medicine, Deparment of Hematology, Erciyes Transplant Center, Kayseri, Turkey

2 Erciyes University, Faculty of Medicine, Deparment of Hematology, Erciyes Transplant Center, Kayseri, Turkey

3 Erciyes University, Faculty of Medicine, Deparment of Hematology, Erciyes Transplant Center, Kayseri, Turkey

4 Ankara University, Medical School, Deparment of Hematology, Ankara, Turkey

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