

* CHAPTER 30

HSCT for Hodgkin's lymphoma in adults

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1. Introduction

Newly diagnosed patients with advanced stage Hodgkin's lymphoma (HL) have an excellent prognosis and the vast majority of them can be cured with initial treatment. In contrast, the prognosis of most patients relapsing after first-line therapy remains poor. In patients in sensitive relapse or in second complete remission (CR) high-dose chemotherapy and auto-HSCT is nowadays considered to be the treatment of choice. Auto-HSCT is also an option for those patients with primary refractory disease (PRD). Allo-HSCT is still considered an experimental procedure for patients with relapsed or refractory HL (1).

2. Auto-HSCT in refractory/relapsed Hodgkin's lymphoma

2.1. Conditioning regimens in the auto-HSCT setting

There has never been a randomised trial comparing preparative regimens for transplant for relapsed HL. The only recent study addressing this question was a retrospective review by investigators at the Fred Hutchinson Cancer Research Center. Between 1990 and 1998, 92 patients with relapsed HL were transplanted with either a TBI - based regimen or busulfan/melphalan/thiotepa. There was no difference in 5-year OS (57 vs. 52%) or EFS (49 vs. 42%) rates for patients treated with TBI or chemotherapy only. Given the reports of increased risk of second cancers and myelodysplasia following TBI, a chemotherapy-only preparative regimen is currently favoured by most transplant centres.

2.2. Auto-HSCT for relapsed Hodgkin's lymphoma

The use of auto-HSCT is now considered the standard of care for relapsed HL patients (1). The first randomised trial of transplant for relapsed disease was a small trial from the British National Lymphoma Investigation (BNLI) comparing auto-HSCT with BEAM to mini-BEAM without auto-HSCT (2) in patients with active HL, for whom conventional therapy had failed. Twenty patients were assigned to treatment with BEAM plus auto-HSCT and 20 to mini-BEAM. All had been followed up for at least 12 months (median 34 months). Five BEAM recipients died compared with 9 mini-BEAM recipients. That difference was not significant ($p = 0.318$) and there was no difference in OS. However, both 3-year EFS and PFS showed significant differences in favour of BEAM plus auto-HSCT ($p = 0.025$ and $p = 0.005$, respectively).

In the second randomised trial, which was performed by investigators of the German Hodgkin's disease Study Group and the Lymphoma Working Party (LWP) of the EBMT, 161 patients with relapsed HL were randomly assigned two cycles of Dexa-BEAM and either two further courses of Dexa-BEAM or high-dose BEAM and auto-

HSCT (3). Of the 117 patients with chemosensitive relapse there was a significant improvement in 3-year freedom from treatment failure (FFTF) for patients undergoing auto-HSCT compared to 4 cycles of Dexamethasone-BEAM (55 vs. 34%, $p = 0.019$). With a median follow up of 39 months, the 3-year FFTF was significantly better for patients treated with BEAM. No significant improvement of auto-HSCT over conventional salvage chemotherapy (CT) in terms of FFTF could be observed in the small sub-group of patients treated for multiple-relapsed disease ($n = 24$). There was no statistically significant difference in OS for any sub-group of patients.

2.3. Auto-HSCT for patients with primary refractory disease

The prognosis of patients with PRD, defined as progression during first-line CT or within 3 months after the end of therapy, is extremely poor. Nevertheless as opposed to non-Hodgkin's lymphoma there seems to be a general consensus that even patients who fail first- and second-line CT may still enjoy a 20%–30% chance of cure with auto-HSCT.

In the EBMT registry analysis (4), 175 HL patients with PRD were reviewed. Actuarial 5-year PFS and OS were 32 and 36%, respectively. In the Autologous Bone Marrow Transplant Registry (ABMTR) analysis on 122 patients undergoing auto-HSCT after an induction failure (IF) (5), actuarial probabilities at 3 years were 38 and 50% for PFS and OS, respectively. Lazarus et al. (5) found that the presence of B symptoms at diagnosis as well as Karnofsky status at auto-HSCT correlated with survival. In the EBMT analysis (4), patients receiving more than one line of CT before transplantation did worse, both in terms of OS and PFS.

The long-term outcome of 75 consecutive patients with biopsy-confirmed HL at the completion of primary CT has been summarised by the Memorial Sloan Kettering Cancer Center group (6). All patients underwent standard-dose salvage therapy followed by involved field radiotherapy (RT). Patients without progression went on to receive high-dose etoposide, cyclophosphamide and either total lymphoid irradiation or carmustine followed by bone marrow or peripheral stem cell rescue. Patients who had shown less than a 25% decrease in tumour burden with standard salvage therapy ($n = 27$) prior to auto-HSCT had a 10-year EFS of 17 versus 60% for those with at least a 25% decrease on standard salvage therapy ($n = 48$).

3. Allo-HSCT in refractory/relapsed Hodgkin's lymphoma

3.1. Myeloablative conditioning and allo-HSCT in Hodgkin's lymphoma

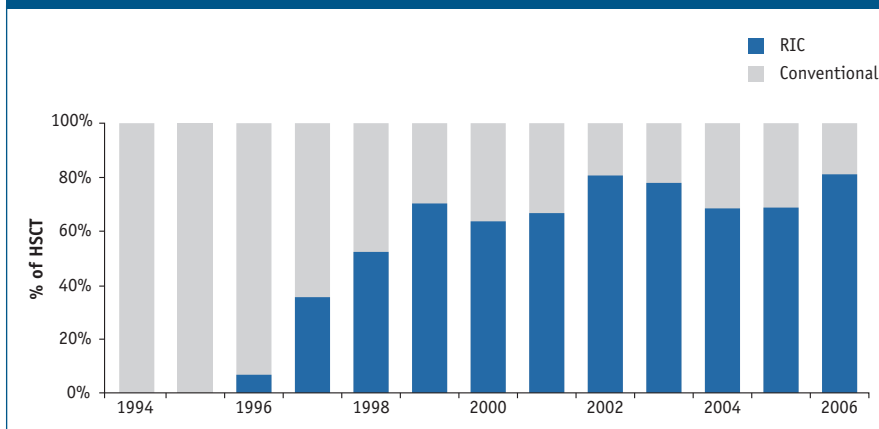
The first reports on allo-HSCT in patients with HL appeared in the mid-eighties. Two larger registry-based studies published in 1996 gave disappointing results. Gajewski

et al. analysed 100 HL patients allografted from HLA-identical siblings (7). The 3-year rates for OS, DFS, and the probability of relapse were 21, 15 and 65%, respectively. The major problems after transplantation were persistent or recurrent disease, or respiratory complications, which accounted for 35 to 51% of deaths. Acute and/or chronic GvHD did not significantly reduce the risk of relapse. A case-matched analysis including 45 allografts and 45 autografts reported to the EBMT (8) did not find significant differences in actuarial probabilities of OS, PFS, and relapse rates between allo-HSCT and auto-HSCT (25, 15, 61% vs. 37, 24, 61%, respectively at 4 yrs). The actuarial TRM at 4 years was significantly higher for allografts than for autografts (48 vs. 27%, $p = 0.04$). Acute GvHD \geq grade II was associated with a significantly lower risk of relapse, but also with a lower survival rate.

3.2. Reduced intensity conditioning and allo-HSCT in Hodgkin's lymphoma

Since the first clinical experiences that suggested that allo-HSCT after a nonmyeloablative conditioning (RIC allo-HSCT) might represent an interesting alternative to classical allo-HSCT, a number of reports have addressed the question whether RIC allo-HSCT might also work for patients with HL (Figure 1). Several groups have already published their results in small groups of patients with a relative short follow-up (9–12) (Table 1). The largest cohort of patients treated with RIC allo-HSCT in HL was recently reported by the LWP of the EBMT (13) and

Figure 1: Allo-HSCT for relapsed and refractory Hodgkin's lymphoma. Comparison between conventional conditioning and RIC regimens



Experience of the LWP of the EBMT (with permission)

Table 1: Clinical characteristics and outcome of patients with relapsed or refractory Hodgkin's lymphoma treated with a RIC allo-HSCT

	BBMT 2004 (12)	BMT 2005 (9)	Lancet 2005 (11)	BBMT 2006 (10)
N. of patients	27	58	49	40
Sex (M:F)	–	–	25 / 24	24 / 16
Age [median (range)] in years	37 (21–65)	32 (19–59)	32	31 (16–53)
Previous lines of CT [median (range)]	5 (2–9)	5 (2–9)	5 (3–8)	4 (2–6)
Prior RT (%)	25 (92)	44 (75)	–	23 (58)
Prior auto-HSCT (%)	24 (89)	48 (83)	44 (89)	29 (73)
Dx to RIC-allo [median (range)] in months	–	23 (9–145)	4.8 (0.6–14.8)	37 (11–300)
Auto-HSCT to RIC-allo [median (range)] in months	16 (2–78)	5 (1–34)	–	17 (4–146)
Disease status at RIC-allo (sensitive/refractory)	20 / 7	30 / 28	36 / 13	20 / 2
Type of donor (MRD / UD)	18 / 9	25 / 33	31 / 18	38 / 2
aGvHD (grades II-IV)	47% (MRD) / 55% (UD)	28%	16%	45%
cGvHD	50% (MRD) / 60% (UD)	74%	14%	45%
100-day TRM	7%	7%	4.1%	12%
1-year TRM	35%	15% (24 months)	16% (2-year)	25%
PFS	11% (MRD) / 35% (UD) (1-year)	32% (24 months)	32% (4-year)	32% (2-year)
OS	39% (MSD) / 75% (UD) (1-year)	64% (24 months)	56% (4-year)	48% (2-year)

M: Male; F: Female; CT: Chemotherapy; RT: Radiotherapy; auto-HSCT: Autologous stem cell transplantation; Dx: Diagnosis; RIC-allo: Reduced intensity allogeneic stem cell transplantation; MRD: Related donor; UD: Unrelated donor; aGvHD: Acute graft versus host disease; cGvHD: Chronic graft versus host disease; TRM: Transplant related mortality; PFS: Progression free survival; OS: Overall survival

included 374 patients. Patients had received an average of four lines of prior therapy (1–8) and 288 patients (77%) had failed one or two auto-HSCT. At the time of allo-HSCT, 79 patients (21%) were in CR, 146 patients (39%) had chemosensitive disease and 149 patients (40%) had chemoresistant disease. Two hundred and thirty-four patients (63%) were allografted from a matched sibling donor, 112 (30%) from a matched unrelated donor, and 28 from a mismatched donor (7%). Grade II-IV acute GvHD (aGvHD) was reported in 27% of patients, chronic GvHD (cGvHD) in 40% of patients at risk. The 100-day TRM was 12% but increased to 20% at 12 months, and to 22% at three years; it was significantly worse for patients with chemoresistant disease. Two-year PFS was 29% and again significantly worse for patients with chemoresistant disease ($p < 0.001$). In a landmark analysis the development of either acute or chronic GvHD by 9 months post transplant was associated with a significantly lower relapse rate.

3.3. Comparison of myeloablative and reduced-intensity conditioning prior to allo-HSCT in relapsed and refractory Hodgkin's lymphoma

The LWP of the EBMT has performed the only analysis reported so far which compares outcomes after reduced-intensity ($n = 97$) or myeloablative conditioning ($n = 93$) and allo-HSCT in patients with HL (14). Non-relapse mortality was significantly decreased in the RIC allo-HSCT group [HR 2.43 (95% CI 1.48–3.98), $p < 0.001$]. PFS and OS were also better in the reduced intensity group [HR 1.28 (95% CI 0.92–1.78), $p = 0.1$ and HR 1.62 (95% CI 1.15–2.28), $p = 0.005$]. The development of cGvHD significantly decreased the incidence of relapse after transplantation, which translated into a better PFS. This analysis indicates that RIC allo-HSCT is able to significantly reduced TRM after transplantation and improves the long-term outcome of relapsed and refractory patients treated with an allograft.

3.4. Graft-versus-Hodgkin effect

The significant reduction of the TRM observed in the RIC allo-HSCT has been able to put in evidence the existence of a graft-versus-HL effect. Direct evidence of a graft-versus-HL effect comes from two main sources: the demonstration that the development of acute or chronic GvHD after allo-HSCT is associated to a lower relapse rate and the clinical information coming from donor lymphocyte infusions (DLIs). Relapse rate is significantly lower in those patients developing GvHD after transplantation. Additionally, reported disease responses to DLIs range between 30 to 55% (9–11, 13).

4. Conclusions

The use of auto-HSCT is now considered the standard of care for relapsed HL patients. Two randomised trials showed significant benefit in FFTF for auto-HSCT

over conventional chemotherapy for relapsed disease. The results of these trials have resulted in the recommendation of auto-HSCT at time of first relapse for even the most favourable patients. Results of auto-HSCT in PRD are poor and new therapeutic alternatives should be sought for these patients. Allo-HSCT has been increasingly used in relapsed or refractory HL patients with the introduction of RIC protocols. RIC allo-HSCT significantly decreases TRM in relation to conventional protocols and improve long-term outcome of these patients. The significant reduction of the TRM observed in the RIC allo-HSCT setting has been able to demonstrate the existence of a graft-versus-HL effect mostly associated to the development of GvHD after transplantation. Nevertheless, allo-HSCT in HL is still considered an experimental procedure and patients should be included in prospective clinical trials.

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Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **In terms of indications for auto-HSCT in patients with HL in 1st CR, choose the correct answer:**
 - a) Nowadays auto-HSCT is not indicated for patients with HL in 1st CR
 - b) Autografting should be considered for patients in 1st CR with at least 3 adverse prognostic factors at diagnosis
 - c) Auto-HSCT can be done, but we have to take into consideration the excessive risk of secondary malignancies after auto-HSCT
 - d) The published phase II trials indicate a higher than usual TRM in this subgroup of patients
2. **Which do you consider the best therapeutic strategy for a 40-year old female with relapsed HL? The duration of the 1st CR was 10 months and the Ann Arbor stage at relapse was IVB:**
 - a) Collection of peripheral blood stem cells and auto-HSCT without prior salvage chemotherapy

- b) Consider an allo-HSCT as the best therapeutic option. Look for a matched unrelated donor if the patient does not have a matched sibling donor available.....
- c) Treat the patient with a salvage chemotherapy protocol, collect peripheral blood stem cells and proceed to auto-HSCT.....
- d) If the patient has not received RT before, consider RT in all involved areas as a curative treatment.....

3. In patients with primary refractory HL, all of the following statements are true except one. Indicate the incorrect answer:

- a) The TRM of an autologous procedure is similar to that experienced by patients autografted in sensitive relapse.....
- b) Response to second line chemotherapy is one of the best prognostic indicators of the long-term outcome of an auto-HSCT.....
- c) New therapeutic strategies need to be developed. The results obtained with an auto-HSCT are clearly inferior to those in relapsed patients.....
- d) There is no indication for an auto-HSCT in primary refractory patients due to the extremely poor long-term outcome of this subgroup of patients with the autologous procedure.....

4. Indicate the correct answer in relation to the conditioning regimens used in patients with HL:

- a) In the allogeneic setting, the use of low dose TBI seems to improve the outcome after transplant.....
- b) The use of TBI in the autologous setting seems to be associated with an increased risk of secondary malignancies.....
- c) The protocol CBV (cyclophosphamide, BCNU and VP-16) is superior to the BEAM regimen (BCNU, VP-16, ARA-C and melphalan) for HL patients in the autologous setting.....
- d) Myeloablative conditioning regimens are increasingly being used in the allogeneic setting.....

- 5. We have a 50-year old female patient with HL who relapses 13 months after an auto-HSCT with advanced stage disease and we want to consider an allo-HSCT as a therapeutic option for her.**

Indicate the correct answer:

- a) There is no indication for an allo-HSCT in HL nowadays
- b) There is no indication for an unrelated donor search in this patient.
Results of allo-HSCT from matched unrelated donors have been
demonstrated to be inferior to those with HLA matched sibling
donors
- c) The use of RIC regimens has not allowed us to reduce the high TRM
associated with conventional conditioning regimens
- d) It has been demonstrated that the best GvHD prophylaxis needs to
include Campath 1H