Autologous stem cell transplantation in Hodgkin’s disease

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The majority of patients with Hodgkin’s disease (HD) are curable with first-line therapy; however, 10–20% of patients with advanced HD will not enter complete remission (CR) with conventional first-line therapy and a further 20–30% will relapse after having initially achieved CR [1–3]. New first line protocols such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), used in patients with high-risk HD, might reduce the relapse rate [4, 5]. However, there will still be patients who continue to relapse and therefore need further treatment. Furthermore, it is too early to assess the long-term side effects of these new aggressive regimens (e.g. incidence of secondary leukaemia) that might affect long-term overall survival (OS).

Patients with relapsed or primary progressive HD are usually treated with salvage (second-line) chemotherapy, followed by autologous stem cell transplantation (autoSCT), or less frequently by some form of allograft.

These salvage treatments (including ESHAP, IVE, mini-BEAM, DHAP, DICEP) may obtain a response in up to 85%, including CR rates of 26–62% [6, 7], depending on whether patients are treated for first relapse, later relapse or primary resistant disease. Unfortunately, these ‘post-salvaged remissions’ are not durable in the majority of patients, particularly in those who were refractory to first-line therapy, or who relapsed within 1 year of initial treatment, for which the cure rate is ∼10%. Even those with an initial remission of 12 months or more have only a 25–35% chance of long-term disease-free survival [1, 8].

Compared with historical controls, high-dose therapy (HDT) followed by autografting significantly improves survival in those groups of poor prognosis patients [9]. Long-term freedom from progression (FFP) with HDT in patients with relapsed/refractory HD approaches 40–60% [10–12]. The only prospective randomised trial that compared mini-BEAM (salvage therapy) with BEAM followed by autoSCT, confirmed the advantage of BEAM with autoSCT in these patients (induction failure/early relapse), who obtained a significantly better event-free survival (EFS) compared with the mini-BEAM group: 53% versus 10%, respectively [13]. There was no significant difference in OS, which might be explained by the fact that a significant number of patients in the mini-BEAM arm who relapsed were then rescued with a BEAM autograft [13].

The main indication for autografting in HD is still relapsed disease [14, 15], but primary refractory disease may also be an indication [15–17]. Autograft in first CR, used as consolidation therapy for patients with high-risk HD, has failed to improve patient’s DFS and OS (A. M. Carella, HD01 study, personal communication, 2002).

Autologous stem cell transplantation in patients with relapsed/refractory HD

It now seems clear that HDT followed by autoSCT can improve outcome of patients with refractory/relapsed HD [13–16]. A 5-year EFS (event-free survival) of 40–50% had been reported in several clinical trials [11, 18–21].

Retrospective analyses of prognostic factors predicting outcome of autoSCT revealed that bulky/non-responsive disease at transplantation had a significant negative influence on post-transplant DFS [11, 15, 18, 20, 22]. Baker et al. [23] reported 5 year failure free survival (FFS) of 9% in children and adolescents with resistant disease, compared with 35% for patients with sensitive relapse. Salvage therapy given pre-transplant is mainly aimed at reducing tumour mass and identifying patients with chemo-sensitive disease that might benefit from receiving HDT [7, 15].

Other factors that might predict better outcome with SCT include late relapse (>12 months since CR) [21], no B symptoms or extra-nodal involvement at relapse [18], normal lactate dehydrogenase (LDH) level [23], less than two lines of therapy prior autoSCT [15] and good performance status at transplantation [16, 24].

Because of the poorer outcome of autoSCT in patients with refractory disease, some centres do not recommend autoSCT for patients who have not achieved CR after three courses of chemotherapy [25]. However, HDT with autoSCT has recently been reported to improve outcome of patients with refractory HD, with 3 year OS of 32–50% [15, 16]. Sureda et al. have analyzed the outcome of four hundred and ninety-four HD patients who were treated with autoSCT for relapsed/refractory HD disease or as consolidation in first CR (n = 57). Two hundred and three patients (41%) were in CR, 216 had sensitive disease (defined as reduction of at least 50% in tumour mass with salvage chemotherapy) and 75 had resistant disease (49 primary refractory disease; 26 resistant relapse) at transplantation. Nine per cent of the patients died in the first 100 days post-transplant. Five-year time to treatment failure (TTF) was 63.2% for patients transplanted in CR, 37.3% for...
patients with sensitive disease and 17.4% for patients transplanted with resistant disease. Five year OS in these three groups were 70.4%, 41.4% and 32.8%, respectively. Disease status before autoSCT was found to be the most important prognostic factor for final outcome. There were no significant differences between patients autografted in first or later CR. However, there was a trend for a better TTF for patients transplanted in first CR, compared with those transplanted in second or third CR [15].

Lazarus et al. [14] analysed the Autologous Blood and Marrow Transplant Registry (ABMTR) results in 414 HD patients who had been transplanted with relapsed disease \((n = 295)\) or in second CR \((n = 119)\). Three-year DFS and OS were significantly better in patients who had been transplanted in CR, compared with those who were transplanted with relapsed disease (64% and 75% versus 46% and 58%, respectively; \(P < 0.001\)) [14]. However, 3-year OS in patients transplanted with resistant disease was 38% [16].

Special attention had been given to patients who failed to remit with first-line conventional chemotherapy [16, 17, 26]. Their outcome with salvage therapy remains poor, with 8 year OS of 8% [27]. The role of HDT followed by autoSCT has therefore been investigated. Chopra et al. [11] have reported 5-year actuarial progression-free survival (PFS) of 33% in 46 patients with primary refractory HD treated with HDT followed by stem-cell rescue. Similar results were obtained in 19 patients treated by Sloan-Kettering Cancer Center Group [28].

The German Hodgkin’s Lymphoma Study Group (GHSG) analysed retrospectively the outcome of patients with primary progressive HD, defined as a progression during first-line treatment (70%), or within the first 3 months after completing first-line therapy (30%) [26]. Two hundred patients had been treated with salvage radiotherapy \((n = 47)\) or salvage chemotherapy \((n = 153)\) for primary progressive disease. Seventy patients were then referred to HDT followed by autoSCT. Sixty-two out of the 70 patients who were treated with autoSCT had achieved complete/partial response (PR) with salvage therapy, prior to transplantation. The 5-year OS and freedom from second failure (FF2F) for patients who had salvage therapy followed by autoSCT were 43 and 31%, respectively. Multivariate analysis revealed that low performance status at time of progression, age >50 years and failure to achieve temporary remission with first-line chemotherapy were significant adverse prognostic factors for OS. In the presence of the three risk factors, 5 year OS is 0%, compared with 55% for a patient who has none of them [26]. The good results obtained with autoSCT were interpreted by the author to be related mainly to patient selection and not necessarily to autoSCT itself [26].

Andre et al. [29] compared the outcome of HD patients treated with salvage chemotherapy followed by autoSCT for primary induction failure disease \((n = 86)\), with matched, conventionally treated patients \((n = 258)\) [treated with mechlorethamine, vincristine, procarbazine and prednisone (MOPP)]. Six-year OS (counted from diagnosis) for grafted patients was 38%, compared with 29% in conventionally treated patients \((P = 0.058)\). Here too, response to salvage therapy prior transplant was the only significant prognostic factor for survival [PR: relative risk (RR) +2.8, \(P = 0.017\); progressive disease: RR 5.26, \(P < 0.001\)] [29].

However, a different strategy for treating patients with primary induction failure has been suggested by the EBMTR and EBMT (Autologous Group for Blood and Marrow Transplantation) studies, both supporting early transplantation, rather than a salvage therapy followed by an ASCT [16, 17].

Analysis of the ABMTR results in patients treated with autoSCT after failing to achieve CR with conventional treatment have shown a 50% (62/122) CR rate following an autograft (part of these patients were transplanted with sensitive disease, although none of them was in CR at transplantation) [16]. Probabilities of PFS and OS 3 years post-transplantation were 38% [95% confidence interval (CI) 39% to 60%] and 50% (95% CI 28% to 48%), respectively. In multivariate analysis, B symptoms at diagnosis and poor performance status at transplantation were adverse prognostic factors [16]. Surprisingly, disease sensitivity to chemotherapy (known for two-thirds of the patients) was not found to be a significant predictor of survival, although >80% of patients with resistant disease had B symptoms and/or low performance score. It is worth noting that in this study, patients were defined as having a primary induction failure only if their computed tomography (CT) scan showed progression, taking into account that many HD patients might have residual fibrotic mass, even though they are responding to chemotherapy and do not have active disease.

In the analysis of the EBMT results for patients treated with autoSCT for primary resistant disease, 175 patients with primary induction failure (PIF) were analysed [17]. Seventy-five patients were treated with salvage autoSCT without further attempts to induce remission with conventional chemotherapy. The remaining 100 patients had an autoSCT after failing to respond to second-line therapy as well. Thirty per cent of all patients \((n = 175)\) succeeded in achieving CR following transplant, 28% had PR, 28% had no response or continued to progress and 14% died of transplant related complications. Actuarial 5-year OS and PFS were 36% and 32%, respectively. However, patients with primary refractory disease who had an autoSCT without prior salvage therapy \((n = 75)\) had a better PFS and OS compared with patients who had been transplanted after failing to respond to second-line treatment as well. Multivariate analysis revealed that the time from diagnosis to autoSCT had a significant influence on OS in this group of patients. PFS and OS were not significantly different between those patients with disease progression and those who had stable or minimally responsive disease [17].

Results of both studies [16, 17] suggest that patients with primary resistant HD might benefit from earlier autoSCT. Further studies, including prospective randomised trials are needed to clear this issue.
It is important to note that in most studies patients were defined as having resistant disease based on their scanning results. A high proportion of patients with mediastinal HD might still have an enlarged mediastinal mass in their scans, despite achieving CR. Positron emission tomography (PET) and gallium scans might improve evaluation of disease status. However, the fact that these patients were included unknowingly in these studies, including Sweetenham’s, might partly explain the surprisingly good outcome of primary resistant HD patients with autoSCT in registry studies [17].

In summary, it seems that patients who fail to remit with induction chemotherapy might benefit from having autologous transplantation. However, all studies reported are retrospective and apart from the fact that they all summarise results in patients who initially failed to remit, there are still large variations in patients reported. Transplantation in a patient who failed to respond to second-line chemotherapy is not the same as autoSCT in a patient who had PIF but responded to salvage therapy prior to his transplant. It is also important to analyse separately patients who had autoSCT with relapsed, untreated disease and those who entered with disease, after already failing to respond to salvage chemotherapy. Further analysis of each of these subgroups is needed in order to give clinicians a better idea which patients to refer to transplant and which to preclude.

AutoSCT in first CR in patients with high-risk HD

Sureda et al. [15], in their retrospective analysis, noticed a trend (although not significant) for a better TTF in patients transplanted in first CR.

The EBMT/Australian and New Zealand Lymphoma Group (ANZLG) intergroup HD01 trial examined the efficacy of consolidation with autoSCT for high-risk HD patients in first CR. Patient outcome was compared with matched historical controls [30]. Seventeen of 22 patients who had autoSCT in first CR remained in remission at a median follow-up of 86 month, compared with eight of 24 in the control group [30].

Based on these results, Carella conducted a phase III study (personal communication). Patients with high-risk HD who achieved CR after four courses of induction chemotherapy were randomised to up-front autoSCT or four additional courses of the same regimen. Four-year OS, regression-free survival and TTF were 87%, 92% and 84% in autografted patients, compared with 88%, 94% and 83% in the chemotherapy group (personal communication). It seems therefore that there is no place for up-front ASCT in high-risk HD patients.

Toxicity

The high mortality rate (20–25%) initially reported with autoSCT in HD was mainly related to the population of patients who had the transplant in the later stages of their disease; however, pulmonary toxicity associated with prior mediastinal radiotherapy and chemotherapy (carmustine and bleomycin) also contributed [25]. Performing autoSCT in earlier stages (first relapse or second remission), combined with introduction of newer high-dose chemotherapy regimes [CBV (cyclophosphamide, carmustine and etoposide), BEAM (carmustine, etoposide, cytarabine and methotrexate)] and the increasing usage of peripheral stem cell instead of bone marrow harvests (accelerates engraftment), reduced transplant-related mortality to 5–10% [18, 20, 21].

Secondary malignancy

The main problem with introducing autoSCT to HD patients is the relatively high incidence of secondary myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), which approaches 9–18% at 5–7 years post-transplantation [9, 31–34].

The pathogenesis of secondary MDS/AML in these patients, treated prior to transplant with chemotherapy/radiotherapy, is complex, and the contribution of each of these treatments to leukaemia development has not yet been fully elucidated. Retrospective analysis of HD patients treated through the British National Lymphoma Investigation (BNLI) with (n = 595) or without autoSCT (n = 4576) revealed that quantity of prior therapy and treatment with MOPP or lonosotin chemotherapy were the main risk factors for secondary MDS/AML. Relative risk (RR) assessment with autoSCT was 1.83, which does not support a significant increased risk for secondary leukaemia associated with autoSCT [35].

Sureda et al. [15] found adjuvant radiotherapy before transplant, age >40 years at transplantation and use of total body irradiation in conditioning regimen to be associated with increased risk of developing secondary malignancy post-transplantation. Sixteen of 494 HD patients who had been transplanted developed a secondary malignancy [12 MDS/AML; one acute lymphoblastic leukaemia (ALL); one NHL; two solid tumours], with a 5-year cumulative incidence of 4.3%. Krishnan et al. [36] analysed the incidence of transplant related MDS/AML in 612 non-Hodgkin’s lymphoma (NHL) and HD patients who had been treated with HDT with autoSCT rescue. A retrospective cohort and a nested case–control study design were used to evaluate the role of pre-transplant therapeutic exposures and transplant conditioning regimens. Twenty-two of 612 patients developed morphological evidence of secondary MDS/AML. The estimated cumulative probability for developing these changes was 8.6% ± 2.1% at 6 years post-autoSCT. Multivariate analyses revealed stem cell priming with etoposide to be associated with an increased risk for secondary MDS/AML (RR 7.7, P = 0.002). The influence of pre-transplant chemotherapy on the chance of developing secondary MDS/AML was estimated by case–control study. Multivariate analysis found an association with pre-
transplant radiotherapy, but failed to reveal any association with pre-transplant chemotherapy or with conditioning regimens. However, the risk of secondary AML in patients who had stem-cell priming with etoposide was 12.3 times higher than in patients who did not (P = 0.006). Secondary AML in these patients has been found to be associated with 11q23/21q22 abnormalities. Analysis of HD patients only (n = 218) revealed that 11 of 218 patients developed MDS/AML with an estimated cumulative probability of 8.1 ± 2.5% 6 years post-transplant (median time to develop secondary MDS/AML was 3.8 years from diagnosis and 0.9 years from transplant). Multivariate analyses confirmed priming with etoposide to be the only risk factor for secondary MDS/AML. There was no association between pre-transplant stem-cell priming with etoposide and increased risk of secondary AML/MDS in NHL patients. Furthermore, secondary MDS/AML tended to occur later, 2.4 years post-transplant. However, HD by itself was not found to be a risk factor for secondary AML compared with NHL. No association was found between conditioning regimens and risk of developing secondary AML/MDS.

There is no typical chromosomal change for ‘transplant-related leukemia’ in HD patients. Where part of the patients show abnormalities in 11q23/21q22 [36], partial/complete deletion of chromosome 7 [34], translocations involving chromosome 8 [t(8;16),t(21;8)] [37], or other chromosomal changes, others may have no detectable chromosomal abnormalities [37].

A higher incidence of solid cancers has also been reported [34]. Ten of 467 (2.1%) patients who had been transplanted developed secondary cancers (eight solid cancers; two NHL). Andre et al. [34] found age ≥ 40 years and the use of peripheral stem cells as a source of graft to be associated with increased risk of secondary malignancy.

Most probably, patients who received a significant amount of combination chemotherapy/radiotherapy and had multiple relapses are at a higher risk of developing secondary malignancy even without being transplanted. However, it is still difficult to conclude exactly what the influence of stem-cell mobilisation followed by HDT is on this increased risk, and what strategy should be taken in patients which are theoretically at high risk of developing secondary malignancy.

Conclusions and future directions

HDT followed by stem-cell rescue has become a standard treatment for patients who fail to remit on induction chemotherapy or relapse after an initial response. However, nearly half of these patients will eventually relapse post-transplantation. Modifications in transplant conditioning regimen, aimed at reducing post-transplant relapse risk, have been suggested [38].

Bierman et al. [38] have treated 14 patients with chemoresistant/bulky HD with yttrium 90-labelled anti-feritin anti-bodies, followed by HDT (CBV). Four patients were still alive 2 years post-transplantation, three of them in continued CR [38]. The effectiveness and the toxicity of this treatment should first be assessed in patients with less advanced disease and compared with results of conventional autoSCT. The efficacy of post-transplant immunomodulation, using Interleukins [39] or interferon (INF) [40], has not yet been proven.

Although a conventional allogeneic stem cell transplantation might reduce relapse risk, this advantage is offset by an extremely high mortality rate [41]. It has recently been suggested that patients with high-risk HD and patients who have relapsed post-autoSCT, might be considered for Low Intensity allogeneic SCT, aimed at achieving disease cure by inducing a graft versus tumour effect without a significant increase in treatment-related mortality [42].

However, AutoSCT remains the current preferred treatment for patients with relapsed/primary-resistant HD, although attempts to reduce post-transplant relapse risk, and to decrease the treatment related toxicity (mainly secondary malignancies), remain as challenges for the future.

References


