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Introduction

Hodgkin Lymphoma (HL) is a hematologic malignancy treated with multi-agent chemotherapy that is typically associated with high cure rates ¹. ABVD chemotherapy is as effective as the old MOPP chemotherapy and has fewer complications with high cure rates in limited stage presentation ². Recent data suggest that escalating chemotherapy with the use of BEACOPP improves disease control and survival although this is currently being tested in a second international randomized trial³. However, disease that is relapsed after or refractory to primary therapy is not uncommon. Stem cell transplant strategies are typically employed in this area and this treatment modality is supported by varying levels of evidence based on the transplant technique and disease status at the time of transplantation. Herein, we briefly summarize the data and provide recommendations on the use of autologous and allogeneic stem cell transplantation in the management of HL.

Autologous stem cell transplantation in the initial treatment of Hodgkin Lymphoma

High dose chemotherapy and autologous stem cell transplant (HDC/ASCT) in first remission of high risk HL remains unproven. In an uncontrolled prospective study of 24 patients with high risk HL in CR1 receiving HDC/ASCT, the 5-yr overall survival (OS) and progression-free survival (PFS) were 92 and 77% ⁴. Two randomized clinical trials (RCTs) have failed to show improved disease control or survival benefit ^{5,6} in advanced unfavourable HL. The first recruited 163 pts of advanced unfavourable HL and randomized them into HDC with ASCT or anthracycline containing chemotherapy. The 5-yr OS was 88% in both groups ⁶. The second study recruited 112 poor risk HL patients but only 92 received the intended treatment. There was no statistically significant difference between the 4-yr OS of the HDC/ASCT and intensive chemotherapy groups (89 vs. 93%, p=0.90). Unfortunately, no large, high quality studies are available to draw any conclusions about a survival benefit for HDC/ASCT in the initial treatment of standard risk HL. Thus, HDC/ASCT is not recommended in the initial treatment of Hodgkin lymphoma outside of a clinical trial.

Autologous stem cell transplant in the treatment of relapsed Hodgkin Lymphoma

Two RCTs ^{7,8} demonstrated improved disease control and similar overall survival between the HDC/ASCT and conventional salvage chemotherapy. In the largest RCT, 161 patients with chemo-sensitive relapse were randomized between HD-BEAM/ASCT and mini-BEAM salvage chemotherapy ⁸. Both groups were initially treated with two cycles of Dexa-BEAM with responders proceeding to either high dose BEAM and autologous stem cell support or two further cycles of Dexa-BEAM. The 3-yr freedom from treatment failure (FFTF) was in favour of the transplant group (55 vs. 34%, p value 0.019). There was no survival advantage in the transplant arm. Although the BNLI RCT had a small sample

size, it showed an improved event free survival in favour of HDC/ASCT (total of 40 patients) ⁷. In an uncontrolled clinical trial with 102 relapse refractory HL patients receiving two cycles of DHAP salvage chemotherapy followed by HDC/ASCT, the freedom from second failure and OS were 59% and 78% respectively ⁹. In addition, multiple retrospective studies demonstrated better disease control with HDC and ASCT ¹⁰⁻¹⁴, some of which had long term follow up. The largest series, reported by the ABMTR ¹², included 414 patients in first relapse or second complete remission. Most patients received Cyclophosphamide, BCNU, VP-16 (CBV) as their high dose therapy regimen. With a median follow up of 46 months, the 3-yr DFS for patients with first relapse and second remission was 46% and 64% respectively. The 3-yr OS was 58% and 75% for patients with first relapse and second remission respectively. Poor performance status, elevated LDH and chemo-resistance predicted worse disease free survival. In another study that included 140 pts with longer median follow up ¹³, the 10-yr PFS and OS were 45% and 47% respectively. We recommend high dose chemotherapy and autologous stem cell transplant for patients with relapsed Hodgkin's lymphoma not previously treated with a transplant modality.

Chemo-refractory disease

Patients with chemo-refractory disease experience poor outcomes with 5-yr PFS and OS of 17-32% and 36% respectively ^{15,16}. In a study of 72 patients with primary refractory HL (not responding to the induction chemotherapy) from multiple clinical trials ¹⁷, patients undergoing HDC and ASCT had an improved OS when compared to patients receiving salvage chemotherapy, (4-yr OS 81% vs. 38%, p=0.019). Patients not responding to second line chemotherapy have very poor outcomes even with HDC and ASCT, 10-yr OS 17% vs. 66% in responding patients ¹⁸. We recommend HDC and ASCT in patients with chemo-refractory disease only if they respond to a salvage chemotherapy.

Two prospective phase II trials studied the outcomes of double HDC/ASCT for primary refractory or relapse refractory disease ^{19,20}. Although early results appear promising with 5-yr OS and PFS of 54% and 49% respectively, the patients were highly selected and the sample size was small.

Although HDC and tandem ASCT strategies appear promising, they cannot be recommended as standard of care and patients should only undergo these types of treatment as part of a research protocol. Based on current evidence, the standard of care remains one ASCT procedure.

Myeloablative Allogeneic bone marrow transplant in relapse refractory HL

Myeloablative (MA) allogeneic bone marrow transplant in HL with relapsed/refractory disease is characterized by high treatment related mortality and poor long term results. In a study of 100 patients with relapsed/refractory HL ²¹, the 3-yr OS and DFS were 21% and 15% respectively. The 3-yr probability

of relapse was 65%. In another larger study conducted by the EBMT ²², 167 patients were analyzed after their first transplant, a MA-allogeneic or autologous bone marrow transplant. The 4-yr OS, PFS and TRM were 24%, 16% and 52% respectively. We do not recommend MA-allogeneic bone marrow transplant for relapsed/refractory HL outside a clinical trial.

RIC-allogeneic bone marrow transplant in relapse refractory HL

One prospective and multiple retrospective studies have reported reasonable outcomes with reduced intensity allogeneic bone marrow transplant ²³⁻²⁸. Forty patients with relapsed or refractory HL, including post ASCT and multiply relapsed patients, were prospectively enrolled on a phase II trial to evaluate RIC allo-SCT²³. The 1-yr TRM was 25% with 2-yr OS and PFS of 48% and 32% respectively. The largest retrospective study was reported by the EBMT and reported 311 patients with relapsed or refractory HL who underwent RIC allo-SCT. The stem cell source was matched related donors in 63%. The 2-yr TRM was 27% with a 2-yr PFS and OS of 29% and 46% respectively. Another recently published study compared 89 patients with RIC to 79 patients with MA transplants with HL in relapse undergoing first allogeneic transplant ²⁹. The NRM and OS were in favour of RIC with HR of 2.85 (p<0.001) and 2.05 (p=0.04) respectively. A lower relapse rate was observed in patients with chronic GvHD. In addition, there were several responses to DLI suggesting a graft versus Hodgkin lymphoma effect ^{23,26-29}. Given the lower TRM and the evidence of graft versus lymphoma effect, an allogeneic bone marrow transplant can be offered for patients with relapse refractory HL with evidence of chemo-sensitivity who are considered medically fit to undergo such procedure. However, given the high rate of relapse, we recommend patients be enrolled on clinical trial protocols that test strategies to reduce the rate of post-transplant relapse.

Conclusions

- Given the lack of improved disease control or survival benefit in using HDC/ASCT in patients with previously untreated HL, as shown in high quality evidence, we don't recommend HDC/ASCT strategy in this settings.
- We recommend HDC/ASCT strategy in relapsed chemo-sensitive HL as two high quality studies showed improved disease control using this therapy.
- We recommend HDC and ASCT in patients with chemo-refractory disease only if they respond to a second salvage chemotherapy.
- MA-allogeneic bone marrow transplant has high treatment related mortality in relapsed/ refractory HL patients and is not recommended outside a clinical trial.

- Studies with RIC allogeneic bone marrow transplantation have shown a lower TRM and evidence of GvL effect. This modality may be offered to patients preferably in a clinical trial targeting reducing relapse rates.
- As data is limited in the management of HL relapse post autologous stem cell transplantation, it is difficult to recommend any specific strategy. Available strategies include novel drugs, second ASCT, RIC-allo, radiotherapy or palliative therapy.

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