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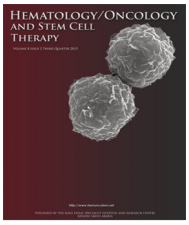

Relapse of Hodgkin lymphoma after autologous transplantation: Time to rethink treatment?

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Abstract
Relapse of Hodgkin lymphoma after autologous hematopoietic cell transplantation (autologous HCT) is a major therapeutic challenge. Its management, at least in younger patients, traditionally involves salvage chemotherapy aiming to achieve disease remission followed by consolidation with allogeneic hematopoietic cell transplantation (allogeneic HCT) in eligible patients. The efficacy of salvage therapy is variable and newer combination chemotherapy regimens have improved the outcomes. Factors such as shorter time to relapse after autologous HCT and poor performance status have been identified as predictors of poor outcome. Newer agents such as immunoconjugate brentuximab vedotin, checkpoint inhibitors (e.g., pembrolizumab, nivolumab), lenalidomide, and everolimus are available for the treatment of patients relapsing after autologous HCT. With the availability of reduced intensity conditioning allogeneic HCT, more patients are eligible for this therapy with lesser toxicity and better efficacy due to graft versus lymphoma effects. Alternative donor sources such as haploidentical stem cell transplantation and umbilical cord blood transplantation are expanding this procedure to patients without HLA-matched donors. However, strategies aimed at reduction of disease relapse after reduced intensity conditioning allogeneic HCT are needed to improve the outcomes of this treatment. This review summarizes the current data on salvage chemotherapy and HCT strategies used to treat patients with relapsed Hodgkin lymphoma after prior autologous HCT.

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Introduction

Autologous hematopoietic cell transplantation (HCT) is an established treatment option for relapsed or refractory Hodgkin lymphoma (HL). However, even after autologous HCT, a subset of poor-risk patients, who present with B-symptoms, bulky disease, advanced stage, or extranodal involvement have a high incidence of relapse. It is particularly challenging to manage such patients because they are often young, without medical comorbidities, and are able to tolerate additional therapies. Hence, the expectations of achieving a cure are high. Multiple options such as single agent chemotherapy, combination chemotherapy strategies, radiotherapy, antibody–drug conjugates, immune checkpoint inhibitors, immunomodulatory agents, small molecule inhibitors, or allogeneic HCT are available for HL relapsing after autologous HCT. This review evaluates the different modalities of treatment for HL patients relapsing after an autologous HCT.

Risk factors for relapse after autologous HCT

It is important to identify HL patients upfront who might be at higher risk of relapse after autologous HCT. In a Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of 606 children, adolescents, and young adults with relapsed/refractory HL who underwent autologous HCT between 1995 and 2010, Satwani et al. [1] identified four risk factors that predicted poor progression-free survival (PFS) following autologous HCT. These include: (1) time from diagnosis to first relapse of $\leqslant$1 year (including primary refractory disease), (2) Karnofsky performance score <90, (3) extranodal involvement at the time of autologous HCT, and (4) chemoresistant disease at the time of autologous HCT. Another study by Hahn et al. [2] also identified similar factors that predicted poor PFS. A retrospective analysis of European Society for Blood and Marrow Transplant (EBMT) data with 2200 adult HL patients identified Stage IV disease at presentation, bulky disease, age $\geqslant$50 years, and poor performance status to be associated with poor outcome [3]. Based on these studies, patients with these high-risk features prior to autologous HCT should be identified earlier and post-transplant consolidation and/or maintenance therapies or clinical trial participation should be considered.

Consolidation/maintenance therapies for HL at high-risk of relapse following autologous HCT

Prevention of disease relapse following autologous HCT in patients with high-risk HL has until recently been an area of unmet medical need. Brentuximab vedotin as a consolidation therapy after autologous HCT in high-risk HL has shown promising results. The results from ATHERA trial showed that median PFS was 42.9 months (95% confidence interval [CI]: 30.4–42.9) for patients in the brentuximab vedotin post-transplant consolidation group compared with 24.1 months for those in the placebo group [4]. Included patients had at least one risk factor for progression after autologous HCT such as primary refractory HL, relapsed HL with less than 12 months of initial remission, or extranodal involvement at the start of pretransplantation salvage chemotherapy and required to have complete remission, partial remission, or stable disease after pretransplantation salvage chemotherapy. However, positron emission tomography (PET)–computed tomography was not mandatory prior to transplant in these patients. Notable side-effects of brentuximab included sensory or motor neuropathy, neutropenia, and infections. While this trial demonstrated that postautologous HCT maintenance brentuximab vedotin is effective in preventing relapse in high-risk HL patients, many questions remain unanswered. The ATHERA trial was limited to brentuximab vedotin naïve patients. Whether the results will hold true in patients with prior brentuximab exposure is not known. The incremental benefit of this consolidation in HL patients with a negative PET scan before autologous HCT, is also not known. The cost associated with maintenance brentuximab is also an important factor to be considered.

Salvage therapies after autologous HCT

Treating relapsed/refractory HL patients failing a prior autologous HCT is a therapeutic challenge. While allogeneic HCT is theoretically a curative option, significant numbers of patients are not eligible due to matched donor availability, poor performance status, or due to chemorefractory disease. In this next section, we discuss conventional therapies for disease control after relapse following an autologous HCT. These conventional therapies are summarized in Table 1.

Conventional chemotherapy regimens

Gemcitabine-based regimens

Gemcitabine has single agent activity in HL, and several gemcitabine-containing combination chemotherapy regimens have shown encouraging activity in HL (Table 1). Beatz et al. [5] evaluated the combination of gemcitabine/dexamethasone/cisplatin as salvage chemotherapy in 23 patients with relapsed, refractory HL (median age 36 years, range 19–57). There were four complete responses and 12 partial responses with an overall response rate of 69.5% (95% CI: 52–87%). Cancer and Leukemia Group B 59804 trial by Bartlett et al. [6] studied gemcitabine/vinorelbine/dexamethasone combination in 91 relapsed HL patients, which included transplant naïve patients and postautologous HCT relapses. The 4-year event-free survival and overall survival (OS) rates in transplant-naive patients were 52% (95% CI: 0.34, 0.68) and 70% (95% CI: 0.49, 0.84) and in the patients in whom prior transplant failed, these were 10% (95% CI: 0.03, 0.22) and 34% (95% CI: 0.17, 0.52), respectively. The overall response rate was 70% (95% CI: 59.8, 79.7), with 19% achieving complete remission.

A multi-center phase II trial evaluated the role of gemcitabine/carboplatin/dexamethasone/rituximab in 51 patients with relapsed/refractory lymphomas, including HL

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