Relapsed/Refractory Hodgkin Lymphoma

What Is the Best Salvage Therapy and Do We Need RIC-AlloSCT?

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KEYWORDS

• Prognostic factors • Salvage chemotherapy • Autologous transplant
• FDG-PET scan • RIC-alloSCT

KEY POINTS

- For RR-HL, standard therapy consists of salvage chemotherapy followed by HDCT/ASCT + RT.
- Key adverse risk factors present at relapse/progression include short response duration <12 months, B symptoms, extranodal disease, as well as advanced stage and anemia.
- There is no obvious superior salvage therapy among the commonly used regimens such as DHAP, ICE, IGEV; maintaining dose-intensity is important for optimal responses.
- Functional imaging using FDG-PET scanning after salvage chemotherapy and before ASCT is a critical predictor of outcome; the goal of salvage should be a negative FDG-PET scan.
- Either a second line of salvage or a tandem ASCT may benefit some patients with residual FDG avidity post-salvage.
- RIC-alloSCT may provide a GVL effect and durable responses in some patients with HL relapsing or progressing after ASCT.
- New agents, particularly Brentuximab vedotin, are being incorporated earlier into the treatment of RR-HL, such as those with FDG-avid chemoresistant disease, those progressing through second-line salvage, or those relapsing after an ASCT.

INTRODUCTION

Most patients with Hodgkin lymphoma (HL) are cured by chemotherapy alone with or without additional external beam radiation; however, up to 10% of patients with early-stage favorable HL and up to 30% of patients with early-stage unfavorable or

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advanced stage disease will either fail to respond to first-line therapy or relapse after an initial complete remission (CR). For those who relapse or fail to achieve a CR, standard therapy involves salvage chemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT).[1–6] Approximately 40% to 50% of RR-HL patients can be cured with HDCT/ASCT, particularly those with more favorable risk features. In contrast, patients with primary refractory disease and/or adverse risk features at relapse, such as extranodal disease or short response duration, may benefit more from other interventions. These alternative approaches include antibody-drug conjugates and reduced-intensity conditioning allogeneic stem cell transplantation (RIC-alloSCT).

SALVAGE THERAPY AND HDCT/ASCT

Which Prognostic Factors at Progression/Relapse Are Important?

Over the last 20 years, there have been several reports identifying key prognostic factors in patients with relapsed/refractory Hodgkin lymphoma (RR-HL) who have undergone salvage chemotherapy and ASCT (**Table 1**).

1. The Groupe d'Etude des Lymphomes de l'Adulte developed a 2-factor model that included as adverse features short CR1 duration, and extranodal disease at relapse.[10]
2. The Autologous Blood and Marrow Transplant Registry identified 3 adverse risk factors including Karnofsky performance score less than 90%, abnormal lactate dehydrogenase (LDH) at ASCT, and chemoresistant relapse.[12]
3. Some of the largest studies of prognostic variables have been conducted by the German Hodgkin study group (GHSG).
   a. In their first analysis of 206 patients with primary progressive disease they identified 3 adverse risk factors including ECOGPS greater than 0, age greater than 50 years, and failure to obtain a temporary remission to initial therapy.[11]
   b. In a subsequent study among 422 patients with relapsed HL, they defined a GHSG Clinical Risk Score using 3 adverse prognostic factors for overall survival (OS) including advanced disease stage III/IV, initial response duration of less than 12 months, and anemia (Hb <120 g/L and <105 g/L in men and women).[17] Rates of freedom from second failure at 5 years for patients failing first-line therapy were 45%, 32%, and 18%, for patients with prognostic scores of 0 to 1, 2, and 3, respectively. Hence, this score has been used widely in prospective trials and treatment approaches.
4. From other large studies, consistent adverse prognostic factors have emerged: short initial response duration, usually within 12 months, advanced stage III/IV at relapse, and extranodal disease (see **Table 1**).[9,10,12,13,17,19–21,26,27]
5. Finally, in a prospective study of ifosfamide, carboplatin, etoposide (ICE) salvage among 85 patients, Moskowitz and colleagues[13] developed a prognostic model of 3 adverse risk factors at relapse, including B symptoms, extranodal disease, and CR duration less than 12 months. The presence of 0 to 1 risk factors was associated with an event-free survival (EFS) of 83%, decreasing to 10% for 3 risk factors.

Which Salvage Regimen?

There are no randomized controlled trials (RCTs) and no consensus as to the most effective salvage regimen for RR-HL. The 2 published RCTs of ASCT (see **Table 2**) used mini-BCNU, etoposide, cytarabine, melphalan (BEAM) or dexa-BEAM as salvage.[28,29] Although these regimens would still be considered standard, several alternative salvage combinations have been used, reporting overlapping response rates from 60% to 85% (**Table 2**).[13,15,26,30–42]