Primary refractory Hodgkin’s disease

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Summary
Primary refractory Hodgkin’s disease may generally be defined as progression of disease during induction treatment or a partial or transient response (<60 days) to induction therapy. Salvage chemotherapy is inadequate in this patient population; fewer than 10% of patients survive for 10 years or longer. Improved outcomes after failure of primary induction therapy have been reported with myeloablative therapy and autografting. The projected event-free survivals ranged from 18%–49% at four years. Highly selected patients may benefit from salvage radiotherapy, but this may be best accomplished in combination with transplantation. A number of strategies might be considered for increasing the cure rate for the small subset of patients with primary refractory Hodgkin’s disease. Among these, identification of patients at high risk for induction failure and modifications of primary treatment to address this risk hold the greatest promise for success.

Key words: autologous transplantation, Hodgkin’s disease, induction failure, primary refractory, salvage chemotherapy, salvage radiotherapy, transplantation

DeVita et al. reported that patients with advanced Hodgkin’s disease who failed to achieve a complete remission with MOPP (mustard, vincristine, procarbazine, prednisone) chemotherapy, termed induction failures, had a dismal prognosis with no patients alive and progression-free at five years [1]. Subsequently, primary refractory Hodgkin’s disease or failure of induction therapy has been defined variably in the literature. Definitions include progression of disease during induction therapy, transient response to induction therapy or failure to achieve a complete response with induction therapy. The latter definition, which was previously so useful, is currently complicated by the regular demonstration of residual radiographic abnormalities following treatment for Hodgkin’s disease with current imaging techniques.

In the early MOPP series, the proportion of patients with advanced stage disease failing to achieve complete remission (CR) was about 20%. In more recent trials with MOPP/ABV(D) (adriamycin, bleomycin, vinblastine, dacarbazine) alternating or hybrid regimens or ABVD alone, the proportion of induction failures ranged from 5%–41% (Table 1) [2–5]. The inordinate magnitude of these differences, despite the use of similar treatments, is the result of differences in the terminology of primary refractory Hodgkin’s disease. Thus, in discussing therapeutic results, distinctions in terminology must be considered.

The management of patients failing induction therapy with primary chemotherapy has consisted of salvage combination chemotherapy, high-dose therapy with transplantation, and radiation therapy. Santoro et al. reported a 52% complete response rate with ABVD in patients progressing during or within 12 months after MOPP chemotherapy [6]. Those with extranodal disease and systemic symptoms were less likely to have a CR. More recently, Bonfante et al. reported that the success of salvage therapy after MOPP/ABVD alternating or hybrid regimens in advanced Hodgkin’s disease was significantly inferior for patients who had less than a CR [2]. Approximately one-third of the 115 patients failing MOPP/ABVD was considered to have primary refractory disease. These patients were treated with salvage chemotherapy, either the CEP (CCNU, VP16, prednimustine) regimen or an ifosfamide- and etoposide-containing combination or high-dose treatments. At eight years, none of these patients was alive and progression-free. In contrast, 22% of patients achieving a CR of one year or less and 44% of patients achieving a CR of greater than one year were alive and progression-free. Overall survival figures at eight years for the three groups of patients were: induction failures, CR <12 months and CR >12 months were 8%, 28% and 54%, respectively (P < 0.001). It is clear that salvage chemotherapy was

<table>
<thead>
<tr>
<th>Group, reference</th>
<th>Therapy</th>
<th>Definition</th>
<th>Induction failure</th>
</tr>
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<tbody>
<tr>
<td>Milan [2]</td>
<td>MOPP/ABVD vs. Hybrid</td>
<td>&lt; CR</td>
<td>9%</td>
</tr>
<tr>
<td>Canada [3]</td>
<td>MOPP/ABVD vs. MOPP/ABV</td>
<td>&lt; PR</td>
<td>12%–17%</td>
</tr>
<tr>
<td>EORTC [4]</td>
<td>MOPP/ABV ± IF RT</td>
<td>&lt; CR</td>
<td>41%</td>
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<tr>
<td>ECOG [5]</td>
<td>MOPP – ABVD vs. MOPP/ABV</td>
<td>PR</td>
<td>16%</td>
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Abbreviations: CCR – complete response; PR – partial response; PD – progressive disease.
inadequate in patients failing induction MOPP/ABVD regimens. A number of groups has reported their data using myeloablative therapy and transplantation for primary refractory Hodgkin's disease. Reece et al. in Vancouver reported on 30 patients with primary refractory Hodgkin's disease who received augmented CBV ± P (cyclophosphamide, BCNU, VP16 alone or together with cisplatin) followed by autologous transplantation [7]. The definition of induction failure used in this study was either progressive disease during primary chemotherapy, biopsy-proven persistent disease, or transient partial remission (PR) ranging from 0.75–8.75 months in duration. Patients in this study received cytotherapy measures prior to high-dose therapy in the form of either conventional chemotherapy and/or local irradiation or high-dose cyclophosphamide as part of hematopoietic stem cell mobilization. With a median follow-up of 3.6 years, the estimated progression-free survival was 42%. More recently, Forrest et al. reported the outcomes of 23 patients with primary refractory disease who had received augmented CBV ± P and autotransplantation in Vancouver five or more years earlier [8]. The 10-year cumulative incidence of relapse for patients autografted after induction failure was 55%, which was significantly higher than the 27% reported for patients in first relapse. The estimated event-free survival (EFS) for patients failing induction chemotherapy was 30% at 10 years compared to 62% for patients in first relapse. These data demonstrate that mature follow-up in refractory as well as recurrent Hodgkin's disease is necessary for proper assessment of therapeutic success. In addition, as with conventional chemotherapy, the data illustrate that patients failing during or shortly after primary chemotherapy have an outcome significantly inferior to patients who achieved an initial CR.

Gianni et al. have described a novel delivery of high-dose therapy in which individual cytotoxic agents are administered in maximal tolerated doses [9]. High-dose cyclophosphamide was used to mobilize peripheral blood progenitor cells which were later used in combination with marrow for autografting after high-dose melphalan and irradiation. In this small series, seven patients had progressive disease during primary induction chemotherapy, and nine achieved a PR only. The estimated four-year EFS for induction failure patients treated with high-dose sequential therapy was 31%. This result was significantly inferior to the 78% estimated EFS for patients achieving an initial CR but relapsing within 12 months.

Wheeler et al. reported results in recurrent and refractory Hodgkin's disease after high-dose cyclophosphamide, carmustine, and etoposide with autologous transplantation [10]. Of interest, EFS was not significantly different in patients treated in first relapse based on response to therapy, defined as no prior CR, CR one year or less, or CR greater than one year. However, EFS for patients progressing on chemotherapy (n = 11) was less than 20% at three years compared with an estimated

### Table 2: Recurrent or refractory Hodgkin's disease. Managed at Stanford University.

<table>
<thead>
<tr>
<th>Percentage four-year EFS</th>
<th>Induction failure</th>
<th>CR ≤ 12 months</th>
<th>CR &gt; 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional therapy</td>
<td>19</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>High-dose therapy and transplantation</td>
<td>51&lt;sup&gt;b&lt;/sup&gt;</td>
<td>56&lt;sup&gt;b&lt;/sup&gt;</td>
<td>51&lt;sup&gt;c&lt;/sup&gt;</td>
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<table>
<thead>
<tr>
<th>Percentage four-year OS</th>
<th>Conventional therapy</th>
<th>High-dose therapy and transplantation</th>
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<tr>
<td>38</td>
<td>37</td>
<td>62</td>
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Abbreviation: CR – complete remission.

* Complete remission or minimal disease after salvage therapy.

<sup>b</sup> P < 0.01.

<sup>c</sup> P < 0.05


40% for patients with a response followed by disease progression within 60 days of the completion of chemotherapy. The result for patients with transient partial responses to primary treatment was similar to the result for patients achieving CR of longer duration. It is intuitive that patients who actually progress during induction chemotherapy are likely to have the most drug-resistant Hodgkin's disease.

In an attempt to compare outcomes with conventional salvage or high-dose therapy in recurrent or refractory Hodgkin's disease, Yuen et al. evaluated a group of patients treated in first relapse with high-dose therapy or conventional salvage therapy with curative intent [11]. The conventional therapy group was selected to match the high-dose group with regard to age and initial stage. Table 2 describes the EFS and overall survival in these two groups according to response to primary therapy. Patients defined as induction failures (progressive disease during treatment or within 60 days of completion) had a significantly superior EFS at four years although there was no significant difference in survival. Of note, high-dose treatment was associated with higher EFS in patients with CR ≤ 12 months, whereas no significant advantage was seen at four years in patients with prolonged remission after primary therapy. These data support an advantage for high-dose treatment and transplantation in selected patients failing induction therapy.

Survival data following three myeloablative regimens, selected on the basis of prior therapy, and autotransplantation in recurrent or refractory Hodgkin's disease were reported from Stanford University by Horning et al. [12]. Twenty-nine patients who had progressed during treatment or within 60 days after treatment were defined as induction failures. The updated results for these patients, followed up to a median of 65 months, are shown in Figure 1. Estimated EFS at four years was 49.5% (95% CI: 39.6–59.3%). Survival data for patients with progressive disease during induction (n = 17), persistent disease (n = 4) or progressive disease within 60 days after
induction \((n = 8)\) treatment were not significantly different. Three patients who progressed during induction had significant delays during treatment due to toxicity or compliance. In two additional patients, persistent disease consisted of radiographic abnormalities and positive gallium scans only. High-dose therapy and transplantation was part of the initial salvage plan in the majority of patients. All patients received cytoreductive chemotherapy and/or radiotherapy prior to transplant in an attempt to achieve a minimal disease state, which was accomplished in the majority of cases. Two patients were considered to have refractory, progressive disease immediately prior to transplant. The relatively favorable results in the Stanford series may result from selection of patients who continued to be responsive to treatment despite failure of induction therapy.

A summary of results with high-dose therapy and autografting from selected centers in patients with primary refractory Hodgkin's disease is presented in Table 3 [7–10, 12, 13]. EFS at 4–6 years ranges from 18%–49%. Although these results indicate that a proportion of Hodgkin's disease patients can be successfully treated after primary treatment failure, the majority will develop recurrent disease. In addition, given the selection of patients prior to referral for transplantation and thereafter, these data almost certainly overestimate the true rate of salvage.

Salvage radiotherapy has been employed in highly selected patients who failed induction chemotherapy for Hodgkin's disease, resulting in series with small numbers of patients. A phase III trial in advanced Hodgkin's disease conducted by the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group and the Groupe Pierre-et-Marie-Curie provided an exception [4]. In their study, 347 patients received MOPP/ABV for six cycles. Those who achieved CR (59%) were randomized to involved field radiotherapy or no further treatment. Patients who achieved PR (37%) received 30 Gy consolidative irradiation. The Kaplan–Meier plots for the combined CR and PR patients in this series do not differ. One interpretation of these data is that radiotherapy salvaged the majority of patients with PR. However, given the regular demonstration of residual radiographic abnormalities with current imaging techniques, it is probable that the majority of patients regarded as partial responders did not have active disease.

Wirth et al. from the Peter MacCallum Institute reported the results with salvage radiotherapy in 52 patients with recurrent or refractory Hodgkin's disease, of whom 18 had a PR or stable disease and four had progressive disease (PD) after induction chemotherapy [14]. The estimated EFS at five years was just 17% for the PR/stable disease patients and none of the PD patients was alive and progression-free. Of interest, B symptoms and extranodal disease were identified as significant poor prognostic factors, similar to the results with conventional chemotherapy and high-dose therapy and transplantation [2, 12].

What can be done to improve the outlook for patients with induction failure? Optimal dose and scheduling of primary chemotherapy may reduce the number of induction failures. Since 1989, investigators at Stanford University have treated bulky and advanced stage patients with weekly chemotherapy in which dose intensity was maintained or increased over standard regimens [15]. Radiotherapy was applied to sites of initial bulky disease. With a median follow-up of approximately five years, the EFS was estimated to be 89% at five years and the overall survival was 96% in 126 treated patients (unpublished data). No patient in this series failed induction treatment. Of the five patients who relapsed within 60 days of the completion of treatment, two did so after chemotherapy and three did so after radiotherapy. All of these patients had advanced disease; four had B symptoms, and four had one or more sites of extranodal disease. Three of these patients, termed induction failures, are alive and disease-free at three, five, and six years following high-dose therapy and transplantation. Two patients have died with refractory Hodgkin's disease.

Recent consensus regarding clinical prognostic factors in Hodgkin's disease affords the study of high-dose treatment strategies in selected patients at high risk for
primary treatment failure [16]. The addition of serologic and pathologic characteristics may further define a suitable high-risk population. Clinical trials are currently being planned in which conventional and high-dose approaches will be compared in Hodgkin's disease patients with multiple adverse prognostic factors.

The characteristics of induction failures define optimum salvage strategies. Patients with significant treatment delays or reductions due to toxicity or compliance may have a better opportunity for cure than those who have progressed despite ideal dose and delivery. Progressive disease restricted to one or two contiguous nodal sites may be excellent candidates for radiotherapy, particularly in combination with high-dose treatment [17]. Progression in extranodal sites and the presence of constitutional symptoms are unfavorable factors for salvage therapy of any type.

Patients with residual radiographic abnormalities present particular challenges. In general, biopsy proof of persistent disease should be obtained whenever possible. There is disagreement in the literature regarding the prognostic significance of residual gallium scan abnormalities in Hodgkin's disease. Salloum et al. recently reported that four of 10 patients who had positive scans after treatment, but only two of these had stable residual disease. Both patients had received combined modality treatment and subsequently relapsed [18]. The other two patients with positive scans had obvious progressive disease. In contrast, Bogart et al. found a 'partial' response by gallium scanning in 10 of 60 patients after chemotherapy. There were no relapses in 8 of these 10 who received further treatment (radiation therapy in 4, more chemotherapy and radiation in 1, and transplantation ± radiation in 3). Two additional patients who had PR by gallium after irradiation, and they have continued to be disease-free with follow-up [19].

Although high-dose therapy and transplantation offers the potential for prolonged remission and possible cures for a subset of patients with primary refractory Hodgkin's disease, more effective salvage therapy is needed. Double transplants have been performed in selected patients with modest results [20]. Studies with immunomodulatory agents administered post-transplantation are in progress. New drugs, new methods of radiotherapy delivery, and new agents will be required for significant advances in this population which is, fortunately, quite small. Identification of patients at very high risk for induction failure and modifications of primary treatment to address this risk hold the greatest promise for cure of the subset of patients with primary refractory Hodgkin's disease.

References


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