Hodgkin’s disease: treatment of relapsed disease

F. G. Cavalli

Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland

Introduction

Hodgkin’s disease (HD) is associated with a high cure rate, but approximately 5–10% of HD patients are refractory to initial treatment and 10–30% of patients will relapse after achieving complete remission (CR) [1, 2]. The most important initial prognostic factor is stage. Currently, the cure rate in the early stages of HD is above 90%, and with the latest generation of chemotherapy regimens (BEACOPP, Stanford V, Hybrid regimens), even the cure rate in advanced stages is most probably in the order of 80–85% [3]. This improvement in outcome implies that the few cases of non-responding or relapsing patients present a cohort which prognostically is becoming ever more unfavourable as primary results get better. This fact should always be kept in mind when data of current salvage treatments are compared with results that appeared in the literature 20–30 years ago [3].

Although late relapses >10 years after primary treatment have been reported in HD, relapse generally occurs within 1–5 years of primary therapy [1, 2]. At relapse, a new historical work-up should be obtained, as the risk of second tumours is increased [4]. A new biopsy at the time of relapse or disease progression is also required, in order to exclude a wrong primary diagnosis or composite lymphomas [5]. A technique playing an increasingly more important role in this work-up is positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET), which is mainly used for the evaluation of residual masses after completed treatment [6]. This is particularly true for the mediastinum, where remaining masses most often represent fibrotic tissue, but discrimination by computed tomography (CT) is usually not possible. A negative FDG-PET indicates that an HD patient with a residual mediastinal mass is unlikely to relapse before 1 year, if ever, whereas a positive PET indicates a probability of 50–70% of relapse [6–8].

Relapse after irradiation for early-stage disease

Primary radiotherapy alone has been used more extensively in the past than in current practice where most cases will receive a combination of chemotherapy [most often vinblastine, bleomycin, methotrexate (VBM) or doxorubicin, vinblastine, bleomycin and dacarbazine (ABVD)] from the very beginning along with some form of radiotherapy (most often involved fields). Patients who experience relapse after radiotherapy alone have satisfactory results with combination chemotherapy and are not considered candidates for high-dose chemotherapy (HDCT).

Stage at relapse is an important prognostic factor in radiotherapy failures as demonstrated by a study from Stanford and an analysis using the International Data Base on HD [9, 10].

Relapse after primary chemotherapy

It is well known that the length of remission after first-line chemotherapy has a decisive effect on the ability of patients to respond to subsequent salvage treatment [11]. On this basis, chemotherapy failures can be divided into three subgroups:

- primary progressive HD (∼10% of all cases), representing patients who never achieved a complete remission;
- early relapses within 12 months of CR (∼15% of all cases);
- late relapses after CR lasting >12 months (∼15% of all cases).

Conventional chemotherapy has always been of little use in primary progressive disease. In contrast, until recently patients with late relapses were considered to be candidates for repeat of the first-line chemotherapeutic therapy, whereas cases with early relapses were considered to be more suitable for more aggressive regimens [1, 2]. However, improved results with the use of HDCT followed by re-infusion of peripheral stem cells (ASCT), as well as a decrease in the chemosensitivity (at least to conventional agents) of the relapses, which are observed after more modern and aggressive primary chemotherapy, have somewhat diluted this difference. Nowadays, most centres consider HDCT as the second-line treatment of choice in most relapses.

Salvage radiotherapy

There are relatively few instances in which radiotherapy alone would be considered a standard salvage treatment with curative possibilities. This is the case in patients with limited disease, without B-symptoms and who have not been given radiation previously or who experience a local-regional relapse outside the initial radiation field [12].
Primary progressive disease

The outcome of patients with primary progressive disease, defined as progression during induction treatment or within 90 days after the end of treatment, is dismal. Treatment results with second-line chemotherapy produces low remission rates, with long-term disease-free survival in 0–10% of cases [13, 14]. Therefore, in most instances HDCT is currently considered to be the treatment of choice in these cases. A retrospective analysis of the data of Groupe d’Étude des Lymphomes de l’Adulte (GELA) showed, for example, a statistically significant difference ($P = 0.0001$) with regard to the estimated 5-years survival for patients treated with HDCT as compared with those without [15]. Recently, the German Hodgkin Lymphoma Study Group (GHSG) analysed the prognostic factors and treatment outcome in 206 primary progressive patients out of 3807 cases recruited in trials carried out from 1988 to 1998 [16]. Seventy patients (34%) were treated with HDCT. The 5-year freedom from second failure and overall survival for all patients were 17% and 26%, respectively. In multivariate analysis low performance status (PS), age >50 years and failure to achieve a temporary remission on first-line treatment were significant adverse prognostic factors [16]. Also, as in other studies [17, 18], patients receiving HDCT followed by ASCT seemed to fare better. However, this might be due to an important selection bias. In fact, a proportion of patients are not included in HDCT programs because of rapid disease progression, older age, poor PS or insufficient stem cells harvest. Allowing for relevant patient characteristics and for chemosensitivity salvage therapy, the course of the HDCT group was not found to be significantly better than that of the other group of patients [16]. Therefore, HDCT followed by ASCT seems to be an impossible or an inappropriate choice for an important percentage of patients with primary progression of HD. Only patients with somewhat favourable prognostic factors seem to fare better with this treatment. For the others, different innovative therapies will have to be developed. Recently, encouraging results have been reported with the use of tandem autologous stem-cell transplantation in this subset of patients [19], while so far preliminary results with allogeneic transplantation seem to be somewhat disappointing [16].

Treatment at relapse

In the past, it was practice for patients with late relapse after complete response (for >1 year) to be treated with the same chemotherapeutic regimen as they received in the first-line treatment [1, 2]. More than 80% of patients with late relapse achieve a second CR, with a median survival of about 4 years [13]. In contrast, for patients with a relapse within 12 months, a number of new salvage chemotherapeutic regimens were tested. These regimens incorporated drugs not used in the initial combination, which was generally MOPP, ABVD, or some combination of both [20–22]. Results with these chemotherapies are summarised in Table 1. Detailed analysis of this data is difficult because the trials are hampered by the low number of patients, the heterogeneity of the cases and the fact that an important number of these patients also received subsequent HDCT plus ASCT treatment. No randomised trials exist comparing the effectiveness of different conventional salvage chemotherapeutic regimens.

Currently, however, HDCT is considered to be the treatment of choice in all relapses after CR [1, 2]. Phase II studies showed that HDCT followed by ASCT produce 30–65% long-term disease-free survival [23, 24]. Following that, two randomised studies performed by the British National Lymphoma Investigation and the GHSG European Bone Marrow

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients</th>
<th>RR (%)</th>
<th>Plus HDCT (no. of patients)</th>
<th>RFS (%)</th>
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<tbody>
<tr>
<td>CEP</td>
<td>75</td>
<td>54</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>CEVD</td>
<td>32</td>
<td>48</td>
<td>–</td>
<td>22</td>
</tr>
<tr>
<td>Dexa-BEAM</td>
<td>56</td>
<td>56</td>
<td>19</td>
<td>25</td>
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<tr>
<td>Mini-BEAM</td>
<td>44</td>
<td>84</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>MIME</td>
<td>47</td>
<td>63</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>DHAP</td>
<td>19</td>
<td>68</td>
<td>–</td>
<td>NE</td>
</tr>
<tr>
<td>ASHAP</td>
<td>56</td>
<td>70</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>MINE</td>
<td>100</td>
<td>75</td>
<td>72</td>
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</tbody>
</table>

ASHAP, doxorubicin (adriamycin), high-dose arabinoside, and cisplatin (platinum); CEP, CCNU, etoposide, and prednimustine; CEVD, CCNU, etoposide, vindesine and dexamethasone; Dexa-BEAM, dexamethasone, BCNU, etoposide, arabinoside and melphalan; DHAP, dexamethasone, high-dose arabinoside and platinum; HDCT, high-dose chemotherapy; MIME, methyl-GAG, ifosfamide, methotrexate and etoposide; MINE, methyl-GAG, ifosfamide, vinorelbine and prednisone, leucovorin, arabinoside, cyclophosphamide and etoposide; NE, not evaluated; RR, response rate; RFS, relapse-free survival.
Transplantation Group have shown improved outcome in patients with relapsed HD treated with HDCT followed by ASCT as compared with ‘conventional’ salvage regimens [25, 26]. In both studies the event-free survival after 3 years of patients treated with HDCT was well over 50% [25, 26]. Although these results indicate the superiority of HDCT compared with conventional chemotherapy in patients with relapsed HD, a proportion of patients with early relapse will develop recurrent disease after this treatment modality. On the other hand, a considerable number of good-risk patients (mainly late relapses) might be overtreated with HDCT. Therefore different groups are attempting to develop prognostic models, assessable at the time of relapse, which could guide the physician in selecting the most appropriate therapeutic regimen and help to evaluate new experimental approaches in very poor-risk relapses [15, 27]. A study of the GHSG found that time to relapse, clinical stage and anaemia are relevant prognostic factors and could be used to design a prognostic score for choosing the best treatment for HD patients at relapse [27]. In contrast, in a study by GELA the only two factors which were of prognostic significance were B-symptoms at progression and the degree of chemosensitivity of the disease before HDCT [15].

In conclusion, patients who experience relapse after radiotherapy alone for localised HD have satisfactory results with combination chemotherapy. In the case of patients with relapse and refractory disease after combination chemotherapy, current data support the use of HDCT, with ASCT as the second-line treatment.

New treatments

Among the recently developed cytotoxic drugs, only vinorelbine [28] and gemcitabine [29] have shown promising activity in heavily pretreated patients, including some cases who relapsed after HDCT.

Different monoclonal antibodies, including those conjugated with immunotoxins or radioisotopes have been evaluated [1]. So far, it has not been possible to generate encouraging data, despite a phase I/II study with 90Y-labeled polyclonal antiferritin antibodies for refractory HD followed by autologous bone marrow transplantation [30]. Of 17 patients, seven achieved a CR lasting from 2 to 26 months. Based on these encouraging results radio-immunotherapy appears to be a new promising option.

Because the CD20 antigen is expressed on all malignant cells in paragranuloma or lymphocyte-predominant Hodgkin’s disease (LPHD), this entity might be a good target for treatment with rituximab [31]. An international study is currently investigating the outcome in patients with relapsed or refractory LPHD and other multiple relapsed CD20-positive cases of HD: first results are encouraging (V. Diehl, unpublished data).

References

17. André M, Henry-Amar M, Pico JL et al. Comparison of high-dose therapy and autologous stem-cell transplantation with conventional


