Review

Treatment of relapsed Hodgkin’s disease: Strategies and prognostic factors

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Summary

The major points in salvage therapy of patients in relapse following combination chemotherapy for advanced disease are: (1) success of any second-line approach is determined by prognostic factors which include age, duration of the initial remission, and quantity of disease at relapse; (2) induction failures (progression without remission or incomplete remission and short initial remission) require innovative therapy which currently entails high-dose chemotherapy with peripheral or bone marrow autologous support; (3) late relapse still retains an order to sensitivity to chemotherapy and can be treated with conventional dose combination with complementary radiation therapy to previously unirradiated bulky sites. The choice of regimen is empiric and can include a repeat of the regimen used for the original remission or induction. The relative advantage of HDC in this favorable group is uncertain.

Key words: Hodgkin’s disease, prognostic factors, relapse, salvage chemotherapy

Introduction

Despite all of the advances in the treatment of localized and advanced Hodgkin’s disease (HD), relapse of the disease occurs in a significant minority of patients. The biologic features of the disease which permit the success of radiation and chemotherapy also apply to the use of second-line (salvage) therapy since, despite relapse of the disease, second-line cures are possible in some patients. The likelihood of successful salvage therapy is determined by biologic features, which may be linked to certain clinical features. These include: rate of relapse; quantity of disease at relapse; presence or absence of symptoms; and age at diagnosis. Although the overall cure rate in large series of patients with all stages is high (approximately 75%), this statistic includes the ability to cure patients who relapse from primary treatment [1]. It is not entirely unique to HD since this can be seen in some subgroups of large-cell lymphomas, but in the latter, this almost always requires intensive high-dose chemotherapy (HDC). Second-line salvage of HD, however, can be achieved, in some patients, with conventional dose chemotherapy alone; radiation therapy alone in selected patients as well as with combined modality at conventional doses. Some clinical circumstances clearly will require innovative and/or intensive HDC. The details of the latter approach will not be a major component of this paper. The issues to be discussed are divided between: (1) relapse following radiation therapy for apparent localized HD (stage I–II); and (2) relapse following combination chemotherapy alone or combined modality for advanced stages (stage III–IV).

Management of relapse following radiation therapy for localized disease

Primary radiation therapy alone had been used more extensively in the past than in current practice. The demonstration that long-term toxic effects of radiation therapy can include a rising incidence of secondary cancers and cardiac complications has been a concern [2]. The demonstration of lower relapse rates with combined modality therapy for localized disease as well as the relative sparing of bone marrow stem- and germ-cell toxicity by non-alkylating agent containing regimens has resulted in a marked increase in the use of combined modality therapy obviating the need for staging laparotomy [3]. The current approaches tend to use less extensive fields of irradiation and in some settings combined with shorter duration of chemotherapy. The wide application of computerized tomography has resulted in the phenomenon of minimal residual disease or complete remission undetermined (CRV) in many instances [4]. The status of residual masses, which may be composed of fibrotic/necrotic tissue, can be assessed by 67gallium nuclear scans [5–7]. Thus, patients considered to be only in partial remission may in fact be in complete remission, and the introduction of second-line therapy may not be necessary. Therefore, progression-free survival is emerging as a more valid measure of the impact of a treatment.

The patterns of relapse have changed as a result of changes in management. In the era of clinical staging only (prior to computerized tomography), radiation therapy alone for apparently localized disease had a 40%–50% relapse rate which has improved markedly to ~15% when laparotomy staging defined the final pathologic
stage as I–II [8]. Accompanying this, there was a decrease in early relapse because of the discovery of cryptic intra-abdominal disease and the application of combined chemotherapy-radiation therapy for the more advanced disease detected by laparotomy. Common sites of relapse following definitive radiation therapy are those unirradiated iliac/inguinal nodes and extra nodal visceral sites, such as lungs and pleura. In the field or marginal recurrences are a minority (20%) of all relapses [9]. Factors which predict relapse from primary radiation therapy are: age, stage (I or II); histology (nodular sclerosis vs. mixed cellularity); clinical staging vs. laparotomy staging; and/or number of nodal sites above the diaphragm [10–12].

Although meticulous surgical staging and/or combined modality therapy has decreased the previously noted early relapse pattern, the incidence of late relapse (relapse occurring after three years) was not changed [8]. Late relapse can occur in about 10%–15% of patients depending on the series. Relapse beyond five years has been noted in 3.5% of cases in the EORTC series (European Organization for Research and Treatment of Cancer) which had an overall relapse rate of 32.6% [13]. Late relapse in that series was correlated with male gender, B symptoms, mediastinal involvement and treatment with combined modality versus radiation therapy alone. The Royal Marsden series showed that only age and initial stage (I vs. II) were significant factors predicting for late relapse. The use of combined modality also lessened the chances of late relapse in that series [8]. Histology and B symptoms were of borderline significance. Apart from estimates of 'tumor burden' most other factors receded from significance in a Copenhagen series [14].

The vast majority of those patients who relapse following primary radiation therapy will require systemic therapy. The original experience was based on the use of MOPP (mustargen, oncovin, prednisone, procarbazine) after it was shown that relapse from radiation therapy can be successfully treated [15]. The Stanford group showed that the likelihood of freedom from second relapse was 57% at 10 years using MOPP or regimens similar to it [16]. In that series, there was a suggestion that combined modality had a superior outcome.

There has been a gradual replacement of MOPP by ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) after the latter has shown to be equivalent in outcome without the long-term bone or germ-cell toxicity [17, 18]. Randomized prospective trials have shown that hybrid MOPP/ABV or MOPP alternating with ABVD are not superior to ABVD alone [19, 20]. In a Canadian series, a subset of patients with radiation relapse showed superiority for alternating MOPP-ABVD over hybrid MOPP/ABV in failure-free survival (94% vs. 73%). The significance of this is uncertain since the hybrid regimen was in fact more dose intense [21].

Prognostic factors have been determined which predict the outcome from systemic therapy given for relapse from radiation therapy [10]. Table I shows data from three series (Stanford, Joint Center at Harvard, Royal Marsden/Univ. of Copenhagen) consisting of a total of 720 patients. The factors identified are: (age > 40 years), clinical stage at relapse (I–IV); and histology (nodular sclerosis, lymphocytic predominant vs. mixed cellularity; and possibly relapse following combined modality [16, 22, 23]. It is possible that the patients treated with combined modality had more unfavorable features, which requires a more intensive initial approach. The issue of long-term outcome as a function of early vs. late relapse from radiation therapy is controversial. The EORTC series suggested that early relapse had a poor outcome, with 31% surviving at 20 years compared with 72% for late relapsing patients [13]. A recent report from Toronto, suggested that early relapse had a 10-year survival of 46% compared to 68% after early relapse in a series of 206 patients [60]. The Royal Marsden/Univ. of Copenhagen series did not find any difference in 10-year survival according to initial disease-free interval [23].

The impact of systemic therapy is considerable with a high order of second-line complete remission (in the range of 80%–90%) with a 10-year overall survival and freedom from second relapse in the range of 60% [16, 22–24]. An issue which plagues all such survival statistics is the complicating factors of second tumors, sepsis and cardiovascular disease, which are the end result of therapy. A series of 172 patients treated with definitive radiation therapy (including 134 laparotomy staged pathologic stage I–II patients) had an 82% 10-year survival with 76% relapse-free. Over a 10-year follow-up period there were 19 second tumors [12]. The likelihood of developing secondary malignancy increases with time and the risk approaches > 20% at 20 years [25].

**Management of relapse following systemic therapy for advanced stage disease**

Combination chemotherapy can cure advanced HD. Outcome, however, will also be determined by clinical prognostic factors. Although the complete remission rate is high, (~80%) relapse will occur in ~30% of patients who present with advanced disease. The pattern of relapse will be influenced by the use of complementary radiation therapy since chemotherapy alone will demonstrate relapse in predominantly unirradiated nodal areas previously known to be involved [26]. The clinical factors, which predispose to a higher rate of relapse from...
complete clinical remission, have been recorded in a number of series summarized in references [27–31]. These features were found to be statistically significant in three series included: age > 40 or 45 years; stage III vs. IV; bulk of disease; low hemoglobin or hematocrit; multiple extranodal sites; bone marrow and/or inguinal node involvement; B symptoms: lymphocyte count ≤ 0.75 or 0.6 x 10^9/l; male gender. Defining a uniquely unfavorable group has been difficult. The analysis of the Christie Hospital (Manchester, UK) series could not demonstrate a subgroup in which an event-free survival from completion of therapy was worse than 57% at five years [31]. The latter was composed of patients in stage III–IV with bulky tumor and/or B symptoms; low lymphocyte count (≤0.6 x 10^9/l) or bone marrow involvement. The International Prognostic Factor Project, which included 5141 patients from 23 study groups, is the basis of a new prognostic scheme, which correlated prognosis with the total number of unfavorable features at diagnosis. Those features were: low albumin, low hemoglobin, male gender, age over 45 years, stage IV, leukocytosis, and lymphocytopenia. This analysis could separate the event-free survival from 45% (five or more factors) to 80% (no factors) [32].

The survival benefit of additional low-dose (usually 20 Gy) radiation therapy for patients with advanced stage (III–IV) disease treated with combination chemotherapy is controversial. Two prospective randomized trials (the Southwestern Oncology Group (SWOG) and the German Hodgkin groups) have shown no overall survival value, with only a delay in the time to and pattern of relapse [33, 34]. A single randomized trial from Argentina of 151 patients with previously untreated clinical stages III or IV HD compared six cycles of CVPP (cyclophosphamide, vincristine, procarbazine, prednisone) alone with a combination of CVPP and radiotherapy (30 Gy to originally involved site). The trial demonstrated complete remission in 86% of patients treated with combined modality therapy, compared to 73% of those treated with chemotherapy alone and the failure-free survival at seven years with 45% with combined modality, compared to 21% with chemotherapy alone (P = 0.0016) [35]. The latter is a particularly poor chemotherapy-only outcome. Meta-analysis of randomized trials suggests a small relapse-free but no overall survival advantage [36]. There is variability in the published experience of criteria for offering complementary radiation therapy. Policies varied from any nodal site ≥ 6 cm to any mediastinal mass over 1/3 the transverse diameter of the chest in an upright chest film.

This 30% of relapsed patients will be composed of progressive or refractory disease (10%) with the remainder divided between those whose remission was <12 months (10%–12%) and those whose remission was >12 months (7%–8%) [36]. The 12-month period is an arbitrary interval, which in many series assumes prognostic significance. If early relapse <12 months or refractory disease is characterized by intrinsic cellular resistance to chemotherapy, then it identifies a particularly unfavorable group for second-line chemotherapy. Conversely, if late relapse connotes recovery of incompletely treated but still drug-sensitive tumor, then this is likely to be a more favorable group. The impact of second-line therapy appears to correlate with this pattern.

Prognostic factors which determine the benefits of second-line therapy are shown in Table 2 [37–41]. These include: the duration of first remission; age; stage at relapse; the presence of B symptoms; and whether the initial stage was IV. The Cancer Control Agency of British Columbia has shown a dramatically favorable (~80% failure-free at 5 and 10 years) outcome for patients who fulfill their favorable category of no stage IV at diagnosis; absence of B symptoms at relapse and initial remission >12 months [38]. The Milan series emphasized the particularly poor outcome of second-line therapy in achieving failure-free and overall survival at eight years for induction failures (0.8%) and those whose initial remission was <12 months (22.28%) in contrast to the >12 months group with (44.54%) [37]. The issue of the duration of initial remission may be less important when considering the impact of HDC. A recent analysis of the University College Hospital (London) series showed no difference in relapse-free survival according to the duration of initial remission [42]. Table 3 outlines the differences in failure-free and overall survival using conventional-dose and high-dose therapy. The long-term benefits of HDC in patients whose initial remission is >12 months is ~55% disease-free at five years [43]. Considering that there is selection in all series, especially the HDC series, these results are not sufficiently better than those achieved with conventional dose therapy in a similar group. This is suggested in a comparative analysis (from Stanford) of patients matched for duration of first remission and the salvage impact of conventional dose chemotherapy compared to HDC [44]. It is uncertain, then, whether there is an advantage for proceeding directly to HDC in patients whose relapse has favorable prognostic features, such as an interval of first remission >12 months and localized, asymptomatic relapse. All other patterns of failure require innovative and/or intensive approaches such as HDC.

<table>
<thead>
<tr>
<th>Table 2. Relapse from systemic therapy for advanced disease: Favorable prognostic factors* in salvage therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ref.</strong></td>
</tr>
<tr>
<td>Milan</td>
</tr>
<tr>
<td>Cancer Control Agency (British Columbia)</td>
</tr>
<tr>
<td>Hôpital St. Louis (Paris)</td>
</tr>
<tr>
<td>NCI (Bethesda)</td>
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<tr>
<td>GELA (France)</td>
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</table>

* Statistically significant.
cannot be appreciated since the numbers in the trials are small and many patients went on to HDC. Many patients used such as etoposide, mitoxantrone, ifosfamide, and the nitrosoureas (BCNU or CCNU). Second-line therapies composed of some agents not previously used such as etoposide, mitoxantrone, ifosfamide, and the nitrosoureas (BCNU or CCNU). Second-line regimens employed for relapsed HD published since 1990 are outlined in Table 4 [41, 45-50]. The true impact of salvage chemotherapy according to duration of prior remission (> 12 months vs. < 12 months).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total patients</th>
<th>Failure free &lt; 12 months</th>
<th>Survival &gt; 12 months</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan</td>
<td>115</td>
<td>22%</td>
<td>44% (8 years)</td>
<td>[37]</td>
</tr>
<tr>
<td>NCI (Bethesda)</td>
<td>107</td>
<td>14%</td>
<td>55% (5 years)</td>
<td>[40]</td>
</tr>
<tr>
<td>CALGB</td>
<td>45</td>
<td>15%</td>
<td>35% (4 years)</td>
<td>[48]</td>
</tr>
<tr>
<td>High dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCH (London)</td>
<td>133</td>
<td>54%</td>
<td>48% (5 years)</td>
<td>[42]</td>
</tr>
<tr>
<td>Nebraska</td>
<td>85</td>
<td>32%</td>
<td>47% (5 years)</td>
<td>[43]</td>
</tr>
<tr>
<td>Stanford</td>
<td>60</td>
<td>58%</td>
<td>58% (4 years)</td>
<td>[44]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimens</th>
<th>No. of pts</th>
<th>CR</th>
<th>Duration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABDIC continuous infusion (doxorubicin, bleomycin, dacarbazine, lomustine, prednisone)</td>
<td>19</td>
<td>53% PR, 11% CR</td>
<td>12, 27 months (7 to ABMT)</td>
<td>[45]</td>
</tr>
<tr>
<td>CAPE/PALE (cyclophosphamide, doxorubicin, prednisone, etoposide, lomustine (CCNU))</td>
<td>25</td>
<td>52%</td>
<td>Five patients in CR (42±80+ months)</td>
<td>[46]</td>
</tr>
<tr>
<td>CAV (lomustine (CCNU), melphalan, etoposide)</td>
<td>59</td>
<td>29%</td>
<td>18-month median survival</td>
<td>[47]</td>
</tr>
<tr>
<td>EVA (etoposide, vinblastine, doxorubicin)</td>
<td>45</td>
<td>40%</td>
<td>11 of 18 CR have not relapsed, used in MOPP failures only</td>
<td>[48]</td>
</tr>
<tr>
<td>MINE (mitoguazone, ifosfamide, vinorelbine, etoposide)</td>
<td>100</td>
<td>34%</td>
<td>70% to ABMT, 20 patients NED</td>
<td>[41]</td>
</tr>
<tr>
<td>Mini-BEAM (BCNU, etoposide, cytostim, arabinoside, melphalan)</td>
<td>44</td>
<td>32%</td>
<td>26 patients to ABMT</td>
<td>[49]</td>
</tr>
<tr>
<td>VIM-D (etoposide, ifosfamide, mitoxantrone-dexamethasone)</td>
<td>15</td>
<td>27%</td>
<td>2-14 months (10 patients to ABMT)</td>
<td>[50]</td>
</tr>
</tbody>
</table>

The selection of second-line chemotherapy regimens again will depend on the pattern of relapse. Both the NCI (Bethesda) and Milan series suggest that late relapse can be successfully treated with the same regimen used for initial remission induction with quite favorable results if a second CR is achieved [37, 40]. Induction failures and early relapse will most likely require chemotherapy regimens composed of some agents not previously used such as etoposide, mitoxantrone, ifosfamide, and the nitrosoureas (BCNU or CCNU). Second-line regimens employed for relapsed HD published since 1990 are outlined in Table 4 [41, 45-50]. The true impact cannot be appreciated since the numbers in the trials are small and many patients went on to HDC. Many of these regimens then serve to test the drug sensitivity of the relapsed patient as well as serve to facilitate the harvest of peripheral stem cells prior to HDC. These regimens also demonstrated a better progression-free survival in patients whose first remission exceed 12 months [41, 48].

Radiation therapy in the salvage of patients in relapse from systemic therapy for advanced disease

Radiation therapy alone is rarely if ever used as the sole salvage modality. These are small series when this was applied resulting in a small number of long-term disease free survivors. Table 5 demonstrates that selected patients who relapse from chemotherapy in an isolated nodal site can sometimes be salvaged by radiation alone [51-55]. However, the data suggest that combined modality rather than radiation alone yields a superior long-term result [51]. The complementary role of radiation therapy in salvage high dose chemotherapy is uncertain but remains to be investigated.

Biological agents investigational use if in refractory Hodgkin's disease

Immunotoxins have been produced which focus on antigens, which occur on Reed-Sternberg cells. These include CD15, CD25, CD30, CD40 and CD80 [56]. The immunotoxins employed in limited clinical trials are anti-CD30 immunotoxin linked to Saporin [57] and anti-CD25 linked to ricin A-chain [58]. Clinical responses were of minor extent and duration with a genesis of antimouse and antitoxin antibodies. Other biologic agents include a bispecific monoclonal antibody (anti-CD16 and anti-CD30) used to treat 15 patients resulting in two responses [59]. In IL-2 fusion toxin (diphtheria toxin) was infused into 15 patients resulting in a single complete remission [60].

References

complete remission (1-6 months; 7-12 months; >12 months) does not predict outcome following BEAM and autotransplantation for Hodgkin's disease in first relapse. Blood 1997; 90: 496.


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