Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin’s disease

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Background: An important variable affecting outcome in relapsed and refractory Hodgkin’s disease (HD) is the potential of conventional salvage chemotherapy to reduce tumor volume before high-dose chemotherapy (HDCT) and autologous stem cell transplantation. Currently, the optimal salvage chemotherapy regimen for these patients is unclear. Since dexamethasone/cisplatin/cytarabine (DHAP) given at 3–4 week intervals has been shown to be very effective in patients with relapsed aggressive non-Hodgkin’s lymphoma, we evaluated this regimen given at a median of 16-day intervals in patients with relapsed and refractory HD.

Patients and methods: Patients with relapsed or refractory HD were treated with two cycles of DHAP [dexamethasone 40 mg intravenously (i.v.) day 1–4, cisplatin 100 mg/m² i.v. as 24-h continuous infusion day 1, and cytarabine 2 g/m² i.v. 12q day 2]. Granulocyte colony-stimulating factor (G-CSF) was given at a dose of 5 µg/kg from day 4 until day 13. Patients with partial remission (PR) or complete remission (CR) after two cycles of DHAP received sequential HDCT.

Results: The median age of the 102 patients included was 34 years (range 21–64 years). Forty-two percent of the patients had late relapse, 29% early relapse, 12% multiple relapse and 16% primary progressive/refractory disease. The response rate (RR) after two cycles of DHAP was 89% (21% CR, 68% PR). The RRs for patients with late, early, multiple and progressive HD were 91%, 93%, 92% and 65%, respectively. Using the chi-square test for independence, remission status (relapsed HD versus progressive HD) and stage at relapse (stage I/II versus stage III/IV) were significant factors for response to DHAP. WHO grade 4 leukocytopenia and thrombocytopenia were the main toxicities occurring in 43% (mean duration 1.1 days, range 0–6) and 48% (mean duration 1.4 days, range 0–11) of all courses, respectively. Neither severe infections nor treatment-related deaths occurred. Peripheral blood stem cells (PBSCs) were collected after the first cycle DHAP in eight patients. The hematopoietic progenitors showed a very rapid increase from day 10 with a synchronous and impressive peak on day 12. A mean of 6.1 × 10⁹/kg CD34⁺ cells were collected per apheresis. As originally recommended in the protocol, PBSCs were routinely collected during sequential HDCT in the remaining patients.

Conclusions: A brief tumor-reducing program with two cycles of DHAP given in short intervals supported by G-CSF is effective and well-tolerated in patients with relapsed and refractory HD. This regimen can be used to mobilize stem cells and select those patients with chemosensitive relapse who should subsequently be treated with HDCT.

Key words: Hodgkin’s disease, relapse, salvage chemotherapy
Introduction

Combination chemotherapy is capable of curing patients with Hodgkin’s disease (HD) but those with treatment failure or early relapse have a poor prognosis [1]. High-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) can improve the outcome of relapsed and refractory HD patients as demonstrated in two prospective randomized trials. In a study conducted by the British National Lymphoma Investigation patients with relapsed or refractory HD were treated with conventional chemotherapy [mini-BEAM consisting of BCNU (bis-chloro-ethyl nitrosourea)/etoposide/ cytarabine/melphalan] or HDCT (BEAM) followed by ASCT. The actuarial 3-year event-free survival was significantly better in patients who received HDCT (53% versus 10%) [2]. The largest randomized, multicenter trial was performed by the German Hodgkin’s Lymphoma Study Group together with the European Bone Marrow Transplant registry to determine the benefit of HDCT in relapsed HD. Patients with relapse after polychemotherapy were randomized between four cycles of Dexamethasone/BCNU/etoposide/ cytarabine/melphalan and two cycles of the Dexa-BEAM regimen followed by HDCT (BEAM) and ASCT. Freedom from treatment failure (FFTF) in the HDCT group was 53% versus 39% for patients receiving conventional chemotherapy [3].

Several studies have been performed with conventional salvage regimens before the administration of HDCT [4–8]. Although response rate (RR) and toxicity profile of salvage chemotherapy are different, detailed analyses comparing various regimens are difficult due to the generally small number of patients and the heterogeneous patient population, i.e. patients with primary progressive and relapsed disease. No randomized trial exists comparing the effectiveness of different conventional salvage chemotherapies. Due to the lack of randomized studies, the selection of conventional salvage chemotherapy should be based on the potential to induce high RR with low toxicities allowing the majority of patients to proceed to the final myeloablative regimen.

The most important variables affecting outcome in HDCT studies are chemosensitivity to conventional salvage chemotherapy and the remission status before HDCT [complete remission (CR) > partial remission (PR) > no change] [8–12]. Recent clinical studies demonstrated a clear relationship between chemotherapy dose intensity and tumor response in HD [13]. There are two principal ways to enhance dose intensity. Doses of cytotoxic drugs can be intensified by increasing individual drug dose, or shortening the interval between treatments, or both. The use of granulocyte colony-stimulating factor (G-CSF) for interval shortening has made this approach feasible. The introduction of accelerated chemotherapy regimens by interval shortening with growth factor support has shown promising results in first-line chemotherapy regimens for patients with aggressive HD and non-Hodgkin’s lymphoma (NHL) [14, 15].

In the present study, our objective was to determine the efficacy and toxicity of dexamethasone/cisplatin/cytarabine (DHAP) in relapsed and refractory HD while shortening the intervals between the cycles using G-CSF. We show that this approach is feasible, effective and well-tolerated in patients with relapsed and refractory HD.

Patients and methods

Patient selection

Patients with relapsed or refractory HD were treated in a multicenter phase II study involving 34 centers in Germany (see Acknowledgements). To be eligible, patients between the age of 18 and 65 years had to have biopsy-proven relapsed or refractory HD. Eligibility criteria before study entry included adequate organ function as defined by a creatinine clearance ≥60 ml/min, serum transaminases less than three times the normal value and bilirubin <2 mg/dl, left ventricular ejection fraction >0.45, forced expiratory volume in the first second or diffusion capacity of carbon monoxide >60% of predicted, Eastern Cooperative Oncology Group performance status ≤2, and white blood cell count ≤3500/µl, hemo- globin level ≥8 g/dl, platelets ≥100 000/µl. Patients were required to test negative for antibody against human immunodeficiency virus and to be free of active infection. All patients signed consent forms that were based on the Institutional Review Board Guidelines.

All patients had received COPP/ABVD (cyclophosphamide/oncovin/ procarbazine/prednisone alternating with doxorubicin/bleomycin/ vinblastine/darcarbazine), ABVD (doxorubicin/bleomycin/vinblastine/ darcarbazine), BEACOPP (bleomycin/etoposide/doxorubicin/cyclophos- phamide/oncovin/procarbazine/prednisone) or similar regimens as front-line chemotherapy. Primary progressive/refractory disease was defined as disease progression during first-line chemotherapy, or only transient response (CR or PR lasting <90 days) after induction treatment. Progressive disease required the following: (i) ≥5% increase from nadir in the sum of the products of the greatest diameter of any previously identified abnormal node for partial responders or non-responders; (ii) appearance of any new lesion during or ≥90 days after the end of therapy. Relapsed HD was defined as a complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy for ≥3 months. Early relapse required a CR lasting ≥3 months to 12 months. A CR in late relapses must last ≥12 months. All patients had biopsy-proven relapsed or refractory HD.

DHAP salvage chemotherapy and G-CSF administration

All patients received two cycles of DHAP as salvage treatment in order to reduce tumor volume before HDCT. DHAP consisted of dexamethasone 40 mg i.v. day 1–4, cisplatin 100 mg/m² i.v. as 24-h continuous infusion day 1, and cytarabine 2 g/m² i.v. over 3 h 12q day 2. Hydration (250 ml/h) was started 6–2 h before cisplatin infusion. Corticosteroid eye drops were given topically beginning 12 h before and continuing for 2 days after administration of cytarabine to prevent conjunctivitis. To minimize nausea and vomiting, patients were given ondansetron 8 mg i.v. on day 1 and 2. Twenty-four hours after the last dose of cytarabine, G-CSF was given at doses of 5 µg/kg/day subcutaneously until leukocytes increased to ≥25000/µl for 3 days.
**Staging procedures**

Before salvage chemotherapy, the extent of disease was assessed by chest X-ray, abdominal sonography, computed tomography, and bone marrow biopsy. Restaging was performed after two cycles of salvage therapy. After two cycles of DHAP all sites of initial disease manifestation were reassessed by adequate methods, including pathological restaging for patients who had bone marrow involvement before salvage therapy.

**Definition of response and statistics**

CR was defined as the disappearance of all clinical and radiographic evidence of disease for at least 1 month. PR was defined as a greater than 50% reduction in the product of the largest diameter and its perpendicular of measurable disease lasting >1 month. Any response less than PR was considered as treatment failure. Demographics and disease characteristics were summarized using descriptive statistics. The significance of differences in the RR according to various features was calculated by chi-square testing \[16\].

**Kinetics of hematopoietic progenitor release and peripheral blood stem cell harvest**

Surface phenotype analysis using flow cytometry was performed as reported previously \[17\]. Mononuclear cells were stained with fluorescein isothiocyanate- and phycoerythrin-conjugated CD34 (anti-HPCA-2) monoclonal antibodies with mouse IgG as negative control. More than 20000 cells were analyzed with flow cytometry using a FACScan flow cytometer (Becton Dickinson, Basel, Switzerland) with Lysis II software.

**Results**

**Patient characteristics**

Patient characteristics are listed in Table 1. One hundred and two patients were included in this study. The median age at study entry was 34 years (range 18–64 years). Forty-four patients (42%) had late relapse, 29 patients (29%) early relapse, 17 patients (16%) primary progressive/refractory disease and 12 patients (12%) multiple relapse. Most of the patients (62%) had extensive disease (stage III/IV) at relapse. B symptoms (fever, night sweat, weight loss) at relapse were present in 36 patients (34%). In 79 patients (77%) hemoglobin was less than 12 g/dl in male patients or less than 10.5 g/dl in female patients. Front-line chemotherapy consisted of COPP/ABVD in 51 patients (50%), BEACOPP baseline in 24 (24%), ABVD in 13 (13%), BEACOPP escalated in eight (8%), BEACOPP-14 in two (1%), and other regimens in four patients (4%). Sixty-one of the patients (60%) were treated with combined chemoradiotherapy during first-line therapy. Relapse or progression was proven by biopsy in all patients.

**Toxicity of DHAP**

Results are summarized in Table 2. A total of 201 courses were administered in 102 patients. The main toxicity of DHAP was myelosuppression with leukocytes of less than 1000/µl (median duration 1.1 days; range 0–11 days) and thrombocytopenia of less than 25000/µl (median duration 1.4 days; range 0–11 days) in 43 and 48% of all courses, respectively. The mean number of platelet transfusions was 0.4 (range 0–4). The mean number of red blood cell units transfused was 0.5 (range 0–4). In 18 courses patients developed fever (mean 0.3 days; range 0–8 days). WHO grade 3 and 4 nausea/vomiting occurred in 24 and 2% of all courses. Two patients developed WHO
grade 3 ototoxicity and one patient developed polyneuropathy. No patient died due to treatment-related toxicity.

Cycle interval

Results are summarized in Figure 1. The median time between the first and second DHAP cycle was 16 days (range 12–31 days). The second DHAP cycle was administered in 74% of patients between 12 and 17 days after starting the first course. All cycles could be administered at the calculated full dose.

Response and factors predicting response to DHAP

RRs are listed in Table 3. The overall RR for all patients after two cycles of DHAP was 88% (21% CR and 67% PR). The results were comparable in patients with late relapse (RR 91%, CR 26%, PR 65%), early relapse (RR 93%, CR 17%, PR 76%) and multiple relapse (RR 92%, CR 23%, PR 69%). The RR in patients with progressive/relapsed HD was 65% (CR 12%, PR 53%).

The following factors were analyzed for predicting response (CR and PR) to DHAP [18]: gender (male versus female), remission status (relapsed HD versus progressive/refractory disease), stage at relapse (stage I/II versus stage III/IV), hemoglobin at relapse (male ≥12 g/dl; female ≥10 g/dl versus male <12 g/dl; female <10 g/dl), and B symptoms at relapse.

Using the chi-square test for independence, remission status (relapsed HD versus progressive HD) and stage at relapse (stage I/II versus stage III/IV) were significant factors for response to DHAP (Table 4).

At 18 months of median follow-up (range 3–31 months) FFTF for the whole high-dose sequential treatment program is: early relapse HD 64%; late relapse 68%; PR 30%; multiple relapse 55%.

Stem cell mobilization

Peripheral blood stem cells (PBSCs) were collected after the first DHAP cycle in eight patients. The hematopoietic progenitors showed a very rapid increase from day 10 with a peak on day 12. A mean of 6.1 × 10^6/kg CD34+ cells (range 3.1–59.4 × 10^6/kg) were collected by apheresis. As originally recommended in the protocol, PBSCs were routinely collected during sequential HDCT (cyclophosphamide or etoposide) in the remaining patients. PBSC harvest was successful in 96% of all patients.

Discussion

The following findings emerge from this study: (i) Two cycles of DHAP given in short intervals is a very effective regimen before HDCT in patients with relapsed and refractory HD. (ii) The regimen was well-tolerated with hematological WHO grade 3 and 4 toxicities occurring in only 48% of all courses. (iii) DHAP plus G-CSF is also suitable for progenitor cell mobilization in relapsed or refractory HD.

An important variable affecting outcome in patients with relapsed or refractory HD is the potential of conventional salvage chemotherapy to reduce tumor volume before HDCT [8, 19]. Patients who relapse after chemotherapy but respond to subsequent conventional salvage therapy make up most of the long-term survivors in transplantation programs. Nevertheless, the role of conventional salvage chemotherapy before HDCT has not clearly been defined in relapsed or refractory HD. Different regimens have been used in the past for initial tumor reduction thereby evaluating chemosensitivity often while logistic arrangements are underway for HDCT.

Since 1985, a number of new salvage chemotherapy regimens have been investigated incorporating drugs not used

Table 2. WHO grade 3/4 toxicity of the dexamethasone/cisplatin/cytarabine regimen (total 201 courses)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of courses (%)</th>
<th>WHO grade 3</th>
<th>WHO grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytopenia*</td>
<td>50 (25)</td>
<td>86 (43)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>42 (21)</td>
<td>97 (48)*</td>
<td></td>
</tr>
<tr>
<td>Anemia*</td>
<td>33 (16)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Infection†</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>49 (24)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*Duration of WHO grade 3 leukocytopenia: median 1.1 days (range 0–6).
†Mean number of thrombocyte transfuision: 0.4 (range 0–4).
‡Duration of WHO grade 4 thrombocytopenia: median 1.4 days (range 0–11).
‡‡Mean number of red blood cell units transfused: 0.5 (range 0–4).
§Days with fever ≥38°C: 0.3 (range 0–8).
in first-line treatment. Because most first-line treatment programs employ MOPP (mustine/vincristine/procarbazine/prednisone), ABVD, or combinations of both, new salvage regimens have been designed anticipating resistance to previously used drugs in patients who have relapsed [20–25]. Table 5 lists second-line salvage regimens for HD published since 1985. However, a detailed analysis and interpretation is difficult because generally the number of patients is small and the clinical status of patients is highly variable. In addition, the duration of first remission is heterogeneous and a large number of these patients also received subsequent HDCT plus ASCT. No randomized trial exists comparing the effectiveness of different conventional salvage regimens.

In patients with relapsed and refractory HD only a few studies have been reported evaluating the efficacy of cisplatinum-containing regimens. In vitro studies using cisplatinum and high-dose cytarabine suggest that there might be a synergistic effect of this combination in human tumors [26]. In 1986, Velasquez et al. [27] reported that the DHAP regimen was effective in 16 patients with relapsed HD. Recently, two studies have been published using novel platinum-based combinations such as ASHAP (doxorubicin/solumedrol/high-dose cytarabine/cisplatinum) or ESHAP (etoposide/high-dose cytarabine/cisplatinum) in patients with HD [5, 6]. Rodriguez et al. [6] reported the results of a modified DHAP regimen adding doxorubicin (10 mg/m2 i.v. day 1–4) as continuous infusion (ASHAP). Fifty-six patients were treated with up to three cycles before HDCT followed by ASCT. All patients developed WHO grade 3 or 4 neutropenia. The overall RR was 70% with 34% achieving CR. However, patients with refractory disease, defined as response duration of less than 6 months, responded only in 56% of cases. In a study reported by Aparicio et al. [5], 22 patients with relapsed or refractory HD received another modified DHAP regimen with etoposide (ESHAP). Fifty-six patients were treated with up to three cycles before HDCT followed by ASCT. All patients developed WHO grade 3 or 4 neutropenia. The overall RR was 70% with 34% achieving CR. However, patients with refractory disease, defined as response duration of less than 6 months, responded only in 56% of cases. In a study reported by Aparicio et al. [5], 22 patients with relapsed or refractory HD received another modified DHAP regimen with etoposide (ESHAP). Fifty-six patients were treated with up to three cycles before HDCT followed by ASCT. All patients developed WHO grade 3 or 4 neutropenia. The overall RR was 70% with 34% achieving CR. 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In view of the results reported in our study and lack of a prospective randomized trial, the benefit of adding more cytotoxic drugs to the DHAP regimen has not become clear. Considering dose intensity, an alternative to dose escalation of single cytotoxic drugs or adding new drugs to established salvage regimens is the use of colony-stimulating factors (CSFs) to shorten treatment intervals. Pfreundschuh et al. [29] recently reported the results of a prospective randomized trial in patients with relapsed or refractory HD. Patients were randomized to receive the dexamethasone/BCNU/etoposide/cytarabine/melphalan (dexa-BEAM) regimen plus G-CSF to shorten the intervals between each cycle. The median time between the first and second cycle of DHAP was 16 days (range 12–31 days). This represents a dose escalation by a factor of 1.8 compared with DHAP given at 28-day intervals. The second DHAP cycle was administered between 12 and 17 days after starting the first course in 74% of cycles. All cycles could be administered at the full calculated dose. The RR after two cycles of DHAP was 89% (21% CR, 68% PR) and thus at least comparable with results observed with other salvage regimens. The RR for patients with late, early and multiple relapsed HD were not different (91%, 93% and 92%, respectively). However, the RR for patients with progressive HD was only 65%. Using chi-square testing for independence, remission status (relapsed HD versus progressive HD) and stage at relapse (stage I/II versus stage III/IV) were significant factors for response to DHAP. The toxicity profile was excellent with WHO grade 4 leukopenia and thrombocytopenia occurring in 43% (mean duration 1.1 days, range 0–6) and 48% (mean duration 1.4 days, range 0–11) of all courses. Neither severe infections nor TRM occurred.

The potential to mobilize PBSCs is an important requirement for a pre-ASCT cytoreductive regimen. Since the initial study protocol included both HD and aggressive NHL, PBSCs were collected after the two DHAP cycles during sequential HDCT. Subsequently, PBSCs were collected in eight patients with relapsed HD after the first cycle of DHAP. A mean of 6.1 × 10^6/kg CD34+ cells (range 3.1–59.4 × 10^6/kg) were harvested. These results are in accord with previously published results by Oliveri et al. [30] using DHAP plus G-CSF for priming of PBSCs in patients with lymphoma.

In conclusion, a brief tumor-reducing program with DHAP supported by G-CSF is a very effective and well-tolerated approach before HDCT in patients with relapsed and refractory HD. The regimen is also suitable for collecting PBSCs. As a direct consequence of the present study, DHAP was implemented into the new prospectively randomized HDR-2 study. Here, the German Hodgkin Lymphoma Study Group together with the European Group for Blood and Marrow Transplantation and the European Organization for Research and Treatment for Cancer are comparing two cycles of DHAP plus G-CSF followed by BEAM with two cycles of DHAP.
followed by a sequential HDCT and BEAM in patients with relapsed HD [31].

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