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High-dose chemotherapy and hematopoietic stem cell rescue in patients with relapsed Hodgkin's disease

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Summary. Fifty-one consecutive patients with Hodgkin's disease (HD) have been treated with high-dose chemotherapy (HDT) and transplantation of autologous bone marrow (BM) (n = 44), autologous BM plus peripheral blood stem cells (PBSC) (n = 2), PBSC (n = 1), syngeneic (n = 1), or allogeneic BM (n = 3). All patients had received standard salvage chemotherapy prior to HDT and were classified as sensitive (n = 33) or resistant (n = 17) to this treatment; one patient was in untreated relapse prior to BMT. The preparative regimens for patients receiving autologous BM and/or PBSC consisted of cyclophosphamide, VP 16, and BCNU (CVB) (n = 44) or BCNU, etoposide, ara-C, and melphalan (BEAM) (n = 3). The patients receiving allogeneic transplants were treated with the CVB regimen (n = 2) or busulfan (16 mg/kg body wt.) and cyclophosphamide (200 mg/kg body wt.). With a median follow-up of 12 months, overall survival for 44 patients grafted with autologous BM is 61% ± 9%, progression-free survival for patients with sensitive disease is 44% ± 11%; no patient with resistant relapse survived beyond 1 year post transplant. Two of three patients grafted with allogeneic BM still survive 15 and 24 months after BMT with Karnofsky performance scores of 70% and 100%, respectively. The main toxicity encountered with the CVB regimen was interstitial pneumonia (IP), seen in four of 15 patients (27%) receiving ≥ 600 mg/m² of BCNU. Three of these patients have died. The results show that HDT followed by hematopoietic stem cell rescue may effectively salvage an important fraction of patients with relapsed HD who respond to standard chemotherapy. The same approach is largely unsuccessful in patients with proven refractoriness to standard chemotherapy. Whether HDT followed by BMT or PBSC support is superior to intensive chemotherapy without stem cell support can be answered only by a prospectively randomized trial.

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Introduction

With modern radiotherapy and combination chemotherapy the majority of patients with Hodgkin's disease (HD) can be cured. However, approximately 40%–50% of patients with advanced-stage disease fail because of recurrence or primary refractory disease. Although the prognosis of such patients is not necessarily unfavorable but depends on the presence of specific prognostic factors, few of these patients (< 20%) will attain durable disease-free survival with conventional salvage therapy [4, 10].

The use of high-dose cytotoxic therapy (HDT) followed by bone marrow transplantation (BMT) [1, 2, 6, 7, 11, 22, 23, 32, 33] and, more recently, peripheral blood stem cell (PBSC) support [14, 15] has become increasingly popular for the treatment of such patients, although the superiority of this approach has never been proven formally. We report a single-center experience of HDT followed by hematopoietic stem cell infusion. While the vast majority of patients were grafted with autologous BM, a few patients received alternative sources of stem cells (autologous PBSC or allogeneic BM) because autologous marrow could not be harvested or was found unsuitable in the individual situation.

Patients and methods

Eligibility criteria

Between December 1986 and June 1992, 51 consecutive patients with HD were treated with HDT and BM transplantation and/or infusion of PBSC at the BMT unit of the University of Kiel. Eligibility criteria included (a) failure of primary (and subsequent) chemotherapy or relapse of HD considered incurable with radiotherapy or standard chemotherapy; (b) age no more than 60 years; (c) normal marrow histology at the time of marrow harvest (a

history of prior marrow involvement did not exclude patients); and (d) absence of severe co-morbid illness that would preclude use of intensive chemotherapy.

Patient characteristics

Patient characteristics are shown in Table 1. Twenty-eight were female and 23 were male; the median age was 27 years (range 13–59 years). At diagnosis 36 patients had nodular sclerosing histology, nine had mixed cellularity, three had lymphocytic predominance, and one patient showed lymphocytic depletion histologically. For two patients information on the histologic subtype was not available. The initial stage of disease for all patients is given in Table 1. All patients had previously received multiagent chemotherapy with a median exposure to three regimens (range 2–7) and 12 cytostatic drugs (range 7–15) in addition to prednisolone or dexamethasone. Alternating cyclophosphamide, vincristine, procarbazine, and prednisone (COPP), and doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy given as primary treatment was counted as one regimen. In addition, 43 patients (84%) had received radiotherapy administered either as involved-field, mantle-field, inverted Y, or total-nodal irradiation. Eight patients had never achieved a complete remission (CR) after induction plus salvage chemotherapy; the other patients had achieved at least one CR but had relapsed subsequently. All patients received salvage chemotherapy prior to HDT in order to reduce the tumor burden. The salvage protocols, as well as the numbers of cycles given to each patient, varied over time and depended on the institution which had cared for the patient until referral. Specifically, 28 patients received 1–4 (median 2) courses of DEXA-BEAM [20], five patients were given high-dose cytosine-arabinoside, mitoxanthrone (HAM) [9], four patients received the CEVD protocol [19], three patients received alternating cycles of COPP, ABVD, IMEP (ifosfamide, methotrexate, VP 16, prednisone), two patients each received DHAP [31] or ABVD, and one patient each was treated with MOPP, IMVP 16, or the CEP protocol as salvage therapy prior to high-dose therapy. Four patients received individual combinations of cytostatic agents mostly containing etoposide and prednisolone. More than one salvage regimen was administered to some patients in order to achieve at least a partial remission prior to HDT. Patients who had achieved less than a partial remission after salvage chemotherapy were considered to suffer from "resistant relapse", while those achieving at least a partial remission (PR) immediately before transplantation were classified to have "sensitive relapse" [21]. Of the 33 patients with sensitive disease, 16 patients were in CR and 17 patients were in PR immediately before HDT; 17 patients were in resistant, one patient in untested relapse. At the time of protocol entry the median Karnofsky performance score was 80%. The median duration of disease before transplantation was 2.9 years (range 0.6–11.3 years).

Table 1. Patient characteristics

Characteristics	*n*
Sex	
Male	23
Female	28
Median age, 27 years (range 13–59 years)	
Stage at diagnosis	
I A (B)	1 (1)
II A (B)	8 (11)
III A (B)	6 (9)
IV A (B)	5 (10)
Histology at diagnosis	
Nodular sclerosing	36
Mixed cellularity	9
Lymphocyte predominance	3
Lymphocyte depletion	1
Subtype unknown	2
Prior therapy	
Chemotherapy	51
Median number of drugs (range)	12 (7–15)
Median number of regimens (range)	3 (2–7)
Radiotherapy	43
Prior complete response	43
Disease status at BMT	
Sensitive relapse	33
Resistant relapse	17
Untested relapse	1
Median duration of disease before transplant, 2.9 years (range 0.6–11.3 years)	
Conditioning regimen	
Busulfan and cyclophosphamide	1
Cyclophosphamide, VP-16, BCNU (CVB regimen)	47
BCNU, etoposide, Ara-C, melphalan (BEAM regimen)	3
Type of transplant	
Autologous BM	44
Autologous BM plus PBSC	2
PBSC	1
Allogeneic BM	3
Syngeneic BM	1

Conditioning regimens

Except for one patient who was prepared with busulfan (16 mg/kg body wt.) and cyclophosphamide (200 mg/kg body wt.) prior to an allogeneic BMT, high-dose chemotherapy consisted either of the BEAM or the CBV protocol. BEAM combination chemotherapy administered to three patients consisted of BCNU 300 mg/m^2 on day −6, etoposide 200 mg/m^2 and cytosine-arabinoside 200 mg/m^2 on days −5 to −2, and melphalan 140 mg/m^2 on day −1 [7]. The CBV protocol [11], combining BCNU 300 mg/m^2 on day −6, etoposide 250 mg/m^2, and cyclophosphamide 1.5 g/m^2 on days −6 to −3, was given to the majority of patients ($n = 30$). However, 16 patients received 500–800 mg/m^2 of BCNU; three patients received 4.2, 4.5, and 4.8 g/m^2 of cyclophosphamide because symptoms of cardiac failure had developed while high-dose chemotherapy was still in progress.

Source of hematopoietic stem cells

Forty-four patients received autologous BM, and two patients were given autologous BM plus PBSC; one patient each received PBSC or syngeneic BM. Three patients had an allogeneic BM transplant from an HLA-identical MLC-negative sibling donor.

For patients receiving autologous BM or PBSC the marrow was documented to be histologically normal by bilateral BM biopsies obtained at the time of harvest. The median interval from marrow harvest to transplantation was 3.2 months (range 0.6–15.3 months). Standard procedures of marrow harvest, cryopreservation, and reinfusion were used. Marrow was stored in a liquid nitrogen freezer at −196°C.

Peripheral blood stem cells were harvested with a Fenwal CS 3000 blood cell separator (Baxter Deutschland GmbH, Munich, Germany). No manipulations to increase the number of stem cells circulating in the blood were used in the first two patients, while harvesting was started at the time of marrow recovery from combination chemotherapy in the last patient. This patient additionally received Neupogen (G-CSF) (10 μg/kg body wt. s.c.) for stem cell mobilization [27] from the first day after chemotherapy till the last day of PBSC harvesting. In this patient a total of four leukapheresis yielded 2.37×10^5 CFU-GM/kg, while in the former patients

eight and 12 leukaphereses were performed. For this study, patients were eligible for PBSC harvest and transplantation only if an attempt to harvest BM cells had yielded fewer than 1×10^8 MNC/kg body wt.

Supportive care

Patients were treated either in single hospital rooms or in rooms with high-efficiency particulate air (HEPA) filtration. All blood compounds administered after HDT were irradiated to 1500 cGy; transfusions were from CMV-negative blood donors whenever possible. Patients received them as needed to maintain the hemoglobin level at >10 g/dl and the platelet count $>20\times10^9$/l. Broad-spectrum antibiotics, antifungal and antiviral therapy, i.v. pain medication, and parenteral hyperalimentation were used as indicated. Twenty-five patients received GM-CSF ($n = 7$) or G-CSF ($n = 18$) to accelerate neutrophil recovery after BMT. The latter patients participated in an ongoing randomized trial to demonstrate the effectiveness of G-CSF in accelerating granulocyte recovery after autologous BMT [25].

Evaluation

Immediately before treatment, all patients were restaged clinically and by CT scans of the thorax and abdomen. The results were compared with those of similar investigations performed prior to the first cycle of salvage chemotherapy for assessment of chemosensitivity of the tumor. Patients were also assessed by serum chemistry, creatinine clearance, cardiac ejection fraction, and pulmonary function tests. In the absence of obvious progression, all patients were routinely restaged at day +100 and day +365 after transplantation. Thereafter, patients were studied annually or if recurrent symptoms or signs developed.

Definitions

Complete response was defined as the total disappearance of tumor plus survival to at least day +100. In addition, patients who achieved a very good partial remission ($>90\%$ tumor reduction in their overall cross-sectional tumor dimensions but with persisting radiographic abnormalities not changing for >6 months) were considered complete responders. Partial responders were defined as $\geq 50\%$ reduction in cross-sectional tumor dimensions and survival to at least day +100.

Statistical methods

End points considered in the data analyses were as follows:

1. Survival (i.e., from transplantation until death) – all patients were evaluated, and observations were censored only by end of follow-up.
2. Total responses (i.e., partial and complete responses) – all patients were evaluated.
3. Progression-free survival (i.e., from transplantation until disease progression) – all responders were evaluated, and observations were censored by end of follow-up or death without signs of progression.
4. Fatal treatment-related toxicity – all patients were evaluated.

All survival data were calculated from the day of marrow transplantation or infusion of PBSC (day 0) and analyzed as of September 15, 1992. Progression-free and overall survival curves resulting from all patients were plotted using the Kaplan-Meier method. Statistical comparison was made with log-rank tests [17].

Results

Patients were reviewed clinically and on the basis of CT scans of the thorax and abdomen 100 days after infusion of hematopoietic stem cells. Of the 43 patients alive at that time, 31 patients (72%) had achieved CR ($n = 19$) or maintained CR ($n = 12$), and six patients (13.9%) were in PR, for an overall response rate of 85.9% for all living patients, or 60.8% of the whole study population. With a median follow-up of 12 months (range 3–59 months) 20 of 51 patients (39.2%) are in continuous CR including one patient thought to be in PR at day +100. In this patient, the lesion supposedly representing active disease at day 100 continued to shrink afterwards without any therapeutic intervention and thus may have represented residual fibrotic tissue. Twelve of the CR patients have relapsed and five of them are currently under treatment. Three patients have died of relapse; three other patients are in second CR after successful radio- ($n = 2$) or chemotherapy ($n = 1$). Accordingly, 23 patients (45.1%) are currently alive and well without evidence of disease. One patient with relapse is lost to follow-up. Three of the patients with PR at day +100 have progressed with HD 4, 5, and 7 months after BMT. Two other PR patients died of transplant-related complications 6 and 8 months after BMT without signs of active disease. Six patients (13.9%) showed no response to high-dose therapy. One of them had received a syngeneic transplant for refractory bulky abdominal disease; the other five patients were given autologous BM for HD refractory to 2–5 chemotherapy regimens. Three of the nonresponding patients have already died; the other three are alive with disease 11, 14, and 32 months after ABMT, having failed further radio- and chemotherapy.

The overall survival for all patients who received autologous BM ($n = 44$) is shown in Fig. 1. The actuarial progression-free survival for patients with sensitive disease is $44\% \pm 11\%$, whereas none of the patients grafted for refractory relapse has become a long-term survivor so far (Fig. 2). The two patients who received BM plus PBSC have died of recurrent tumor or procedure-related complications (BM hypoplasia and *Candida* pneumonia). The patient given G-CSF-mobilized PBSC had an uneventful early post-transplant course and is alive and well in CR 3 months after HDT. Two of the three patients who received allogeneic transplants survive in CR 15 and 24 months after BMT; the second patient, however, is suffering from extensive chronic GVHD, with a Karnofsky score of 70%. The third patient given an allogeneic BMT died 57 days thereafter from *Candida* septicemia.

The major procedure-related toxicities were neutropenia and thrombocytopenia. This did not result in serious complications except in two patients who suffered extraordinarily long periods of neutropenia. These patients both received autologous BM harvested after multiple courses of chemotherapy and radiotherapy and were grafted for refractory relapse. In one of these patients we had been unable to harvest $>1\times10^8$ MNC/kg body wt. Therefore, this patient was grafted with BM and PBSC which also showed poor in vitro growth. Mucositis necessitating parenteral alimentation and i.v. pain medication was noticed in nearly all patients.

Overall, 16 patients have died after infusion of autologous BM or PBSC. Six patients succumbed to recurrent or progressing HD, while ten patients (20.8%) have died

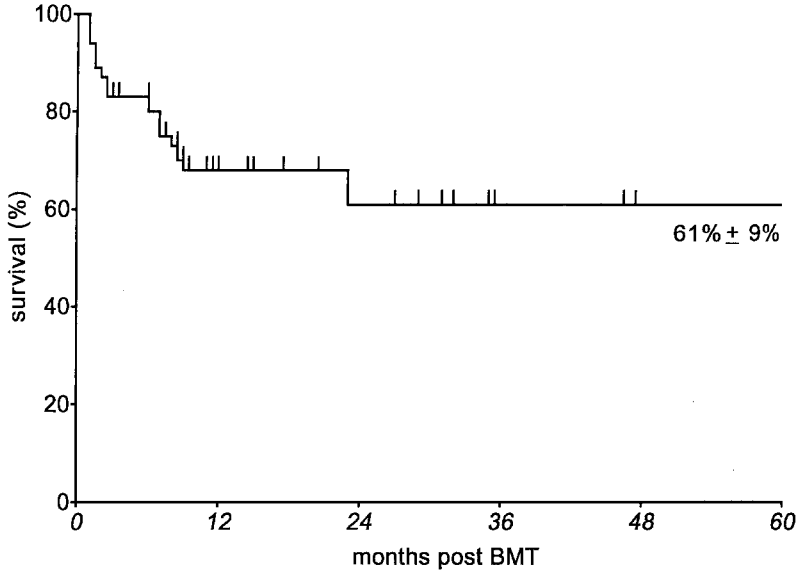

Fig. 1. Overall survival of 43 patients who received high-dose chemotherapy and autologous bone marrow transplantation

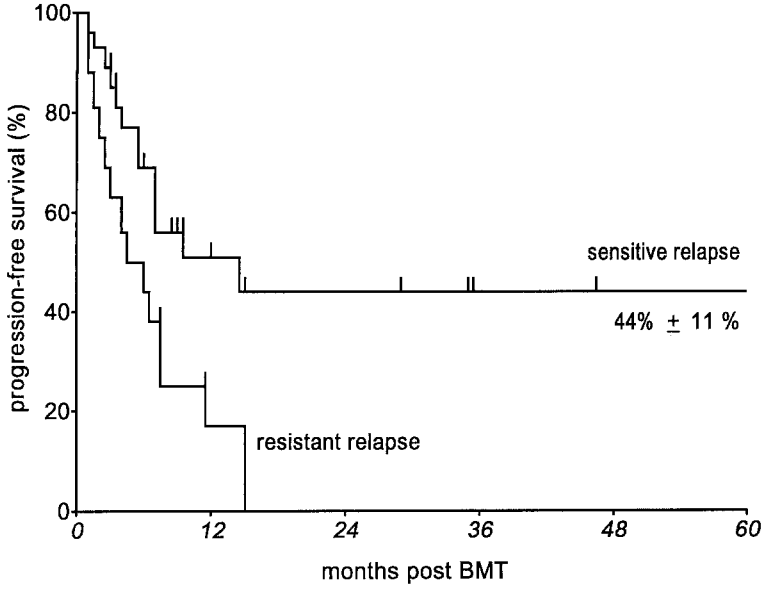

Fig. 2. Progression-free survival of 16 patients with chemotherapy-resistant relapse and 28 patients with chemotherapy-sensitive relapse following autologous BMT ($p = 0.01$, log-rank test)

of procedure-related complications. Specifically, one patient each died of cardiac failure, veno-occlusive disease, *Pneumocystis carinii* pneumonia, acute respiratory distress syndrome, and pneumonia of unknown origin. The two patients who died of infectious complications (*Pseudomonas aeruginosa* and *Candida* pneumonia) with BM hypoplasia 78 and 237 days after BMT have been mentioned above. Three patients died of IP 30, 44, and 51 days post BMT. In two of them no organisms were found at autopsy, while autopsy was not permitted in the third patient. The patients who experienced fatal IP had received 600 mg/m² ($n = 1$) or 800 mg/m² ($n = 2$) of BCNU as part of their preparative regimen.

Discussion

The chance of cure for patients with advanced HD who fail combination chemotherapy or relapse shortly (within 12 months) after such treatment is poor, with a 5-year-survival rate $< 20\%$ if standard salvage chemotherapy is administered [3, 8, 18, 19, 24, 26, 28, 30]. Although selected cases may have a better prognosis, a recent report demonstrates that even for those cohorts of patients deemed to carry a more favorable prognosis long-term disease-free survival is rare [16].

Several groups have recently demonstrated that HDT followed by autologous BM transplantation or PBSC support is a promising alternative for patients with relapsed HD [5, 7, 11, 12, 14, 22, 23]. However, as with other treatment modalities, the probability of survival and disease-free survival after these new treatment strategies is dependent on prognostic factors. Among others, the performance status prior to HDT, the number of chemotherapies failed, the size of the tumor mass at ABMT, transplant at first vs. later relapse, and, most importantly, the question of remaining sensitivity to standard chemotherapy have been mentioned [7, 11]. Indeed, some of the

good-risk criteria cited may not be totally independent; for example, the chance of being in good general condition may be higher in patients transplanted for sensitive as opposed to refractory relapse.

All of the patients entered into this study had one to four courses of standard chemotherapy in order to define the chemosensitivity of their disease. As demonstrated in Fig. 2, disease-free survival was significantly better for patients with sensitive relapse, and none of the patients with refractory disease survived free of disease much longer than 1 year after BMT. This poor outlook for patients with refractory disease is partly explained by the high relapse rate; on the other hand, procedure-related toxicity is also high. Whether still more intensive preparative regimens or immunomodulatory interventions (e.g., IL-2 administration after BMT) are able to improve the results in this cohort of patients who most urgently need effective salvage therapy remains to be settled. For the time being, it has been our policy to increase the doses of VP-16 in patients grafted for resistant disease. Alternatively, the rare patient with an HLA-identical donor may be offered an allogeneic BM transplant. Two of our patients grafted with allogeneic BM for multiply relapsed or refractory HD survive free of disease 24 and 15 months after BMT, possibly due to the recently described graft-versus-lymphoma effect [13]. This approach, however, is not without risks because the toxicity of an allogeneic BM transplant especially in patients with Hodgkin's disease is substantial [12, 13].

While the overall and progression-free survival in our cohort of patients is within the range of results reported by other transplant teams, the treatment-related mortality seems relatively high. Besides the fact that, in general, we grafted a heavily pretreated patient population having failed a median of three regimens and 12 drugs prior to HDT, two characteristics may explain this finding. First, some patients with extremely high-risk features were grafted. The poor graft function leading to fatal infectious complications in two patients must be attributed to the large amounts of cytotoxic drugs these patients had received before BM and PBSC could be harvested. The poor in vitro growth characteristics of their BM and PBSC indeed caused us serious concern while we were deciding to graft these patients. However, we thought that the clinical situation of these patients justified the decision to proceed to HDT. Second, three patients who had received 600 or 800 mg/m^2 of BCNU died of IP, which was idiopathic in at least two of them. Altogether, four of 15 patients (27%) given 600 or 800 mg/m^2 of BCNU experienced IP, whereas no such episodes have been observed in 32 patients given less than < 600 mg/m^2 BCNU. Wheeler et al. [32] also described a higher frequency of IP in patients given 600 mg/m^2 of BCNU, and we have limited the maximum BCNU dose to 300 mg/m^2 in more recent patients.

Although the results of this and other studies with HDT necessitating the infusion of hematopoietic stem cells show that a substantial percentage of patients with relapsed HD may be effectively salvaged by this approach, it is not clear if HDT followed by hematopoietic stem cell support generates superior results compared with intensive salvage therapy without stem cell rescue, especially when newer drug combinations using higher doses of cytostatic agents are administered [29]. The only way to answer this important question will be to launch a prospectively randomized trial in patients with comparable histories of disease.

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