Haematologica 1999; 84:1007-1011 original paper

Salvage chemotherapy with mini-BEAM for relapsed or refractory Hodgkin's disease prior to autologous peripheral blood stem cell transplantation

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Abstract

***Background and Objectives*. High-dose chemotherapy and autologous bone marrow transplantation (ABMT) has become the standard approach for most patients with relapsed or refractory Hodgkin's disease. Disease status at transplant has been correlated with outcome following ABMT. In light of this, we employ mini-BEAM (BCNU, etoposide, cytarabine and melphalan) salvage therapy in order to achieve a state of minimal residual disease prior to transplantation.**

***Design and Methods.* From February 1992 to June 1998 twenty-four patients receiving mini-BEAM therapy for resistance or relapse of their Hodgkin's disease were included. Four patients had obtained no response with initial chemotherapy (refractory), eight had obtained an incomplete response, seven were in first relapse and five in second or subsequent relapse. Fifteen patients received mini-BEAM as first salvage chemotherapy regimen. The remaining nine patients had previously been exposed to a median of one salvage regimen. Patients received a median of three cycles of mini-BEAM.**

***Results*. Sixteen patients achieved complete remission and four partial remission, yielding an overall response rate of 83%. No significant differences in response were observed between patients who received mini-BEAM as initial salvage therapy and those who had received a prior salvage regimen. Eighteen out of the twenty responding patients went on to intensive therapy and peripheral blood stem cell transplantation. With a median follow-up of 52 months, the cumulative probability of 7-year overall survival is 71% for the responders and that of the 6-year disease-free survival is 42%. No treatment-related deaths were observed.**

***Interpretation and Conclusions.* Mini-BEAM is an effective salvage regimen with moderate toxicity that may be useful for cytoreduction prior to stem cell procedures.**

Key words: Hodgkin's disease, recurrent disease, salvage therapy, mini-BEAM, bone marrow transplantation.

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Although initial treatment of Hodgkin's disease induces complete remission in most patients,[1] a subset of patients either fail to enter remission (20%) or relapse after a complete response (30% to 40%). In these patients a variety of standard dose salvage regimens have been used with different results, but only 20-40% of cases are cured.[2] High-dose combination chemotherapy with autologous bone marrow or peripheral blood stem cell transplantation has become the standard approach in most patients who fail to achieve complete remission with initial chemotherapy or relapse after previous complete remission. Prior to administering intensive therapy with ABMT many centers employ some form of conventional-dose treatment for cytoreduction in patients with relapsed/refractory Hodgkin's disease. This approach is based on several observations: first, bulky disease at the time of ABMT has been correlated with decreased survival following ABMT:[3-5] second, response to cytoreductive therapy (sensitive relapse) may correlate with outcome following ABMT.[6] Different salvage regimens have been proposed. Our center has used mini-BEAM salvage chemotherapy to reduce tumor burden prior to peripheral blood stem cell transplantation (PBSCT). The purpose of this report is to evaluate our experience with this regimen.

Design and Methods

Patients

From February 1992 to June 1998 twenty-four patients received mini-BEAM for resistance or relapse of their Hodgkin's disease. The median age of the patients was 33 years (range 18 to 59) and there were 17 males and 7 females. The histologic diagnosis was nodular sclerosis in 19 patients, mixed cellularity in 3 patients, lymphocyte predominance in one patient and one case was unclassified (according to the REAL classification). Ann Arbor's stage at mini-BEAM therapy was II in five patients, III in ten and IV in nine. Fourteen patients had B symptoms. At the time of mini-BEAM treatment the status of the patients was as follows: four were refractory to initial therapy, eight were partial responders, seven were in their first relapse and five in their second or

subsequent relapses. The median interval between diagnosis and mini-BEAM treatment was 17 months (range 8 to 325 months). First-line combination chemotherapy regimens included MOPP (two patients), ABVD (three patients), MOPP alternating with ABVD (eleven patients) and COPP alternating with ABVD (seven patients). In addition to chemotherapy, ten patients had received radiotherapy as part of their initial management. Fifteen patients received mini-BEAM as first salvage chemotherapy. The remaining nine patients had previously been exposed to a median of one salvage regimen (ABVD, lomustine + etoposide + prednimustine and ifosfamide + etoposide + CCNU).

Treatment

All patients received the mini-BEAM regimen consisting of BCNU 60 mg/m^2/day, VP-16 300 mg/m^2/day, Ara-C 800 mg/m^2/day and melphalan 30 mg/m^2/day for one day. The chemotherapy was generally administered every four weeks if there was hematologic recovery. Three patients received two courses of mini-BEAM and 15 patients received three. In five patients a fourth course was administered for the purpose of maximum tumor reduction. After treatment complete restaging was repeated.

Response assessment and PBSCT

A complete response (CR) was defined as complete resolution of all signs and symptoms of disease, including abnormalities on CT. A partial response (PR) was defined as 50% or greater reduction in the measurable disease. If the response was less than that, it was designated as non-response.

Patients who achieved CR or PR were eligible to proceed to blood progenitor collection and PBSCT. The mean interval between the beginning of mini-BEAM therapy and transplant was 6.6 months (SE ± 0.91). PBSC were mobilized with G-CSF at a dose of 10 µg/kg/d for five days according to protocols in effect in our institution. The conditioning regimen used was BEAC (BCNU 300 mg/m^2/d on day -6, VP-16 200 mg/m^2/d on day –5 to -2, Ara-C 200 mg/m^2/d on day –5 to –2 and cyclophosphamide 1400 mg/m^2/d on day –5 to –2).[7] Patients with no response to mini-BEAM were offered other second-line salvage chemotherapy regimens (DHAP).[8]

Statistical analysis

Fisher's exact test was used to evaluate significant differences between subgroups of patients. Overall survival was calculated from the beginning of salvage therapy to the date of death or last follow-up. Disease-free survival was measured from the beginning of salvage therapy to the date of relapse (if any). Survival analyses were performed using Kaplan and Meier's method. Differences in survival between groups (responders vs non-responders and partial-responders vs complete responders) were identified by log-rank analysis.

Results

Twenty-four patients (median age 33 years, range 18 to 59) were treated with 2-4 courses of mini-BEAM as salvage therapy in order to achieve effective cytoreduction and proceed to PBSCT with minimal disease. Sixteen patients achieved complete remission and four partial remission, resulting in a response rate of 83%. In the 15 patients who received mini-BEAM as first-line salvage treatment, the response rate was 87% (12 CR, 3 PR). In the group of nine patients who received mini-BEAM as second or third-line salvage therapy there were seven responders (6 CR, 1 PR; response rate 78%). There was no statistical difference in response between patients who received mini-BEAM as initial salvage therapy and those who had originally received another salvage treatment. We observed no significant differences in either response or complete remission rate whether this regimen was given to those refractory to initial therapy (response rate 3/4), to those who were partial responders (response rate 8/8), to those in first relapse (response rate 4/7) or to those in second or subsequent relapse (response rate 5/5). There was no difference in response between patients who had received prior radiotherapy and those who had not. The response to mini-BEAM in relation to the patients' main characteristics is shown in Table 1. Twenty patients had a sufficient response to proceed to intensive therapy and PBSCT. Two of them refused and 18 were transplanted. At the time of blood cell collection no patient showed signs of bone marrow involvement by Hodgkin's disease.

Table 1. Response to mini-BEAM in relation to patients' main characteristics.

	Patients (No.)	*Complete remission*	*Overall response*
Response to induction therapy			
Refractory	4	3	3
Partial response	8	5	5
First relapse			
CR ≤12 months	2	1	1
CR >12 months	5	3	3
Second or subsequent relapse			
Previous CR ≤12 months	0	0	0
Previous CR >12 months	5	4	5
Systemic symptoms			
No	10	6	9
Yes	14	10	11
Disease extent			
Nodal only	10	7	9
Extranodal + nodal	14	9	11
Previous salvage regimens			
No	15	10	13
Yes	9	6	7
Previous radiotherapy			
No	14	9	11
Yes	10	7	9

Toxicity

There were no treatment-related deaths. Myelosuppression was the main toxicity. Non-hematologic toxicities, such as gastrointestinal side effects and mucositis, were mostly mild. There were neither transplantation-related deaths nor secondary leukemia/myelodysplasia.

Outcome

At present, in the group of 20 responding patients (18 transplanted), 13 patients remain alive in continuous CR with a median follow-up of 52 months (range 7-84 months), six have relapsed and one has died due to gelatinous degeneration of marrow (21 months after PBSCT). Both of the patients who achieved CR and refused PBSCT have relapsed (disease-free-survival 18 and 71 months, respectively). Four patients who did not respond to mini-BEAM received another salvage regimen (DHAP) in an attempt to produce adequate cytoreduction before PBSCT. Only one of these patients responded to alternative salvage therapy and underwent PBSCT but he relapsed four months later and died due to disease progression. The remaining three non-responders succumbed to progressive disease. Therefore, all patients who did not respond to mini-BEAM died.

The cumulative probability of 7-year overall survival is 71% for the responders. Mean survival at 7 years is 67 months (95% CI, 54 to 81 months) compared to 17 months (95% CI, 6 to 28 months) for non-responders (Figure 1) and the difference is significant (p<0.0002, log-rank test). Mean survival at 7 years for transplanted patients in CR and in PR was 70 months (95% CI, 55 to 84) and 46 months (95% CI, 25 to 67) respectively, with no significant difference between them.

The 6-year mean disease-free-survival (DFS) is 51 months (95% CI, 40 to 63) (Figure 2). Mean DFS at six years for patients transplanted in CR following salvage therapy is 56 months (95% CI, 45 to 67) compared to 21 months (95% CI, 19 to 24) for patients transplanted in PR. Comparison of these results showed a statistically significant improvement in disease-free survival in patients who were transplanted in CR compared to those transplanted in PR (p<0.0165, log-rank test).

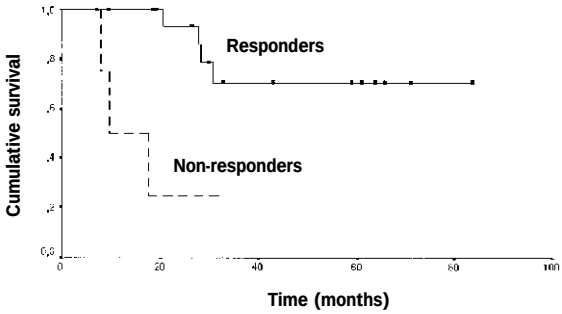

Figure 1. Survival in relapsed or refractory Hodgkin's disease patients treated with the mini-BEAM regimen.

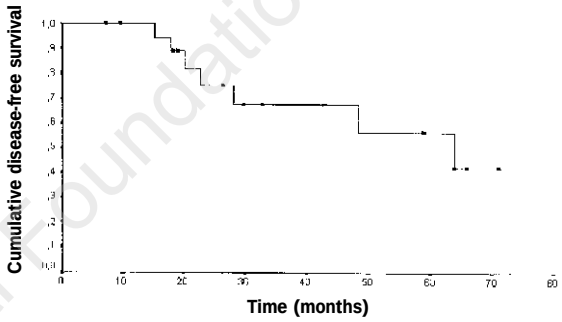

Figure 2. Disease-free survival in patients who achieved a complete or partial response with mini-BEAM (including non-transplanted patients).

Discussion

Several centers have reported that remission status at transplant is an important predictor of outcome.[4] Different salvage regimens have been employed with the aim of achieving a state of minimal residual disease prior to transplant. We evaluated the use of mini-BEAM as a salvage regimen in patients with relapsed or refractory Hodgkin's disease in order to produce maximum tumor reduction prior to PBSC collection and transplantation. An overall response rate of 83%, with a CR rate of 67%, was obtained and there were no significant differences in response regardless of whether this regimen was given as a first, second or third-line salvage regimen. This high response rate with mini-BEAM agrees with previously published findings and compares favorably with other conventional salvage regimens (see Table 2). There were no cases of treatment-related mortality nor secondary leukemia or myelodysplasia, however longer follow-up is necessary to estimate the leukemia risk described to be associated with the use of alkylating-containing regimens.[21,22]

The CR rate obtained with the administration of mini-BEAM in our series is higher (32%) than that described by Colwill *et al*.[20] The reason for this difference may be related to patient selection. Seventeen of the thirty-three relapsed patients in Colwill's study had a short (<1-year) prior remission, which confers a bad prognosis, whereas only two of our twelve relapsed patients had a such short prior response to chemotherapy. It should also be noted that most of our patients received three cycles of mini-BEAM while the number of cycles administered in other studies was lower.

Table 2. Results of several salvage regimens for relapsed or refractory Hodgkin's disease.

Regimen	*Author, Year (Ref. no.)*	*Patients (No.)*	*Overall response rate*	*CR rate*
ABVD	Santoro *et al.*, 1982[9]	54	72%	59%
ABDIC	Tannir *et al.*, 1983[10]	34	70%	35%
B-CAVe	Harker *et al.*, 1984[11]	48	71%	44%
CEP	Santoro *et al.*, 1986[12]	58	54%	40%
CEVD	Pfreundschuh *et al.*, 1987[13]	32	56%	44%
DHAP	Brandwein *et al.*, 1990[14]	37	43%	11%
HOPE-Bleo	Perren *et al.*, 1990[15]	44	82%	59%
Dexa-BEAM	Pfreundschuh *et al.*, 1994[16]	55	60%	31%
MINE	Ferme *et al.*, 1995[17]	100	75%	34%
ASHAP	Rodriguez *et al.*, 1997[18]	57	70%	35%
Mini-BEAM	Chopra *et al.*, 1992[19]	23	65%	4%
Mini-BEAM	Colwill *et al.*, 1995[20]	44	84%	32%
Mini-BEAM	Present study	24	83%	67%

We have obtained a DFS and an overall survival (OS) rate at 2 years of 75% and 93% respectively. The DFS and OS rates at 5 years were 56% and 71% respectively. Chopra *et al*.[18] reported OS and progression-free survivals at 2 years of 61% and 46% respectively (including two patients who did not proceed to transplantation). Preliminary results obtained by Colwill *et al.*[20] indicated a progression-free survival rate of 60% and an OS rate of 78% in twenty-six transplanted patients (median follow-up duration from the last mini-BEAM was 13 months).

In our study patients transplanted in CR enjoy a greater long-term DFS than those in PR. This supports the idea that disease status at time of transplant is an important predictor of outcome.

Some trials have compared high-dose therapy and PBSCT with conventional salvage treatments. The *British National Lymphoma Investigation* (BNLI) undertook a prospective randomized comparison of high-dose chemotherapy (BEAM) plus ABMT versus mini-BEAM alone, in relapsed and resistant Hodgkin's disease.[23] The trial was closed early but suggests that despite the high overall response rate of 60% achieved with mini-BEAM in this study, BEAM plus ABMT treatment results in a significantly better event-free and progression-free survival than treatment with mini-BEAM alone. Overall survival was also higher in the ABMT group, but the difference did not reach statistical significance. Another study, undertaken by Stanford University,[24] compared patients with Hodgkin's disease in first relapse or with refractory disease treated with high-dose therapy and autografting with a matched group of similar individuals treated with conventional salvage therapy. Overall survival, event-free survival and progression-free survival were all better in the high-dose group. So, responders to mini-BEAM seem to benefit from subsequent high dose chemotherapy with stem cell support. Interestingly, the two patients in RC who refused PBSCT relapsed after more than one year.

Only one of our four patients who did not respond to mini-BEAM responded to alternative salvage therapy but his outcome was poor. The rest of the patients failed to respond to additional therapy. This result might indicate that mini-BEAM selects patients with chemotherapy-sensitive disease.

We conclude, within the limits of this study, that mini-BEAM is an effective salvage therapy with moderate toxicity which is applicable in patients who are refractory to initial therapy, partial-responders and relapsed patients and that it may also be useful for cytoreduction prior to stem cell procedures.

Contributions and Acknowledgments

All the authors contributed to the conception of the study, analysis of the data and writing of the paper.

The order in which the names of the authors appear is based on their contribution to the study, except for the last author who is the head of department and gave the final approval.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received April 12, 1999; accepted August 10, 1999.

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