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Papers

Haematological Toxicity of Radiotherapy Following High-dose Chemotherapy and Autologous Bone Marrow Transplantation in Patients with Recurrent Hodgkin's Disease

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17 patients with recurrent Hodgkin's disease received 21 courses of radiotherapy (RT) 1–23 months after high-dose chemotherapy and autologous bone marrow transplantation. WHO grade III–IV haematological toxicity, of median duration 38 days (range 4–236), was observed following 10 courses of radiotherapy in 9 patients. This haematological morbidity could be predicted with an 80.0% sensitivity when the pre-RT white cell count was $< 5 \times 10^9$/l or the platelet count $< 100 \times 10^9$/l. It occurred in 9/11 patients wth initial stage III–IV disease, including all 6 given extended radiotherapy fields, but in no patients with initial stage II disease ($\chi^2 = 9.35$, $P < 0.005$). Age, histology, the presence of B symptoms, performance status, previous radiotherapy or chemotherapy, the interval between autologous bone marrow transplantation and radiotherapy, the high-dose regimen used, and the radiotherapy dose or field size, did not appear to affect haematological toxicity. The median survival was 18 months from the date of starting radiotherapy. 7 patients remain alive and progression-free 8–51 months (median 21 months) after radiotherapy. Radiotherapy may contribute to durable remissions in patients with relapsed or residual Hodgkin's disease after autologous bone marrow transplantation, but significant haematological toxicity may be expected in those with mild pancytopaenia prior to radiotherapy, particularly with initial stage III or IV disease.

Key words: Hodgkin's disease, autologous bone marrow transplantation, radiotherapy
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INTRODUCTION

HIGH-DOSE CHEMOTHERAPY with autologous bone marrow transplantation (ABMT) is increasingly used in patients with refractory Hodgkin's disease relapsing after treatment with standard chemotherapy regimens [1–4]. Although the evidence for benefit of high-dose over conventional dose chemotherapy is not fully proven, a recent randomised trial of high-dose chemotherapy and ABMT against standard salvage chemotherapy at doses not requiring marrow engraftment demonstrated an improvement in relapse-free and event-free but not overall survival [2]. However, even with aggressive high-dose chemotherapy, only 30–40% of patients remain in remission [2–8]. The major site of relapse following salvage therapy is in areas of previous disease involvement, particularly where this was bulky [6–8], and such relapse carries a poor prognosis with a median survival of less than 1 year [8].

Radiotherapy is an effective local treatment in early Hodgkin's disease [9]. It can be used as salvage therapy [10, 11], and may potentially reduce the rate of local failure following high-dose chemotherapy and ABMT. It has been utilised as part of the pretransplantation induction regime to previously involved lymph node areas [5, 7], as total lymphoid irradiation [12], as total body irradiation supplemented by involved field radiotherapy [6], or as consolidation therapy for residual masses after transplantation [2, 3].

Haematological toxicity due to extensive irradiation of the bone marrow may limit extended field radiotherapy, particularly in heavily pretreated patients. Following high-dose chemotherapy and ABMT, bone marrow function may be compromised further but the tolerance to radiotherapy after ABMT is not clear. We have assessed the haematological toxicity in terms of peripheral blood parameters in patients who received radiotherapy as part of salvage therapy following high-dose chemotherapy and ABMT. The results may help to predict

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Table 1. Characteristics of patients and their disease at presentation of Hodgkin's disease

Age (years)	
Mean	28.9
Range	16–45
Sex*	
Male	12
Female	5
Stage*	
II	6
III	5
IV	6
B symptoms*	12
Histology*	
Lymphocyte predominant	1
Nodular sclerosing	10
Mixed cellularity	3
Lymphocyte depleted	3

*No. of patients.

whether haematological toxicity will permit the use of radiotherapy in this group of patients and elucidate the radiation tolerance of engrafted bone marrow.

PATIENTS AND METHODS

Between 1979 and 1992, 111 patients with refractory or recurrent Hodgkin's disease received marrow-ablative high-dose chemotherapy followed by ABMT. 17 patients received subsequent radiotherapy, in 1 case as adjuvant therapy to initial sites of disease and in the remainder as further salvage therapy for residual or recurrent disease. The initial disease and patient characteristics are summarised in Table 1.

Initial treatment comprised chemotherapy in 15 patients (regimes shown in Table 2), and mantle radiotherapy in 2 patients. A median of three (range one to six) chemotherapy regimes had been administered prior to high-dose therapy, and 8 patients had received a total of 12 previous courses of radiotherapy.

The chemotherapy used for induction prior to transplantation has been decribed previously [3]. 12 patients received a combination of BCNU, etoposide and melphalan, 3 melphalan and BCNU, 1 melphalan, etoposide and cyclophosphamide and 1 melphalan and cyclophosphamide.

Table 2. Chemotherapy regimes used as first- and second-line therapy

First-line regimen	No. of patients	Second-line regimen	No. of patients
ChIVPP	10	ABVD	4
ABVD	1	ChIVPP	4
VEEP	1	VEEP	4
LOPP-EVAP	1	EAID	1
ChIVPP-HOPE-Bleo	1	HOPE-Bleo	1
LOPP	1	EPIC	1
MVPP	1	ChIVB	1
MOPP	1		

ChIVPP, chlorambucil, vinblastine, procarbazine, prednisolone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; VEEP, vinblastine, etoposide, epirubicin, prednisolone; LOPP, chlorambucil, vincristine, procarbazine, prednisolone; EVAP, etoposide, vinblastine, doxorubicin, prednisolone; HOPE-Bleo, doxorubicin, vincristine, prednisolone, etoposide, bleomycin; MVPP, mustine, vinblastine, procarbazine, prednisolone; EAID, etoposide, doxorubicin, ifosfamide, dacarbazine; EPIC, etoposide, prednisolone, ifosfamide, cisplatinum; ChIVB, chlorambucil, vinblastine, bleomycin.

All but 1 patient had radiologically-documented residual or progressive disease at the time of post-ABMT radiotherapy. The median interval from high-dose treatment to the first course of radiotherapy was 5 months (range 1–14). The 17 patients received a total of 21 courses of radiotherapy following transplantation. Twelve courses, in 10 patients, were administered with radical intent. Of these, nine comprised extended field treatments of which eight used mantle portals. Nine courses in 8 patients were given with palliative intent. The radiotherapy doses ranged from a 4-Gy single fraction to 45 Gy in 21 daily fractions. Fifteen courses were prescribed at 30 Gy or more, the most frequent (eight courses) being 35 Gy in 20 daily fractions. One patient, who received palliative radiotherapy to the lumbar spine, was not assessable for treatment toxicity as only survival data were available.

The haematological toxicity was assessed by peripheral blood count including total white cell, neutrophil and platelet count and haemoglobin level. This was carried out weekly during treatment and initially monthly after treatment, or more often if clinically indicated. The toxicity was graded according to WHO criteria, where grade 3–4 toxicity indicates a white cell count of less than 2×10^9/l or a platelet count of less than 50×10^9/l, or any episodes of septicaemia or spontaneous bleeding. The duration of toxicity was taken from the first occasion after the start of irradiation when the blood count was reduced to a level lower than that defined above until the recovery of the platelet and white cell count to a level of $>50 \times 10^9$/l and $>2 \times 10^9$/l, respectively.

Survival was recorded from the date of the start of radiotherapy. Actuarial survival was calculated according to the life-table method [13]. The minimum follow-up of surviving patients was 8 months.

RESULTS

17 patients received a total of 21 courses of radiotherapy after high-dose chemotherapy and ABMT. 12 had involved field treatments and 9 extended field radiotherapy, of which 8 had mantle portals. All but 1 of the patients who had assessable morbidity had a full blood count performed immediately prior to radiotherapy. On four occasions patients had a platelet count less than 100×10^9/l immediately prior to radiotherapy, and on six a total white cell count less than 5.0×10^9/l.

Grade 3 or 4 haematological toxicity was observed following 10 courses of radiotherapy (48%) in 9 patients. Of these episodes, four involved leucopenia, three thrombocytopenia and three both. One toxic event, comprising both leucopenia and thrombocytopenia, occurred in a patient with preterminal bone marrow failure due to Hodgkin's disease, who received a single fraction of palliative involved field radiotherapy. The duration of thrombocytopenia appeared longer (median duration 63.5 days, range 9–236) than that of leucopenia (median duration 5 days, range 3–40), but this was not statistically significant ($t = 2.04$, $P > 0.05$). 2 patients were unable to complete their planned treatment because of haematological toxicity. Neither had relapsed at the time of analysis. 4 patients had treatment interruptions of 2–18 days because of haematological morbidity, and 2 have since relapsed and died. No patients had their treatment delayed because of other morbidity.

An increased frequency of thrombocytopenia was observed in

Table 3. Patient and tumour variables and haematological toxicity during radiotherapy

Factor	Grade 0–2 toxicity	Grade 3–4 toxicity	
Mean age (years)	29.7	28.3	
Sex*			
Male	7	4	$\chi^2 = 5.66$
Female	0	5	$P < 0.05$
Initial clinical stage*			
II	5	0	$\chi^2 = 9.35$
III–IV	2	9	$P < 0.005$
B symptoms*	4	8	$\chi^2 = 2.11, P > 0.1$
Histology*			
Lymphocyte predominant	1	0	$\chi^2 = 4.28, P > 0.1$
Nodular sclerosing	4	5	
Mixed cellularity	0	3	
Lymphocyte depleted	2	1	
Plts $< 100 \times 10^9$/l, WCC $< 5 \times 10^9$/l†	1	8	$\chi^2 = 8.1, P < 0.005$
Plts $> 100 \times 10^9$/l, WCC $> 5 \times 10^9$/l†	7	2	

*No. of patients. †No. of courses. Plts, platelets; WCC, white cell count.

patients with a low platelet count at the start of radiotherapy, and of leucopenia in patients with a low white cell count. Grade 3 or 4 thrombocytopenia occurred in all four instances with a preradiotherapy platelet count of $<100 \times 10^9$/l, but in only two of 14 with a higher platelet count prior to treatment. Similarly, grade 3 or 4 leucopenia occurred on six out of seven occasions with a preradiotherapy total white cell count of $<5 \times 10^9$/l at the start of radiotherapy, but on only one out of 11 times when the white cell count was $> 5 \times 10^9$/l. When combined, eight out of nine courses of radiotherapy with a low preradiotherapy platelet or white cell count were followed by grade 3 or 4 haematological morbidity, compared with two out of nine courses when the platelet or total white cell count prior to radiotherapy was normal. Overall, the combination of low platelet and total white cell count at the start of radiotherapy had a sensitivity of 80.0% and a specificity of 87.5% in predicting grade 3 or 4 haematological toxicity.

The presence of grade 3 or 4 haematological toxicity was correlated with disease, patient and treatment characteristics (Tables 3, 4). The presence of stage III or IV disease at initial diagnosis ($\chi^2 = 9.35$, $P < 0.005$) and the patient's sex ($\chi^2 = 5.66$, $P < 0.05$) were related to the incidence of grade 3 or 4 haematological morbidity. The increased morbidity in women probably occurred by chance because of the small number treated in this series, all 5 of whom had stage III or IV disease. The association between gender and stage of disease was statistically significant ($\chi^2 = 3.86$, $P < 0.05$). Age, histology, the presence of B symptoms and performance status were not predictive of toxicity (Table 3). No treatment variable, including the use of previous radiotherapy, the number of courses of chemotherapy received prior to high-dose therapy, the interval between ABMT and radiotherapy, the high-dose regime used and the radiotherapy dose or field size appeared to influence the incidence of grade 3 or 4 toxicity (Table 4).

No patient experienced fatal acute haematological toxicity. Eventual recovery of the blood count to WHO grade 0 criteria (white cell count $> 4.5 \times 10^9$/l and platelet count $> 130 \times 10^9$/l) occurred in all 3 patients with grade 2 toxicity, 2/4 patients with grade 3 toxicity and 0/4 with grade 4 morbidity. One patient developed acute myeloid leukaemia 53 months after irradiation, and died 70 months post-treatment. One patient suffered persistent chest infections following involved field radiotherapy to the mediastinum and right side of neck and 1 patient had acute pneumonitis, but non-haematological morbidity was otherwise mild and limited to skin and upper gastrointestinal reactions.

Table 4. Treatment variables and haematological toxicity during radiotherapy

Factor	Grade 0–2 toxicity	Grade 3–4 toxicity	
Interval between first treatment and radiotherapy (months)	48.9	30.0	$t = 1.21$, $P > 0.2$
Interval between high-dose treatment and radiotherapy (months)	7.4	4.4	$t = 1.71$, $P > 0.1$
Prior chemotherapy (courses, mean)	3.1	2.6	
Prior radiotherapy (courses, mean)	0.7	0.6	
High-dose regime*			
BEM	5	7	$\chi^2 = 0.08$
Other	2	2	$P > 0.5$
Radiotherapy volume*			
IF	7	4	$\chi^2 = 1.82$
EF	3	6	$P > 0.1$

BEM, BCNU, etoposide and melphalan; IF, involved field; EF, extended field. *No. of patients.

8 patients remain alive, of whom 7 are progression-free a median of 21 months (range 8–51) after radiotherapy. The 2-year actuarial survival is 46.6% (Figure 1).

DISCUSSION

Consolidation radiotherapy administered to sites of initial involvement with Hodgkin's disease, particularly when this was bulky, may prevent further progression in patients who have

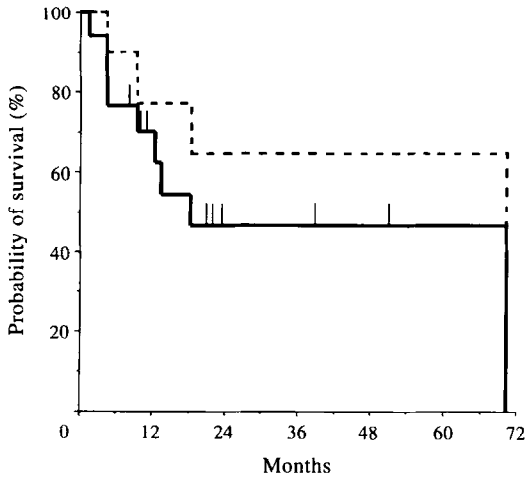

Figure 1. Actuarial survival of patients with Hodgkin's disease receiving radiotherapy post-ABMT. Dashes indicate duration of follow-up of surviving patients. For all 17 patients (———), 2-year actuarial survival was 46.6%. For those treated with radical intent, (-----), 2-year actuarial survival was 64.3%.

received high-dose chemotherapy and ABMT [5, 6]. However, this possibility has been tempered by concern that the use of radiotherapy might produce serious haematological toxicity. Previous series of patients who have been irradiated after high-dose chemotherapy and ABMT have not reported the toxicity of radiotherapy [2, 7]. The aim of this study has been to assess the haematological morbidity of radiotherapy following high-dose chemotherapy and ABMT, and to determine what factors might predict it. The results suggest that radiotherapy may be administered, albeit with significant but manageable haematological toxicity. Such consolidation of salvage treatment may result in durable control of disease.

In an attempt to assess whether the haematological parameters at the start of radiotherapy might provide a very simple guide to the risk of haematological toxicity, the preradiotherapy total white cell and platelet counts were examined separately in relation to leucopenia and thrombocytopenia. In this series, all but one course of radiotherapy in a patient with a white cell count less than 5×10^9/l, or a platelet count less than 100×10^9/l, produced significant haematological toxicity, but this also occurred in two courses with patients with higher counts. This data suggest that the blood count at the start of radiotherapy can be used to indicate an increased risk of leucopenia or thrombocytopenia, but not to exclude the possibility of these side-effects occurring.

Over half the patients receiving radiotherapy after ABMT developed grade 3 or 4 haematological toxicity. The extent of disease at presentation was related to the incidence of haematological toxicity. There is no clear biological explanation why initial stage of disease should correlate with the tolerance to radiotherapy after ABMT, since engraftment had been successful in all these patients, and there was no suggestion of marrow involvement in the majority following transplantation. Unfortunately, the small numbers of patients in each group in this study make conclusions about correlations between patient or treatment variables and morbidity tentative, but the strength of the relationship observed here between initial stage and grade III or IV toxicity suggests that such patients should be watched with particular care after consolidation radiotherapy.

Although it would seem plausible that reducing the size of radiotherapy portals would produce lower haematological toxicity, the use of involved field treatment rather than extended fields was not related to a lower morbidity. However, very few patients in this series received involved field treatment alone, the majority being treated via mantle portals when cure was intended. All patients with initial stage III or IV disease receiving extended field treatment experienced grade 3 or 4 haematological toxicity, while this was seen in none of the patients with initial stage II disease treated in such a fashion. Given the small number of patients in this retrospective series, it is difficult to estimate precisely the effect of the volume of bone marrow irradiated on the haematological toxicity. This could be addressed in a larger prospective study.

It seems likely that the correlation between gender and morbidity is spurious, reflecting the small size of this series and the chance association of gender and stage in this group of patients.

Although over half the patients experienced grade III or IV morbidity, only 4 had clinically significant toxicity with septicaemia (2), spontaneous bleeding (1) or pancytopenia persisting beyond 3 months (1). 2 patients were unable to complete their treatment because of this toxicity. No patient died as a result of acute haematological side-effects.

Radiotherapy has been shown to be an effective local therapy in early stage [9], advanced stage [14] and recurrent [10, 11] Hodgkin's disease. It often achieves local disease control but its effect on survival in advanced or recurrent disease is unclear. With irradiation as a component of the salvage high-dose chemotherapy regime, Reece *et al.* [7] observed only two relapses at irradiated sites in 24 patients. Phillips *et al.* [6] noted a trend toward improved survival in patients receiving radiotherapy prior to engraftment. Conversely, Lazarus [5] was unable to demonstrate a benefit from irradiation. In a series of 95 patients with Hodgkin's disease reported by Vose *et al.*, who had relapsed again after high-dose chemotherapy and ABMT [8], 9 of the 10 patients who were disease-free after further salvage therapy had radiotherapy as part of this treatment. Thus the question arises whether radiotherapy has a role as adjuvant therapy to sites of bulky disease in patients receiving marrow-ablative therapy and ABMT. The use of involved field radiotherapy to the mediastinum prior to ABMT has been associated with fatal interstitial pneumonitis [5, 6]. The present series suggests that adjuvant radiotherapy delivered after high-dose chemotherapy and ABMT may be administered with manageable haematological toxicity, particularly if peripheral blood counts have adequately recovered, and without major pulmonary toxicity.

Given the high incidence of progression following ABMT, particularly at sites of previously bulky disease [8], adjuvant radiotherapy to these sites may have a useful role. No randomised trial has examined the role of adjuvant radiotherapy after ABMT. A formal study of involved field radiotherapy following high-dose chemotherapy and ABMT may be of interest. It could be administered to patients with adequate bone marrow reserve who have not previously received tolerance doses of radiotherapy at these sites. The use of haemopoietic growth factors may also allow radiotherapy to be used in other patients. However, such additional localised radiotherapy at the time of salvage therapy should only be used if it can be shown to improve survival as well as local disease control.

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Informed Consent in European Multicentre Randomised Clinical Trials — Are Patients Really Informed?

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This study was designed to examine the standard of consent used by investigators in European randomised clinical trials (RCT). The participants of 12 multicentre RCTs published in the *European Journal of Cancer* in the years 1990–1992 were asked to complete a short questionnaire regarding their practice of obtaining consent in the trial reported. Anonymity was assured. Replies were received from 60 of 88 clinicians contacted. Data showed that 12% of clinicians did not inform their patients about the trial prior to randomisation. Thirty-eight per cent of clinicians did not always tell patients that they had been assigned to their treatment randomly. Only 32% of clinicians used written consent, 21% used written information without obligatory signing, 42% used verbal consent, and in 5% no consent was sought. Even when information was given, only 58% of clinicians gave full information on all aspects of the trial and 42% gave information on the proposed treatment arm only (27% revealing inclusion in an RCT). When examined by geographical origin, clinicians in northern Europe were more likely to obtain full consent than those from southern Europe. Similarly, the level of consent was higher in trials of supportive care than in trials testing curative or palliative antitumour therapies.

Key words: clinical trials, informed consent
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INTRODUCTION

RANDOMISED CLINICAL trials (RCTs) have become the accepted method of assessing the usefulness of therapies, both new and old. As RCTs have developed, it has become customary, in most developed countries, that patients are asked to participate in the process of deciding whether they should be included in the trial—knowing that they will be allocated to one or two or more treatment options by chance [1]. The standard of such consent usually demanded is one of so-called "informed consent" [2]. Thus, in addition to knowing about the potential randomisation,