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Original Paper

Thoracic Radiation Therapy Before Autologous Bone Marrow Transplantation in Relapsed or Refractory Hodgkin's Disease*

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The aim of this study was to assess the relationship between radiation therapy (RT) and treatment-related mortality in patients receiving high-dose chemotherapy (HDCT) and autologous bone marrow transplantation (ABMT) for recurrent/refractory Hodgkin's disease (HD). Between December 1986 and December 1992, 59 patients previously treated at the Princess Margaret Hospital underwent HDCT (etoposide 60 mg/kg, melphalan 160 mg/m^2) and ABMT, performed for refractory (13 patients) or relapsed (46 patients) HD. RT was incorporated in the salvage treatment with the intent to achieve complete control of disease prior to ABMT. RT was given before ABMT in 33 patients, and after ABMT in 4 patients. Treatment-related (TR) mortality was defined as any death occurring within 100 days of ABMT. Autopsies were performed for all patients with TR deaths. With a median follow-up of 4.6 years (range 1.2–7.4 years), the actuarial overall survival was 41% ± 14% at 5 years. We observed 37 deaths, and 10 of these were TR deaths. Among the 24 patients who received thoracic RT before ABMT, there were 8 TR deaths, 3 of these solely attributable to radiation pneumonitis. The remaining 5 TR deaths all had respiratory failure with complicating sepsis as a major medical problem. The interval from RT to ABMT was shorter for 8 patients dying of TR death (mean 37 days; range 0–103 days), than for the 16 survivors (mean 105 days; range 0–263 days) ($P = 0.026$). Among 9 patients with ABMT within 50 days of thoracic RT, 6 had TR death. In contrast, among the 35 patients without thoracic RT (26 no RT, 9 non-thoracic RT), there were only 2 TR deaths. The 4 patients treated with mantle RT post-ABMT had no serious pulmonary complications. The use of thoracic RT before HDCT and ABMT was associated with a high post-transplant mortality rate. It was most evident in patients who received thoracic RT within 50 days prior to ABMT, or when the target volume included large volume of lung. We recommend that the use of post-transplant RT be investigated to decrease TR mortality. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: Hodgkin's disease, radiation therapy, autologous bone marrow transplant, treatment toxicity
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INTRODUCTION

THE TREATMENT for Hodgkin's disease with radiation therapy and chemotherapy is very successful in producing remission. However, a significant proportion of patients either fail to attain complete remission with initial therapy, or relapse following initial complete response. These patients have a poor prognosis with conventional salvage therapy with radiation therapy [1] or standard chemotherapy regimens [2, 3]. High-dose chemotherapy (HDCT) with autologous bone marrow or peripheral blood stem cell support (ABMT) has become the preferred treatment for these patients. Many series report disease-free survival of 40–70% at 3 or 4 years following

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HDCT and ABMT [4–15]. In patients who received extensive prior treatment with radiation therapy (RT) and chemotherapy (CT), the treatment-related mortality rate following HDCT and ABMT for patients transplanted in the late 1980s to early 1990s varied between 4 [12] and 21% [11]. This high mortality rate is a significant obstacle to improving the cure rate of patients with relapsed or refractory Hodgkin's disease by HDCT and ABMT. An important contributor to post-ABMT morbidity and mortality is pulmonary toxicity [4, 8, 9, 11] for which RT has been suggested to play a major role. Since late 1986, the University of Toronto ABMT programme treated poor prognosis recurrent Hodgkin's disease patients with HDCT and ABMT. RT was frequently applied in sequence with salvage CT in an attempt to achieve complete control of the disease before HDCT and ABMT. The early Toronto experience has been previously reported [4]. Because the previous report identified three cases of fatal interstitial pneumonitis, this study was undertaken to examine the relationship between radiation therapy and the occurrence of post-transplant fatalities. The aim was to identify factors that contributed to a high risk of treatment-related mortality, specifically to the problem of respiratory complications following ABMT.

PATIENTS AND MATERIALS

Patients

Between December 1986 and December 1992, 90 patients with HD were treated with HDCT and ABMT in Toronto. Fifty-nine of these had all or part of their treatment (RT and/or CT) at the Princess Margaret Hospital, and they form the basis of this report. Patient characteristics are summarised in Table 1. The median age at ABMT was 29 years (range, 16–47 years). The median time from initial diagnosis to ABMT was 2.8 years (range, 0.76–10.9 years). The initial treatment at diagnosis consisted of RT alone in 8 patients, combined modality therapy (CMT) in 20, and CT alone in 31. The initial treatment details are summarised in Table 2.

Table 1. *Patient characteristics*

	No.
Gender (Male:female)	32:27
Initial Ann Arbor Stage (No.)	
I	3
II	24
III	15
IV	16
X	1
A	25
B	33
X	1
Histology	
Lymphcyte predominant	1
Nodular sclerosis	46
Mixed celluarity	12
Number of chemotherapy regimens prior to salvage chemotherapy	
1	38
2	16
3–4	5
Remission duration	
$\leq$ 12 months	41 (13 induction failures)
13–24 months	8
> 24 months	10

Salvage treatment and ABMT

HDCT + ABMT was performed for chemotherapy-refractory (13 patients) or relapsed (46 patients) HD. When relapses following chemotherapy or CMT were considered (i.e. ignoring relapses after RT alone for stage I or II disease), there were 29 patients with 1 relapse, 13 with 2 relapses, and 4 patients with 3 or more relapses prior to ABMT. There were no chemotherapy-naive patients entering intensive therapy directly following the failure of RT. Salvage CT protocols are detailed in Table 3. The median number of courses of salvage CT received was two (range 0–10 courses). RT was incorporated in the salvage treatment with the intent to achieve complete control of active disease at relapse or disease progression. RT was given pre-ABMT in 33 patients (3 mantle, 8 mantle with lung, 7 modified mantle excluding axillae, 4 involved field, 1 mantle with total body irradiation (TBI), 1 TBI, and 9 non-thoracic), and post-ABMT in 4 patients (2 mantle, 2 modified mantle). Planned RT tumour dose was 35 Gy over 4 weeks (median 35 Gy, range 25–40 Gy); lower doses were used for lung RT (15–17.5 Gy, corrected for lung inhomogeneity), through transmission blocks. All patients received etoposide 60 mg/kg on day -4 and melphalan 160 mg/m^2 on day -3, with cryopreserved autologous marrow thawed and infused on day 0. Patients were nursed in single rooms in reverse isolation until the absolute neutrophil count reached $\geq 0.5\times10^9$/l for 2 consecutive days. Post-transplant care and follow-up has been described previously [4]. Treatment-related (TR) mortality was defined as any death occurring within 100 days of ABMT. Autopsies were performed for all patients with TR deaths.

RESULTS

We observed 37 deaths, 10 of whom were treatment-related (TR) deaths (Table 4). With a median follow-up of 4.6 years

Table 2. *Initial treatment*

Radiation therapy (RT) only (n = 8)*			
Mantle	2		
Mantle + paraaortic/spleen	6		
Combined modality therapy (n = 20)			
Chemotherapy:		Number of courses:	
MOPP	9	3	2
ABVD	1	4–5	2
MOPP/ABVD	9	6	9
MOPP–ABV hybrid	1	7–8	7
RT:			
Mantle	9		
Mantle + paraaortic/spleen	6		
Involved field	5 (axilla 1, neck 1, spine 1, mediastinum 2)		
Chemotherapy only (n = 31)		Number of courses:	
MOPP	4	3–5	3
ABVD	2	6	15
MOPP/ABVD	14	7–8	9
MOPP–ABV hybrid	8	9–10	4
VECABOP	2		
ChVPP/EVAP	1		

*These 8 patients had recurrences treated with chemotherapy and were either refractory or relapsed following chemotherapy. MOPP, mechlorethamine, vincristine, procarbazine, prednisone; ABV, doxorubicin, bleomycin, vinblastine; ABVD, ABV + dacarbazine; VECABOP, vinblastine, etoposide, cyclophosphamide, doxorubicin, bleomycin, vincristine, prednisone; ChVPP/EVAP, chlorambucil, vinblastine, procarbazine, prednisone.

Table 3. Salvage treatment before HDCT and ABMT

Chemotherapy	No
DHAP only	32
MiniBEAM only	7
DHAP + other	4
DHAP + miniBEAM	8
ABVD	2
MOPP–ABV hybrid	1
CHl/VP/pred	1
No chemotherapy*	4

Number of courses of salvage chemotherapy: median 2, mean 2.8, range 0–10. *2 had salvage radiation therapy, 1 resected and in complete remission, 1 unsure salvage. ABMT, autologous bone marrow transplantation; HDCT, high-dose chemotherapy; DHAP, dexamethasone, cytarabine, cisplatinum. Other abbreviations as in Table 2 legend.

(range, 1.2–7.4 years), the actuarial overall survival was 52% ± 13% at 3 years, and 41% ± 14% at 5 years (Figure 1). Among the 24 patients who received thoracic RT before ABMT, there were 8 TR deaths, with 3 solely attributable to radiation pneumonitis. The remaining 5 TR deaths all had sepsis as a major medical problem with complicating respiratory failure (Table 4). The RT technique and volume are summarised in Table 5.

Thoracic RT, its timing and TR death

The interval from pre-ABMT RT to ABMT was shorter for the 8 patients who died (mean 37 days; range 0–103 days), than for the 16 patients with no TR death (mean 105 days; range 0–263 days) ($P = 0.026$). The distribution of the time from RT completion to ABMT in these two groups of patients exposed to thoracic RT prior to ABMT is shown in Figure 2. Among 9 patients transplanted within 50 days of finishing thoracic RT, 6 died of TR deaths. Histological evidence of residual Hodgkin's disease was found at autopsy in only 2 out of the 8 patients who died of treatment toxicity in the thoracic RT group. In contrast, among the 35 patients without thoracic RT (26 no RT, 9 non-thoracic RT), there were only 2 TR deaths (Table 4, patients 9 and 10), one due

Table 4. Summary of the 10 cases of treatment-related mortality

Patient (age (years) sex)	Initial stage/ Prior RT	ABMT date	Time from RT to ABMT	RT or other therapy	Dose to mediastinum	Lung dose	Symptom onset to death	Time from ABMT to death/ major causes	Autopsy findings
1 (23 M)	cSIIIB/No	24-7-1987	0 d	Mantle + TBI	43.8 Gy + 5 Gy	5 Gy	6 d	68 d RT pneumonitis	Pneumonitis, BO No HD
2 (40 M)	cSIIIB/No	13-1-1989	28 d	Mantle	35 Gy	R 16 Gy L 16 Gy	7 d	87 d RT pneumonitis	Diffuse alveolar damage, No HD
3 (18 F)	cSIVA/No	5-6-1989	26 d	Mantle	35 Gy	R 17.5 Gy L 17.5 Gy	3 d	24 d Pneumonia, ARDS	Limited examination: candida sepsis and pneumonia
4 (29 M)	cSIVA/No	30-4-1990	102 d (intentional delay)	Mantle	35 Gy	R 15 Gy	130 d	77 d Pleural fluid, pneumothorax, sepsis	Pleural/med fibrosis, cardiac tamponade, RT pneumonitis No HD
5 (30 M)	cS1A/ Neck RT	19-10-1990	18 d	Left hemi-mantle	35 Gy	No	5 d	19 d colitis, sepsis, multiorgan failure	Pleural thickening focal alveolar damage, No HD
6 (29 F)	cSIIB/No	23-7-1991	103 d	Mantle	35 Gy	No	5 d	8 d pancytopenia, ARDS	Pulmonary haemorrhage Residual HD
7 (45 M)	cSIIB/No	11-10-1991	11 d	Modified mantle	35 Gy	No	9 d	18 d Sepsis, pulmonary failure	Pleural fluid, diffuse alveolar damage, bacterial pneumonia, No HD
8 (29 F)	cSIVB/ IF med: 30 Gy	20-12-1991	16 d	IF med + inverted Y	25 Gy	No	55 d	74 d Jaundice, pulmonary failure	Pleural fluid, pulmonary consolidation, Residual HD
9 (33 M)	cSIIA/ EF RT: 35 Gy	10-2-1989	No RT	Left pneumon-ectomy	During DHAP for bleeding		20 d	89 d Sepsis, pulmonary failure	Diffuse alveolar damage of remaining R lung Residual HD
10 (41 F)	cSIIIB/No	21-6-1991	No RT				8 d	73 d Clostridial sepsis	Severe colitis Residual HD

cS, clinical stage; med, mediastinum; IF, involved-field; RT, radiation therapy; BO, bronchiolitis obliterans; ARDS, acute respiratory distress syndrome; HD, Hodgkin's disease; TBI, total body irradiation; EF, extended field; L, left; R, right. Other abbreviations as in Table 3 legend.

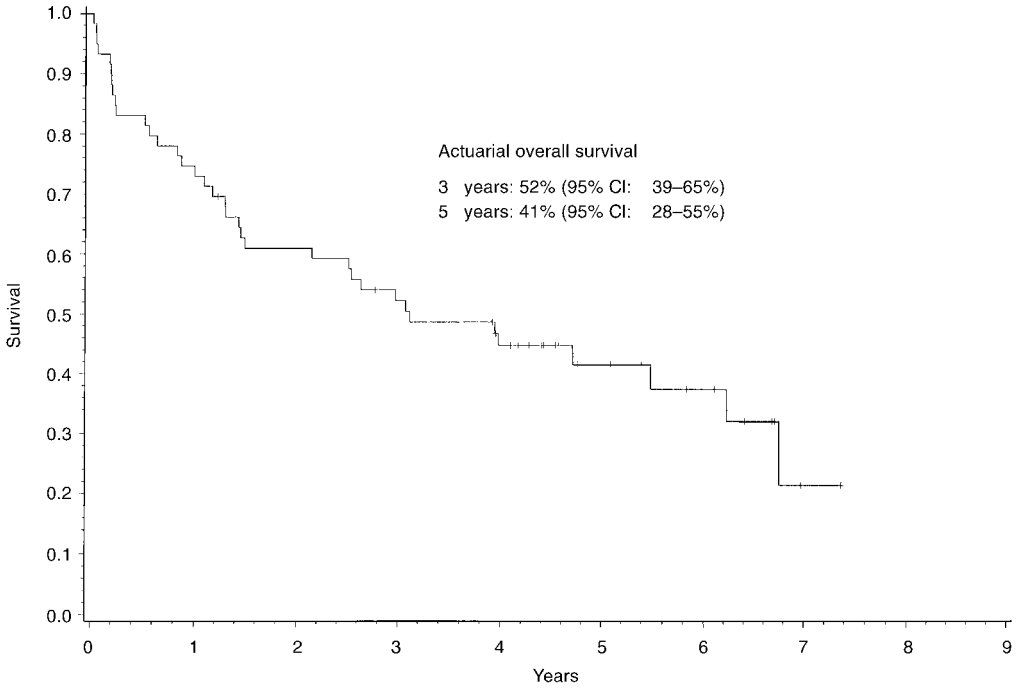

Figure 1. Actuarial overall survival for 59 patients with relapsed or chemotherapy-refractory Hodgkin's disease following high-dose chemotherapy and autologous bone marrow transplantation.

to sepsis and pulmonary failure in a patient with a previous pneumonectomy, and the other with congenital spherocytosis who died of severe sepsis with colitis and fascitis due to *Clostridium septicum*. Both patients had residual Hodgkin's disease at autopsy. The four patients with mantle RT after ABMT had no serious pulmonary complications.

Thoracic RT volume and TR death

Of 10 patients receiving unilateral (15–16 Gy), or bilateral lung irradiation (5–17.5 Gy), 4 died from toxicity (Table 5). Three of these patients had post-mortem findings compatible with radiation pneumonitis characterised by diffuse alveolar damage, interstitial changes in lungs and/or fibrotic changes in pleura and mediastinal tissues (Table 4, patients 1, 2 and 4). Pulmonary infection was not identified and sepsis was not a major component, except for one patient who suffered candida sepsis and adult respiratory distress syndrome (ARDS). The four other deaths in patients who received a full mantle RT ($n = 1$) or more limited field RT ($n = 3$) were associated with other non-pulmonary complications such as sepsis ($n = 3$), colitis ($n = 1$), and jaundice possibly due to veno-occlusive disease of the liver ($n = 1$). Post-mortem findings consisted of pulmonary haemorrhage in 1, diffuse alveolar damage in 1, and focal consolidation and/or alveolar damage in the remaining 2 patients. These latter findings are less specific for radiation pneumonitis.

Beyond 100 days of ABMT, other causes of death included Hodgkin's disease in 22 patients, secondary acute myeloid leukaemia in 3 patients (1, 4 and 6 years after ABMT), progressive multifocal leucoencephalopathy in 1 patient, and hepatitis B infection with liver failure in 1 patient. At the time of this report, 22 patients were alive, with 20 of these being free of Hodgkin's disease. One patient developed a diffuse large cell (B-cell) lymphoma 3 years after ABMT, was treated with chemotherapy and is alive and well 3 years post-treatment.

Table 5. *Radiation therapy* before HDCT and ABMT*

	Thoracic RT ($n = 24$)			Non-thoracic RT ($n = 9$)	
	n	Toxic death		*n*	Toxic death
Mantle	3	1	Inverted Y	3	–
Mantle + 1 lung†	4	1	PA/spleen	2	–
Mantle + bilateral lung‡	5	3	Axilla	2	–
Modified mantle§	6	1	Neck	1	–
Hemi-mantle	1	1	Axilla + neck	1	–
Involved field (IF) chest or mediastinum‖	3	1			
Chest wall¶	1				
TBI, 5 Gy	1				

Prescribed doses: 35 Gy 20; 28 Gy 1 (IF left chest, prior mantle 35 Gy); 25 Gy 2 (both IF mediastinum); 5 Gy TBI 1. *26 pts received no RT, with 2 toxic deaths (previous RT: 19 pts, no previous RT: 7 pts (4 received RT post-ABMT)). †Unilateral lung doses: R 16 Gy, L 16 Gy, R 15 Gy, R 15 Gy. ‡Bilateral lung doses: 17.5 Gy, 17 Gy, 16 Gy, 15 Gy, 5 Gy TBI. §Modified mantle excluding axillae. ‖2 patients had involved field mediastinum (25 Gy, 25 Gy) and abdominal RT (30 Gy, 35 Gy). ¶3 field technique to right chest wall, 35 Gy. Other abbreviations as in Table 3.

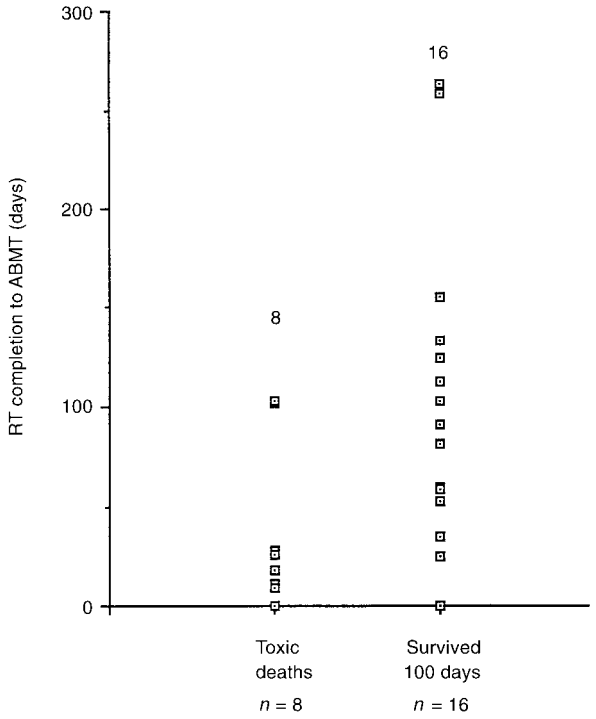

Figure 2. Time interval from completion of radiation therapy (RT) to autologous bone marrow transplantation (ABMT) (days), plotted for the 24 patients who received thoracic RT pre-ABMT, according to treatment-related mortality.

DISCUSSION

The use of radiation therapy (RT) has contributed to the successful management of Hodgkin's disease (HD) in the last 50 years. While extended-field RT is often curative for stage I and II HD [16], CT is required for optimal results for the treatment of stage III and IV disease. Following the successful use of the MOPP regimen in the 1960s to 1970s, newer less toxic and more effective regimens containing anthracyclines have been developed [17]. Patients not achieving complete response to initial chemotherapy or relapsing after complete response are candidates for HDCT and ABMT. Although there is only one small randomised trial supporting the HDCT approach [18], many phase II studies reported prolonged disease-free survivals in the range of 40–70% at 3–5 years in patients with a poor prognosis treated with HDCT and ABMT [4–15, 19, 20]. Many of these programmes incorporate RT in the salvage therapy plan before ABMT. This is based on the success of RT in controlling HD even when the tumour is bulky. The central issues are whether the use of RT contributes to disease control in the ABMT setting, whether the RT volume should cover the involved site (involved field) or encompass adjacent uninvolved nodal sites (extended field), and the optimal timing of RT in relation to HDCT and ABMT.

Our approach has been to use both chemotherapy and RT in the pre-ABMT setting to achieve maximum tumour response, preferably a complete response before instituting HDCT and ABMT [4]. Although the definition of RT target volume is always individualised, our philosophy has been to apply extended field techniques (eg. mantle, inverted Y) in sequence with salvage CT before HDCT and ABMT. We became concerned that this approach contributed to a high post-transplant fatality rate because of possibly RT-related respiratory complications. Other groups have also documented a similar problem. Yahalom and associates reported a 17% fatality rate in 47 patients treated with involved field RT to 15 Gy and total lymphoid irradiation (TLI) to 20 Gy followed by high-dose cyclophosphamide and etoposide and ABMT [8]. The majority of the fatalities were due to pulmonary failure [8, 21]. A direct relationship of the pulmonary complications to the irradiated lung volume, RT dose or the timing of RT pre-ABMT was not reported.

We examined the contributing effects of RT to toxicity and mortality in detail. For patients receiving RT before HDCT and ABMT, post-transplant mortality was confined to those who had received thoracic RT (8/24, 33%), whilst there were no treatment-related deaths in 9 patients who received RT to extra-thoracic areas. There was also a significant correlation between the volume of irradiated lung and the fatality rate, although some patients who received treatment to more limited thoracic fields with modified mantle and involved mediastinal fields also suffered treatment-related death (3/11, 27%). Our data suggested that respiratory failure which occurred when large volumes of lung tissues were irradiated was attributable to radiation pneumonitis, but in the more limited modified mantle fields, radiation may not be a direct cause of pulmonary failure as various other causes that can have adverse effects on lung function were also present. Other contributing factors may have included sepsis with pneumonia, drug toxicity (e.g. previous bleomycin, high-dose melphalan), fluid overload, and cardiac failure. The majority of our patients (57/59) had previous exposure to bleomycin and doxorubicin. At autopsy, most of our patients had diffuse alveolar damage with or without haemorrhage. Alveolar haemorrhage is a well described syndrome in the post-transplant setting in patients who had received CBV (cyclophosphamide, BCNU, VP-16) + total body or total lymphoid irradiation from the Memorial Sloan-Kettering Cancer Center [21]. Residual or progressive Hodgkin's disease may contribute but was not a major factor in our patients because only 2 of the 8 patients in the thoracic radiation group had post-mortem confirmation of residual Hodgkin's disease which were of minimal extent.

The timing of RT in relation to HDCT and ABMT is controversial. The advantages of using RT before transplantation were reviewed by Yahalom [22, 23]. They included the benefits of maximal cytoreduction before HDCT, as patients who achieved complete remission before ABMT had a better outcome than those transplanted in partial remission [4, 24]. Haematological tolerance is better for RT given before transplantation, as a long engraftment period after ABMT can delay the use of RT or increase its myelotoxicity when given after transplantation. There is also a theoretical concern of RT exposure of reinfused haematopoietic stem cells as an added risk factor for myelodysplasia. However, our data suggest that thoracic RT given within 50 days before ABMT is associated with a high rate of treatment-related mortality. In a series of 56 patients treated with CBV and ABMT in Vancouver, patients with chest radiation before ABMT had a significant increase in interstitial pneumonitis compared with those not irradiated or remotely irradiated [11].

During the time period of this analysis, we changed our practice to limit radiation field size and lung exposure, reduced the use of RT before ABMT for patients with non-bulky disease that responded completely to CT, or gave RT after ABMT. The four patients treated with the mantle (2) or modified mantle techniques (2) after HDCT and ABMT

tolerated treatment well with no significant pulmonary toxicity. The strategy of giving RT after ABMT provided further cytoreduction with the HDCT and allowed smaller radiation fields with a resulting decrease in radiation to normal tissues. This approach is preferred by some investigators [25–27]. However, it must be noted that our experience with pulmonary toxicity largely related to the use of wide-field irradiation, including lung(s), and was given within a few weeks before ABMT, in the context of the first 6 years of the ABMT programme. It is quite possible that smaller RT volumes (involved fields) and/or a longer interval from RT to ABMT could also reduce the risk of TR mortality. This may not be desirable if the disease coverage is compromised by the use of smaller RT volumes, or the delay in HDCT and ABMT leads to recurrence or progression of disease outside the radiation fields. However, improved awareness of these issues with more careful planning of radiation fields, along with better post-ABMT supportive care can also reduce the TR mortality rate. The Memorial Hospital experience with pre-ABMT involved-field RT and TLI followed by CBV initially reported a treatment mortality rate of 17% (8/47) [8], decreasing to 6% in 1990–1994 and 2% in 1995–1997 [23]. A similar reduction in mortality was also reported from the University of Nebraska between 1987 and 1991 [28], probably unrelated to the use of RT.

We conclude that thoracic RT contributes significantly to the risk of treatment-related mortality in patients with relapsed/refractory Hodgkin's disease undergoing high-dose therapy and ABMT. The optimal strategy to reduce this risk has not been clearly defined. Possibilities include the use of involved field RT, prolongation of the RT–ABMT interval, or delaying the RT until after marrow engraftment. The contribution of RT to survival in this setting should be tested in a phase III trial.

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