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Conditioning regimens

Outpatient total body irradiation as a component of a comprehensive outpatient transplant program

C Bredeson[1], G Perry[2], C Martens[3], S McDiarmid[3], I Bence-Bruckler[3], H Atkins[3], D Serna[1], H Hopkins[3], J Mikhael[4], P Genest[2] and L Huebsch[3]

[1]*IBMTR/ABMTR Statistical Center, Medical College of Wisconsin, Milwaukee, WI, USA;* [2]*Ottawa Regional Cancer Center, Ottawa, Ontario, Canada;* [3]*Ottawa Hospital Blood and Marrow Transplant Program, Ottawa, Ontario, Canada; and* [4]*The Princess Margaret Hospital, Toronto, Ontario, Canada*

Summary:

Outpatient total body irradiation (TBI) as part of a comprehensive outpatient transplant program was delivered to 142 of 167 (85%) consecutive patients receiving TBI-based conditioning therapy. Outpatients received either a single fraction of 500 cGy (110 patients) or 1200 cGy in six fractions over 3 days (32 patients). Patients were assessed daily and were administered oral ondansetron and dexamethasone for prophylaxis of nausea and vomiting as well as i.v. hydration. Accommodation during outpatient TBI-based conditioning was either the patient's home if within 30 min of the hospital, a hotel on the hospital grounds or on a closed hospital ward. None of the 142 patients required admission to the inpatient program during their TBI. There was no difference in 100-day mortality between those receiving TBI as an outpatient (9%) *vs* as an inpatient (16%). Of four deaths occurring within the first 14 days post transplant, none could be attributed to receiving TBI as an outpatient. Two hundred and six inpatient days were saved through the delivery of outpatient TBI. A comprehensive outpatient program, appropriate patient selection, daily hydration, the use of prophylactic 5HT3 antagonist anti-emetic therapy all contribute to the safe delivery of outpatient TBI.
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High-dose therapy and stem cell transplantation is increasingly used in the management of hematological malignancies and other non-malignant disorders. Total body irradiation (TBI)-based regimens are often used as the conditioning regimen pretransplant. Traditionally, hematopoietic stem cell transplantation (HSCT) including the delivery of TBI as part of the pretransplant conditioning therapy has been performed on an inpatient basis. The introduction of outpatient transplantation programs, however, has resulted in all aspects of stem cell transplantation including the delivery of TBI being considered for a shift from an inpatient to outpatient setting. Improvements in the control of nausea with effective non-sedating anti-emetics,[1] the knowledge that for most patients their blood counts are still adequate during the days of radiation and a better developed infrastructure for addressing patient problems as they arise within outpatient transplant programs make outpatient TBI a reasonable consideration. Initial reports on the feasibility of this approach in select patients were favorable both from the perspective of tolerability and for the potential economic benefits.[2–5] We report on the Ottawa Hospital Blood and Marrow Transplant Program's (OH BMTP) experience with outpatient TBI delivered as part of a comprehensive outpatient transplant program.

Correspondence: Dr C Bredeson, IBMTR/ABMTR Statistical Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA
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Patients and methods

In April 1995, the OH BMTP established a 12 h per day, 7 days per week, outpatient transplant program. Initially two then four inpatient beds on the existing hematology/oncology/BMT ward were utilized as outpatient beds allowing multiple patients to use the same bed throughout the 12 h period that the beds were open each day. Care of inpatients and outpatients was provided by the same multidisciplinary transplant team. Patients participating in the outpatient program were assessed daily by the transplant team and had blood counts and serum chemistries drawn daily. Outpatient care available through the outpatient program included the pretransplant conditioning regimen, anti-emetics, TBI, stem cell graft infusion, intravenous hydration, electrolyte replacement, intravenous antimicrobials, blood product transfusion support, growth factor injection, central venous catheter care and general nursing care. All patients had an indwelling central venous catheter placed prior to starting pretransplant conditioning therapy. TBI was administered by the same radiation

oncology team using the same bunker and linear accelerator at the Ottawa Regional Cancer Center (ORCC) whether the patient was an inpatient or an outpatient.

Patients could participate in the outpatient program if their treating physician felt they were medically suitable based on performance status, co-morbidities and planned therapy, lived or had temporary accommodation within an acceptable distance of the hospital (see below) and were willing to participate in the outpatient program which included the tracking of medication usage, temperature and symptoms. In addition, all patients participating in the outpatient program were required to have a caregiver available to them 24 h a day. The caregiver could be a family member or friend who would be able to assist the patient in taking scheduled and prn medications, monitoring their temperature, measuring their intake and output and assisting in their travelling to and from the outpatient unit.

Due to the geographic referral area for the OH BMTP, several options for accommodation were required to meet the needs of the patients and their caregivers. Patients within a 30 min drive of the hospital could stay at their home. Patients could also stay at Rotel, a not-for-profit motel located on the grounds of the University of Ottawa Health Sciences complex. Patients and their caregiver were also able to stay on a hospital ward that was closed (ie not being used for patient care by the hospital). This ward was located one floor above the transplant unit. There was no general nursing care provided to the rooms on this ward but patients were supplied with a telephone, access to a TV lounge and had an emergency call system to be used in the case of a medical emergency. Calls from patients on the closed ward were handled in the same manner as calls from other outpatients residing off site. Patients in Rotel or on the closed ward ate meals either in the hospital cafeteria or at outside restaurants.

Patients received pretransplant conditioning regimens based on disease and donor type. For patients in the outpatient program, their conditioning regimen was delivered as an outpatient. In general, patients with multiple myeloma or non-Hodgkin's lymphoma or low grade lymphoproliferative disorders received an autologous graft after the regimen of etoposide (60 mg/kg) + melphalan (140 mg/m^2) and single fraction TBI (5 Gy) on day 0 (VP16CyTBI). Leukemic patients receiving allogeneic transplants whether from HLA-matched related, mismatched related or matched unrelated donors received a standard conditioning regimen of cytoxan (120 mg/kg or 180 mg/kg) and TBI 1200 cGy in six fractions over 3 days (CyTBI) or a regimen of cytarabine (2 g/m^2 every 12 h for six doses) + cytoxan (120 mg/kg) and TBI 1200 cGy in six fractions (AraCCyTBI).

On the days of TBI, patients would be seen in the outpatient unit prior to their TBI appointment for routine blood work and clinical assessment. Patients took oral ondansetron 8 mg every 12 h and oral dexamethasone 8 mg twice daily to prevent nausea and vomiting. Initially patients assessed as requiring intravenous (i.v.) hydration were started on i.v. fluids prior to their morning TBI appointment, returning to the outpatient unit after their TBI to be disconnected once they had received 1 liter of i.v. hydration. Eventually, it became standard practice for all patients to receive once daily i.v. hydration as part of the outpatient program. Patients receiving fractionated TBI would return to their accommodation after their morning fraction and would go directly to their afternoon appointment at the TBI unit. Patients would take a repeat dose of ondansetron and dexamethasone prior to their afternoon fraction of TBI. Patients could also take oral prochlorperazine 10 mg every 4 h as required to control nausea.

TBI was given by linear accelerator using a translating patient couch system developed at the ORCC.[6] With this technique, the couch is placed on the floor beneath the accelerator head. A stepping motor attached to a drive screw moves the couch through the radiation field. Patients are treated in both prone and supine positions. Custom-made lead lung attenuators are used on each field. The attenuator thickness (1–3 mm) is determined from a treatment planning CT scan, and is designed to ensure that the lungs receive the same dose as other tissues. Without attenuators lungs receive approximately 10% higher dose. A 2.4 cm thick polymethyl methacrylate beam spoiler is used to provide a full skin dose. Radiation is given at a dose rate of 80 cGy/min at mid-plane. Total time in the radiation bunker per radiation treatment was $<$60 min.

Patients in the outpatient program were admitted to the outpatient program on the day they started conditioning therapy. All care was provided through the outpatient program until the patient recovered from the transplant and was able to be discharged back to the clinic or until medical complications or management issues arose that necessitated admission to the inpatient ward. Patients could be transferred between the inpatient and outpatient programs as tolerated during the course of their transplant.

Demographic data and descriptive statistics are provided for all patients receiving TBI-based conditioning therapy. Patients are grouped based on whether they received their TBI as an inpatient or an outpatient. One patient received her first dose of fractionated TBI as an inpatient because she was also undergoing plasmapheresis for ABO incompatibility with the donor. The patient was transferred to the outpatient program for the remaining 2 days of her TBI and is analyzed with the outpatient group. Chi square or Wilcoxon rank-sum tests were used to compare categorical and continuous variables respectively between the inpatient and outpatient groups. The number of patients transferred from the outpatient program to the inpatient program during TBI-based conditioning and the reasons for transfer were documented. The number of inpatient days (nights in hospital) saved by administering TBI as part of the outpatient program was determined. Deaths occurring $<$14 days post transplant were reviewed to determine whether they could be attributed to participation in the outpatient program. One hundred day and 1 year survival were estimated using the method of Kaplan and Meier. 95% confidence intervals for all probabilities and *P* values of pairwise comparisons were derived from pointwise estimates and calculated using standard techniques.[7]

All patients signed a hospital informed consent to participate in the outpatient program. Patients medically unstable, unable to meet the requirements for the outpatient program or who declined participation in the outpatient program received their TBI as an inpatient.

Results

From April 1995 to December 1998, 167 patients in the OH BMTP received TBI-based conditioning regimens prior to either autologous or allogeneic HSCT. Patient demographics, disease and therapy characteristics are summarized in Table 1. Data on patients who received their TBI as an outpatient are summarized separately from those who received their TBI as an inpatient. Forty-eight patients received 1200 cGy fractionated TBI and 119 received a single fraction of 500 cGy. TBI was delivered as a component of the following conditioning regimens: VP16MelTBI (117 patients), CyTBI (46 patients) or AraCCyTBI (four patients). Sixty-two patients received allogeneic transplants, of these 32 were matched sibling donors, 25 matched unrelated donors, four haploidentical related donors and one twin.

Of the 167 patients, 25 (15%) did not receive their TBI as an outpatient. The reasons for receiving TBI as an inpatient were: physician decision for medical reasons (eight patients), lack of accommodation within an acceptable travel time to the OH and no available acceptable alternate accommodation (six patients), patient choice (six patients), lack of caregiver (four patients) and language barrier (one patient). The medical reasons were poor performance status due either to refractory or relapsed disease at the start of conditioning (six patients), unstable type 1 diabetes mellitus (one patient) and the program's first haploidentical transplant recipient (one patient). There were significant differences in the demographic and disease characteristics of the patients who received their TBI as an outpatient compared to those receiving it as an inpatient (Table 1). Patients receiving TBI as an outpatient were older, more likely male, more likely had a lymphoproliferative disorder for which they were receiving a regimen including a single fraction TBI followed by an autologous transplant. Forty-seven of 61 patients (77%) who were undergoing allogeneic transplants received their TBI as an outpatient and 95 of 105 patients (90%) undergoing autologous transplants received their TBI in the outpatient program. Of a total 263 patient days of TBI, 206 (78%) were delivered as outpatients. Overall, the median (range) length of stay from the initiation of conditioning therapy until the patients were discharged back to clinic was 23 (13–105) days. Of this, a median (range) of 12 (0–91) days were in the outpatient program.

No deaths or medical emergencies occurred during the outpatient TBI. No patients were transferred from the outpatient program to the inpatient program during their TBI-based conditioning regimen.

Sixteen patients died <100 days post transplant. The causes of death and number of days post transplant are listed in Table 2. Of these 16 deaths, four occurred less than 2 weeks post transplant (days +9, +9, +10, +11), all in patient's who received their TBI-based conditioning therapy as an outpatient. Upon review, the two patients who had intracranial hemorrhages and the patient with esophageal bleeding all had normal blood counts during their conditioning regimen. The patient with esophageal bleeding had known amyloidosis and a propensity to easy bruising. There was no indication from their medical records of any problems during their conditioning therapy that would have predicted the bleeding complications that later developed. The patient who died of vancomycin-resistant enterococcus

Table 1 Demographics, disease and treatment characteristics

	Outpatient TBI n = 142	*Inpatient TBI n = 25*	*P value*
Age, median (range), years	49 (9–67)	39 (13–64)	<0.01
Sex, male (%)	97 (68)	11 (44)	0.02
Diagnosis			
Acute leukemia	18	12	0.01
Chronic leukemia	9	2	
Hodgkin's and non-Hodgkin's lymphoma	69	6	
Lymphoma			
Multiple myeloma	43	5	
Other	3	0	
TBI Dose			
500 cGy	110	9	<0.01
1200 cGy	32	16	
Conditioning regimen			
MelVP16TBI	107	10	<0.01
CyTBI	31	15	
AraCCyTBI	4	0	
Type of BMT			
Autologous BMT	8	2	
Autologous PBSCT	84	7	
Autologous BM + PBSCT	3	1	
Matched sibling BMT	26	2	
Matched sibling PBSCT	2	2	
Related haploidentical BM + PBSCT	1	3	
Syngeneic BMT	0	1	
Matched unrelated BMT	18	7	

Table 2 Causes of death occurring <100 days post transplant

	Outpatient TBI		*Inpatient TBI*	
	n	*Days post transplant*	*n*	*Days post transplant*
Bacterial infection/sepsis/multiorgan failure	5	9, 19, 20, 38, 50	1	81
Relapse	2	65,94	1	95
Intracranial hemorrhage	2	9, 11	0	
Graft failure	1	75	0	
Esophageal hemorrhage	1	10	0	
CMV pneumonitis	1	66	0	
Graft-versus-host disease	0	1	42	
Ischemic heart disease	0	1	53	

(VRE) sepsis and VOD had had an uncomplicated course during her conditioning therapy and until approximately 3 days post transplant when she rapidly deteriorated. The patient was not known to be a carrier of VRE.

The 100 day mortality of the outpatient group (9%; 95% CI, 5–15%) was not statistically different to the inpatient group (16%; 95% CI, 6–27%). Survival curves for the two groups are presented in Figure 1. One year overall survival for the outpatient group (79%; 95% CI, 71–85%) and the inpatient group (64%; 95% CI, 42–79%) was not statistically different.

Discussion

Our report demonstrates that TBI can safely be delivered as part of a comprehensive outpatient transplant program and can result in a significant reduction in the number of inpatient days required to deliver pretransplant TBI-based conditioning therapy. Previous reports document the safe delivery of TBI to small numbers of selected pediatric or adult transplant patients.[2,3,5] Applegate *et al*[4] summarized their experience with outpatient TBI in 68 pediatric patients focusing on the feasibility as a result of the improved efficacy of 5-HT3 antagonists. None of the prior reports addressed the possibility that outpatient TBI may adversely effect the period immediately following TBI resulting in early adverse outcomes post transplant. With our approach of delivering outpatient TBI as an integral part of a comprehensive outpatient transplant program. 85% of patients were able to receive TBI-based conditioning therapy as an outpatient. Furthermore, in part due to appropriate patient selection, the delivery of outpatient TBI was not associated with medical complications requiring transfer to the inpatient unit or early deaths that could be attributed to the care model.

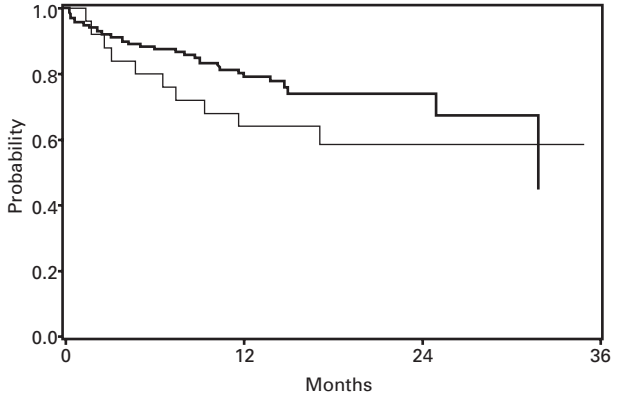

Figure 1 Probability of survival post transplant. (▬), outpatient TBI; (——), inpatient TBI. P = NS.

Differences between patients who received TBI as an inpatient *vs* as an outpatient reflect the age and sex demographics of the diseases for which patients are considered for transplant as well as the conditioning regimen associated with the transplant approach (allogeneic *vs* autologous) specific to those diseases. They also reflect the medical decisions of the transplant physicians as to the suitability of particular patients for the outpatient program and patient choice should they choose not to participate in the outpatient program.

Our study confirms that physicians can identify which patients are not suitable for participation in such a program. Three of the four deaths that occurred <100 days post transplant in the inpatient group were in patients whose physicians felt they were not medically fit enough to participate in the outpatient program while the early deaths in the outpatients could not be linked to participation in the outpatient program.

Other aspects of the outpatient program that contribute to its success are the availability of the care giver, the continuity of care provided by a common multidisciplinary team for both inpatients and outpatients and the advances in supportive care such as long-acting non-sedating anti-emetics and transdermal narcotic patches that facilitate symptom control for outpatients. Accommodation close to the treatment facility, administration of i.v. hydration and the use of 5-hydroxytryptamine receptor antagonist anti-emetics are common features of our program and those that have been previously reported.[2–5]

Along with being well tolerated, outpatient TBI as part of a transplant program was well accepted by patients and care givers. A quality assurance survey regarding the acceptability of outpatient transplants conducted by the OH BMTP in the first 115 patients to participate, indicated that the vast majority of both patients and care givers viewed the experience positively (data not shown).

While outpatient TBI as part of an outpatient program

has allowed us to reduce the hotel costs associated with inpatient days, it may, as has been previously reported result, less in overall cost savings than cost shifting.[8] Furthermore, shifting TBI to the outpatient impacts on how and when members of the health care team can provide education or support to the patient and their family. Nurses in particular have had to modify their time with patients to overlap the delivery of medication with education and supportive counseling. While some attention has been paid to these issues in the medical literature,[9] more is required if outpatient programs are to maintain the high quality of care traditionally associated with inpatient transplant programs.

Outpatient TBI can safely be delivered to autologous and allogeneic transplant recipients including recipients of unrelated allogeneic transplants as part of a comprehensive outpatient transplant program. Maintenance of a consistent care team for both inpatients and outpatients, along with a willingness to adapt new developments in supportive care, can result in a significant reduction in the number of inpatient days without compromising patient safety.

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