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LONG-TERM OUTCOME AFTER STATIC INTENSITY-MODULATED TOTAL BODY RADIOTHERAPY USING COMPENSATORS STRATIFIED BY PEDIATRIC AND ADULT COHORTS

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Purpose: To report the long-term outcome after total body irradiation with intensity-modulating compensators and allogeneic/autologous transplantation, especially in terms of therapy-related toxicity in pediatric and adult cohorts.

Methods and Materials: A total of 257 consecutive patients (40 children and 217 adults) have been treated since 1983 with TBI using static intensity-modulated radiotherapy for hematologic malignancies. The total dose of 12 Gy was applied in six fractions within 3 days before allogeneic (n = 174) or autologous (n = 83) transplantation. The median follow-up was 9.2 years.

Results: The 5-year overall survival rate was 47.9% (49.8% for the adults and 37.5% for the children, p = 0.171). The 5-year tumor-related mortality rate was 23%, and the 5-year treatment-related mortality rate 29.2% (29.5% in the adults and 27.5% in the pediatric patients). Interstitial pneumonitis developed in 28 (10.9%) of 257 patients and in 12.5% of the pediatric cohort. The interstitial pneumonitis rate was 25% in pediatric patients treated with a 12-Gy lung dose compared with 4.2% for those treated to an 11-Gy lung dose. The overall survival rate stratified by lung dose was 26.7% for 12 Gy and 52.4% for 11 Gy (p = 0.001). The incidence of veno-occlusive disease and cataract was 5.8% and 6.6% in all patients and 12.5% and 15% in the pediatric patients, respectively ($p < 0.05$). Secondary malignancies were found in 4.3% of all patients, all in the adult cohort at transplantation.

Conclusion: Static intensity-modulated total body irradiation with a total dose of 12 Gy before allogeneic/autologous transplantation is a successful treatment with good long-term outcome and acceptable therapy-related toxicities. Constraining the lung dose to 11 Gy substantially lowered the actuarial treatment-related mortality. This effect was especially striking in the pediatric patients.

TBI, Bone marrow transplantation in children, Late effects, Compensator, Static intensity-modulated radiotherapy.

INTRODUCTION

Allogeneic and autologous bone marrow and stem cell transplantation are considered curative therapies for adult and pediatric patients with hematologic malignancies resistant to chemotherapy. To achieve engraftment and eradicate cancer cells, the conditioning therapy generally includes fractionated total body irradiation (TBI), in addition to high-dose chemotherapy. However, this therapy concept also carries the risk of severe long-term complications. Increasing the homogeneity of the dose throughout the body, avoiding cold and hot spots, and blocking and reducing the dose to critical structures such as the lung might help to substantially improve the outcome and reduced late sequelae. A high treated partial lung volume itself might represent an important predictive factor for late toxicity (1). Considering TBI, a main problem remains the high volume treated and the inhomogeneity of the dose distribution compared with modern conformal three-dimensional radiotherapy techniques (2, 3). The great variations in body thicknesses and tissue densities over the entire treatment field result in increased dose inhomogeneities using either conventional TBI technique. Both overdosage and underdosage are inevitable and risk complications and/or relapses. Helical tomotherapy or linear accelerator-based intensity-modulated total bone marrow irradiation are modern techniques specifically addressing this important inhomogeneity topic for preconditioning TBI (4, 5).

Another technical solution to this problem is to use compensators. The present report presents the long-term clinical results of a three-dimensional computed tomography (CT)-based planning system with individual hemibody

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compensators for so-called static intensity modulated radiotherapy (sIMRT) TBI. The main rationale for this project was to lower, as much as possible, the typical TBI dose inhomogeneities in the entire treated volume, especially in important organs at risk such as the lung. Furthermore, the intensity modulating compensators were also used to limit the dose to the lung (6, 7). This technique was developed and introduced in 1983. More than 500 patients have been treated using sIMRT at our institution to date.

METHODS AND MATERIALS

Patient characteristics

The data from 257 consecutive patients (40 children and 217 adults) treated at our institution were analyzed. Since 1983, all had undergone TBI with sIMRT before allogeneic (n = 174) or autologous (n = 83) transplantation. The multimodal therapy protocol was performed under the auspices of our institutional review board, and all patients and/or their families provided informed consent. The median age in the pediatric cohort was 10 years. All underwent allogeneic transplantation. Of the 40 children, 19 were girls and 21 were boys; all had different hematologic malignancies in remission. The median age in the adult population was 42 years. The primary disease distribution stratified by the pediatric and adult cohorts is detailed in Table 1.

Table 1. Primary disease distribution

Primary disease	Adults (n)	Pediatric patients (n)
Acute myeloic leukemia	38	10
Chronic myeloic leukemia	25	3
Myelodysplastic syndrome	8	4
Acute lymphoblastic leukemia	51	23
Chronic lymphatic leukemia	18	
Follicular lymphoma (cb cc-NHL)	38	
Mantle cell lymphoma (cc-NHL)	15	
Immunocytoma	12	
Plasmacytoma	8	
Mixed forms	4	
Total	217	40

Abbreviations: cb cc-NHL = centroblastic-centrocytic non-Hodgkin's lymphoma; cc-NHL = centrocytic non-Hodgkin's lymphoma.

Conditioning chemotherapy

Conditioning chemotherapy before allogeneic transplantation consisted of 60 mg/kg cyclophosphamide (3) or etoposide (4). Additional details about the doses and timing of the chemotherapy protocols used have been previously published (7, 8, 9). Graft-vs.-host disease (GVHD) prophylaxis consisted of methotrexate and/or cyclosporine and steroids. Conditioning chemotherapy before autologous transplantation consisted of cyclophosphamide. This protocol has also been previously published (10).

Total body irradiation

Intensity modulating compensators using total body CT scans were generated. The compensator moulds were cut from Styrodur material (Fig. 1) and consecutively filled with Sn granules (time needed, 300 min; Fig. 2).

The dosimetry process consisted of six steps:

1. Radiography of the compensator.
2. Transmission measurements in a water phantom (Table 2 and Fig. 3). For a number of selected points of the mid-plane, the relative dose values (Q_F) were calculated with dose inhomogeneities of <3% using the transmission data (T) and the corresponding depth dose values (PDD) evaluated on the basis of the water phantom measurements and CT scans (S). For a single compensator (without a lung block), the mean value of the relative dose was 1.022 ± 0.021, characterizing the relative homogeneity of the dose distribution.
3. Measurement of the absolute dose and dose rate in a solid phantom for the central ray and lung region. For these measurements, a PMMA (Perspex) phantom was used, taking into account the real geometric setup during treatment of the patient. To determine the dose to the mid-plane, measurements were performed, especially for the lung region, to verify the dose reduction, and for the central ray region to calculate the number of monitor units representing 1 Gy (Fig. 3): $D_{CR}(\text{exp})/D_{CR}(\text{th}) = 1.001 \pm 0.034$ (n = 196). For compensators without a lung block, the experimental relative dose ratio lung vs. central ray was $D_L(\text{exp})/D_{CR}(\text{exp}) = 1.011 \pm 0.039$ (n = 90). The influence of the additional lung block was characterized by the ratio $D_L(\text{exp})/D_{CR}(\text{exp}) = 0.913 \pm 0.032$ (n = 64) and corrected by the reduction ratio of 0.917 (−8.3%) to 0.996 ± 0.035.
4. Calculation of dose for the intersection point of the mid-plane and central ray to determine the monitor units equivalent to 1 Gy.
5. *In vivo* dosimetry using an ionization chamber positioned in between the upper legs. For a small number of patients (and compensators; n = 24), measurements within the mid-plane were done to determine the ratio of the experimental vs. planned (theoretical) dose: $D_{MP}(\text{act})/D_{MP}(\text{pl}) = 0.994 \pm 0.037$. These investigations were needed to measure the actual temperature for correction of the readings.
6. The exact position of the patient relatively to the compensator and the treatment unit during irradiation was verified by daily treatment verification films (Kodak X-OmatV) showing the patient, as well as the compensator, thus ensuring high reproducibility.

Setup was done with the patient in the supine position with a focus–mid-plane distance of 390 cm. The compensator was mounted on standard patient support assembly. The focus–compensator distance varied from 80 to 100 cm, depending on the total body length

Fig. 1. Styrodur mould of compensator.