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The evaluation of a modified technique of Total Body Irradiation in respect of treatment results and toxicity

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Introduction. Total body irradiation (TBI) is a well established part of the conditioning regimen prior to bone marrow transplantation (BMT).
Numerous different techniques are used and every center elaborates own solutions. The aim of our study to present the method of TBI developed in our department, and to discuss the results of treatment with respect of early and late toxicity.
Material and methods. Between 11.2000 and 08.2004 23 patients were treated with fractionated TBI at the Department od Radiotherapy of the M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsawa (MSCMCC). Conditioning chemotherapy and BMT were performed in different hematological departments. All patients were irradiated with a total midline dose of 12 Gy in 6 fractions over 3 consecutive days. Doses to the lung did not exceed 11 Gy.
The TBI method used in our department was evaluated over a few years. The following modifications have been introduced to the previously applied technique: change of photon energy from 6 MV to 15 MV; increase of lung dose from 9 Gy to 11 Gy; the use of an individual bolus as a lung compensator in lateral fields; more frequent boost irradiation of the mediastinum and legs with small fields; calculations of Monitor Units based on dosimetric data. Boost irradiation of the chest wall with electrons has been abandoned.
Results. Median follow up was 12 months. Up till now, 17/23 patients are alive, of these 16 with no relapse. Immediate toxicity was low. Early complications were observed during the first 6 months after BMT in 11 patients. In the case of 4 patients these complications were fatal. Late complications were observed in 10 patients, including chronic GVHD and hormone disturbancy. Only one patient had developed the first symptoms of cataract. In one case Lhermitte's syndrome was observed. One patient died due to liver insufficiency.
Conclusions. The results of treatment and the complications rates in patients treated with TBI at our department are consistent with those published in literature. We conclud that our method of TBI is safe and well tolerated.

Key words: total body irradiation, complications

Total body irradiation (TBI) is a well established part of the conditioning regimen prior to bone marrow transplantation (BMT) in patients with hematological malignances. TBI has been used since the late 1970s, originally as single dose TBI. However this treatment schedule had been associated with relatively high rates of acute and late toxicity. Better understanding of the immunological process led to an improvement of treatment results, while the progress in radiobiology allowed to replace single dose TBI with fractionated radiotherapy. At present numerous different irradiation techniques and fractionation schedules of TBI are used. There is no agreement as to the optimal radiation method for TBI, and every center elaborates its own solutions [1].

Bone marrow transplantation is a complicated procedure, which may lead to early and late toxicity, to a certain extent brought on by TBI, such as interstitial pneumonitis, cataract and less often, thyroid, renal and hepatic complications [2].

In our Department of Radiotherapy TBI has a long tradition. The first patient was irradiated in 1983, using a single dose as high as 10 Gy [3, 4]. From 1997 to 2000, the fractionated regime was being elaborated. Over this period we applied a TBI method involving a reduced lung dose of 9 Gy. This method required supplementary chest wall irradiation with an electron beam. Also, the dose rate into mid point during the whole treatment was kept below 0.15 Gy/min. In November 2000 a modified method of TBI was introduced involving a higher dose to the lungs.

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The aim of our study is to present a modified method of TBI as applied in our department, and preliminary results, especially with respect to early and late treatment toxicity.

Material and methods

Between 11.2000 and 08.2004 23 patients were treated with fractionated TBI at the Department of Radiotherapy of Maria Skłodowska-Curie Memorial Cancer Center.

Conditioning chemotherapy and blood marrow transplantation were performed at the Hematology and Oncology Clinic of the Medical University of Warsaw (17 patients), at Department of Bone Marrow Transplantation of the Military Institute of Health Services (5 patients) and, in the case of one patient – at the Institute of Hematology and Blood Transfusion in Warsaw.

Patient characteristics are presented in Table I.

Table I. Patients characteristic

Gender	
Male	14
Female	9
Age	
<18	1
19-30	10
>30	12
Diagnosis	
ALL	17
AML	3
CHL	2
NHL	1
Treatment	
Primary	16
Secondary	7
Type of bone marrow transplant	
Autogenic	5
Allogenic	18
Related donor	14
Unrelated donor	4

Conditioning chemotherapy

Five patients received 2500 mg etoposid over one day and one patient received a high dose of cyclophosphamid prior to TBI. Seventeen patients were treated with etoposid 40 mg/kg body mass and cyclophosphamid 60 mg/kg body mass administered after TBI.

Radiotherapy

All patients were irradiated with total midline doses of 12 Gy in 6 fractions, over 3 consecutive days. 12 Gy were prescribed to the normalization point in the middle of an abdomen. The dose to the lung did not exceed 11 Gy.

Radiotherapy was given with 15 MV photons. We applied a combination of lateral fields in fractions No 1, 3, 5 and anteroposterior with posteroanterior fields in fractions No 2 and 4. A summary of the arrangements of the TBI treatment is presented in Table II. All irradiations without shielding blocks, which concerned a dose of at least 8 Gy, were performed at extended SSD of about 350 cm using horizontal beams sufficient to encompass the whole body. A suitable filter inserted in the beam improved dose uniformity and reduced the dose rate during irradiation below 0.13 Gy/min in the midpoint. In lateral fields head compensators were used. An arm with an individually shaped bolus provided additional compensation for the lungs.

A wax bolus 6 cm thick was designed from lateral portal film. Its shape corresponded to the visible contour of the lung.

In the anterior field in fraction 2 and in the posterior field in fraction 4 we used partially attenuating individual lung shielding. The lung shielding was made of layers of lead (4-6 mm thick) which reduced the lung dose by about 10%.

The patient lay supine (fraction 2) or prone (fraction 4) on the treatment coach and was treated with 3 fields covering parts of the body at an SSD of about 140 cm. One field to the abdomen was treated with the gantry of 0° and other fields with gantry angles sufficient to compensate for field divergence. In tilted fields suitable filters were used. The dose rate for these fields was about 1.1 Gy/min, except for the first few patients, who were treated with a low dose rate. We had decided to accelerate treatment with shielding to minimize movement since it concerned only 2-4 Gy out of the entire 12 Gy. In all fields a perspex plate 2 cm thick was placed next to the patient in order to prevent skin sparing.

Table II. Summary of the arrangements of the TBI treatment

Fraction	Beam angle	Gantry	SSD	Patient position	Beam modifiers	Field coverage
1, 3, 5	1 2	90	≈350	Supine, left side to the beam Supine, right side to the beam	Filter nr 1, spoiler, bolus-lung compensator, head compensator	Whole body
	3	-22.6	≈150	Supine	Filter nr 2, spoiler, lung shielding	Head, arms and chest
	4	0	≈140		Spoiler	Abdomen and thighs
2	5	22.6	≈150		Filter nr 2, spoiler	Shanks
	6	90	≈350	Straight, on the side, posterior to the beam	Filter nr 2, spoiler	Body without shanks
	7	0	100	Prone	spoiler	Shanks
	3	-22.6	≈150	Prone	Filter nr 2, spoiler, lung shielding	Head, arms and chest
	4	0	≈140		Spoiler	Abdomen and thighs
4	5	22.6	≈150		Filter nr 2, spoiler	Shanks
	6	90	≈ 350	Straight, on the side, anterior to the beam	Filter nr 2, spoiler	Body without shanks
	7	0	100	Supine	spoiler	Shanks
6	Optional, dependent on the in vivo measurements of the lung dose in fractions 1-5					

The 6th fraction was delivered with lateral or AP-PA fields, with or without shielding, depending on the results of the lung dose measurements during the first 5 fractions. To maintain dose homogeneity a supplementary dose of 0.5-1.5 Gy was given using small AP-PA fields to the mediastinum and, occasionally, also to the pelvis and legs.

The introduction of TBI to our departamental practice had been preceded by extensive dosimetric evaluation of the large fields under TBI conditions. Monitor units for each field were calculated for 1 Gy of the midpoint dose basing on SSD measurements, patient thickness and basic dosimetric data. Doses to the midpoint, head, lungs, legs and mediastinum were also calculated from entrance and exit dose measurements with MOSFET (Metal-Oxide Semiconductor Field-Effect Transistor) detectors or TLD (thermo luminescent) discs and, additionally, for the midpoint – with ion chambers.

Basing upon these measurements small corrections were made in the irradiation procedure in order to achieve maximally homogenous dose distribution within all parts of body (e.g. thickness of boluses was modified).

The results of the *in vivo* dosimetry measurements using ionization chambers remained in unison with the calculations of the dose at midpoint. Standard deviation of dose differences calculated for 185 measurements was equal to 2.4%, which means, that the difference between measurements and calculations did not exceed 5% in 95% of the cases.

The TBI method applied at our department was evaluated over a few years. To summarize: the following modifications have been introduced to the previously applied TBI: an increase of photon energy from 6 MV to 15 MV; an increase of the lung dose from 9 Gy to 11 Gy; application of individual boluses as lung compensators in the lateral fields; more frequent boost irradiation of the mediastinum and legs with small fields; calculations of Monitor Units basing on dosimetric data. Boost irradiation of the chest wall with electrons has been abandoned.

The purpose of the changes in photon energy and application of small AP-PA fields to the mediastinum and legs was to achieve an increase in dose homogeneity. The boluses in the lateral fields were applied in order to decrease the dose to the lung, while maintaining higher doses to the frontal and back part of the chest wall. In view of the higher dose to the lung it was possible to give up the electron boost to the chest wall.

Some smaller technical changes were also introduced to improve dose homogeneity. For example, a suitable filter has been designed for tilted fields. During AP or PA field irradiation the patient lay straight on the side. The legs usually had to be irradiated with an additional field. Previously our patients lay with legs bent and were irradiated only with one field but usually in those cases the dose to the legs was significantly lower in this fraction, which could be discerned with *in vivo* dosimetry.

Sixteen patients had undergone' prophylactic or therapeutic whole brain radiotherapy in doses of 18-30 Gy from 1 to 12 months before TBI, depending on the treatment protocols.

Sixteen patients received TBI as primary treatment, and 7 were treated due to relapse.

Evaluation of side effects

We evaluated all side effects possibly connected with TBI. Immediate toxicity was evaluated prior to each fraction (twice a day). We considered all complications observed during the first 6 months after the graft as early complications.

All complications diagnosed more than 6 months after irradiation, especially pulmonary complications, were recognized as late toxicity. Clinical pulmonary complications and X-ray findings were graded according to the scale presented by Lohr [5] (Table III). Renal dysfunction was assessed on the basis of the serum creatinine and urea levels 6 months after the completion of radiotherapy. Ocular complications, especially cataract, (proven ophtalmologically) were assessed during follow-up more than 6 months after treatment. Other complications, such as as hormonal insufficiency, xerostomia and alopecia were also evaluated.

Table III. Late pulmonary complications (Lohr scale)

Grade	Details
1	No lung complications at all, no X-ray findings
2	Lung complications / X-ray findings – minor clinical
3	Severe pulmonary complications
4	Fatal lung complications

The survival data were calculated according to the Kaplan-Maier method.

Due to the limited number of patients we refrained from performing any further statistical analyses.

Results

The follow-up was closed on March 30th, 2005.

Median follow-up was 12 months (range: 5 days – 52 months). At present 17 patients are alive, of these 16 with out relapse. Six patients have died, 5 due to complications of treatment, and one with recurrent disease and complications after the second graft. The probability of overall survival is presented in Figure 1.

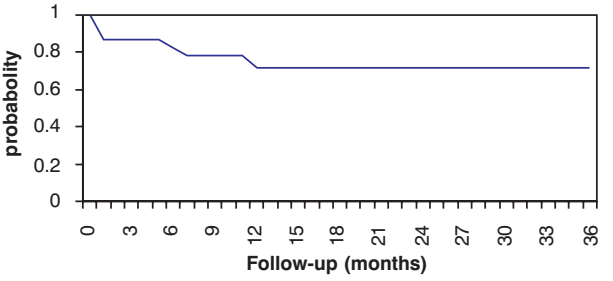

Figure 1. Overall survival after TBI

Patients who had received TBI as primary treatment have achieved significantly better event-free survival than patients treated due to relapse (p=0.046).

Immediate toxicity

Main symptoms observed during irradiation included mild nausea and emesis in 12 patients. Mild xerostomia (mouth dryness, slightly thickened salivary, slightly altered taste) was observed in 11 patients. Two patients reported mild gastro-intestinal effects, such as loss of appetite and mild diarrhea. Generally TBI tolerance was good.

Early complications – were observed during the first 6 months after transplantation in 11 patients and included: interstitial pneumonitis in 2 cases, oesophagitis in 1 case, trombocytopenia in 2 cases, hemorrhagic cystitis in 2 cases and acute GVHD in 6 cases. In 4 cases these complications were fatal. One patient died 5 days after

treatment due to immediate complications related to the transplant. Two patients died after one month – one because of multiorgan insufficiency and one due to cytomegalovirus infection. The fourth patient developed acute GVHD, and died among symptoms of interstitial alveolar pneumonitis and fungoidal infection 6 months after the transplant.

Late complications

Only one patient died due to late complications, after a period of 12 months due to Hepatitis B Virus infection and liver insufficiency.

Among the 16 patients, who are alive without relapse after six months, late complications were observed in 10 cases. Thirteen patients showed no radiographic changes on chest X-ray, in 3 cases we have not obtained the chest X-rays, but they do not report nor show any clinical pulmonary symptoms. They are all pronounced as grade I acc. to the Lohr scale. Only one patient reports first symptoms of cataract, proven ophtalmologically, 36 months after treatment. Three patients had elevated serum creatinine and urea levels, but they had all been administered cyclosporine. All women alive without relapse (i.e. 5) have ovary function disturbances, associated with preliminary menopause symptoms.

We have observed persistent mouth dryness in 3 cases and mild allopecia in 2 cases. One patient reported "shocks" along the spine, recognised as Lhermitte's syndrome. These symptoms were mild and transient.

Six patients after allogenic transplant, are alive with symptoms of chronic GVHD.

Discussion

Different irradiation and fractionation schemes were used for total body irradiation, depending on local facilities and study protocols. Generally, the symptoms of toxicity depend on the total dose, fractionation doses and patient related factors, as well as on transplantation modalities [2, 6, 7].

Overall and disease-free survival rates of 3-5 years in larger patient populations have been reported by some authors to reach 50-70% [8, 9, 10]. The results depended on diagnosis, type of treatment (primary vs. for relapse), patient age etc. Our results – 74% and 70%, respectively, resemble those reported in literature.

Immediate toxicity during fractionated TBI was low in our patient group. The main symptoms consisted of mild nausea and emesis and xerostomia, observed in about 50% of patients. The incidence of diarrhea was as low as 8%. These observations are similar to those presented by other authors [11].

Early and late toxicity is related to the cytoreductive regimen (conditioning chemotherapy and radiotherapy) and to the transplantation itself. Acute GVHD (graft-versus-host disease) is a syndrome consisting of dermatitis, hepatitis and enteritis, which appears within 100 days of allogenic transplant. Interstitial pneumonitis is related to the severity of acute GVHD. Chronic GVHD, which develops more than 100 days after allogenic graft, tends to result in widespread organ involvement (skin, liver, lungs, eyes and GI tract) and behaves like an autoimmune process [1].

In our study 4 patients died due to early complications, related directly to the transplantation itself.

Total body irradiation can be responsible for some late complications. Of these one of the most important is interstitial pneumonitis (IP). One of the causes of IP is GVHD the case of patients treated with allogenic bone marrow transplant. The incidence of IP in these patients could be as high as 25% and fatal for many of them (20%) [12].

In patients treated with autogenic BMT the overall 5-year IP incidence is less than 20%, depending on the dose-rate of TBI and the age of the patients [5, 9]. In order to prevent lung complications, many centers apply individual lung shielding and the lung dose was limited to 9 Gy [2, 9, 10, 13-15]. However, some authors have reported a low incidence of lung complications after higher radiation doses, up to 12-13 Gy [5, 7, 16].

When the lung dose is reduced to 9 Gy, the chest wall has to be treated with supplementary electron fields. In order to encompass ribs, electron energy has to be relatively high. Therefore the electrons penetrate deep in the lung and the effect of lung sparing is lost. Electron chest wall irradiation is especially difficult in women because of the presence of breasts.

In our material, despite the higher lung dose, within the range of 10-11 Gy, only 2 (8%) patients developed symptoms of IP within a period of 6 months after the transplant. In the remaining patients we did not observe any lung complications, which was confirmed by chest X-ray.

Because the lung complication rate was low, we conclude that the treatment regime applied in our department is safe.

TBI also can be responsible for some other late organ complications, such as cataract or liver insufficiency. Post-TBI cataract is observed in 10-30% of patients, 2 a years and more after treatment. The estimated cumulative risk for cataract development at 15 years is reported to exceed 50% [17]. Single fraction high dose TBI may be associated with a higher risk of cataract than fractionated schedules [2, 17, 18]. In our data, the first symptoms of cataract were diagnosed in one patient only, but longer follow-up is necessary.

The risk of renal toxicity after TBI is low. Borg at al. presents only one case of radiation nephritis in a study encompassing 59 patients – 24 months after completion of TBI [19]. In our study, 3 patients had elevated serum creatinine and urea levels, probably related to the cyclosporine, which they had been administered.

Gonadal failure is a common long-term consequence both of chemotherapy and radiotherapy, and the ovaries are more vulnerable to irradiation and chemotherapy than the testes [6]. In our patient group all women

suffered disturbances in ovarian function, associated with preliminary menopause syndrome.

Radiation myelitis has been reported as an unexpected complication following TBI, allogenic stem cell transplantation and mediastinal involved field irradiation [20]. We have observed symptoms of Lhermitte's syndrome in one patient, but they were mild and transient.

This particular patient had also undergone prophylactic whole brain irradiation.

In conclusion, the results of treatment and complication rates observed in the patient group treated with TBI at our department resemble those reported by other authors. We conclud that our TBI method is safe and well tolerated, but a longer follow-up period is necessary to present more complex results.

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