Total body irradiation prior to bone marrow transplantation - the experience of the Institute of Oncology “Prof. Dr. Al. Trestioreanu” Bucharest


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Summary

Purpose: To present the technique of total body irradiation (TBI), applied for the first time in Romania, at the Institute of Oncology Bucharest, as part of stem cell transplantation for hematological malignancies.

Patients and methods: The total dose administered was 12 Gy at the reference point, 2 Gy/fraction, one fraction per day, 6 consecutive days, with a total dose of 8 - 11.4 Gy delivered to the lung, using Mevatron Primus linear accelerator (6 MV & 15 MV, 200-300 cGy/min in isocenter), in vivo dosimetry detectors and equipment for the reference dosimetry, personalized blocks for lung shielding sustained by polymethylmethaacrylate (PPMA) plate, Simulix HP simulator, and computer tomographic (CT) scans. Techniques used were: a) two parallel opposed anteroposterior / posteroanterior (AP/PA) fields with the patient in prone and supine position; b) two parallel opposed lateral fields with the patient placed on a lateral table, at 320 cm from the source. The percentage depth dose, tissue maximum ratio (TMR), off axis ratio (OAR) and the reference dose rate were measured for every patient’s geometrical characteristics, with an uncertainty of ± 2.2% and were used to calculate monitor units and to evaluate the dose in organs at risk (lungs, gonads, eyes etc).

Results: 5 patients (3 with the AP/PA technique and 2 with the lateral technique) were irradiated. All patients completed their irradiation in good clinical condition. The acute side effects were minimal (WHO grade 1: nausea/vomiting – all patients; diarrhea – 1 patient; headache – 2 patients; photophobia and diplopia – 1 patient; head and neck skin erythema – all patients). Because of the short follow-up period no safe evaluation of late side effects can be done. However, during this period one patient developed a non-aggressive form of chronic liver graft vs. host disease (GVHD) and one patient died due to acute GVHD.

Conclusion: TBI as part of stem cell transplantation for hematological malignancies was successfully realized at our Institute, with favorable clinical results. This technique is easy to carry out and reproducible.

Key words: hematological malignancies, in vivo dosimetry, radiotherapy, stem cell transplantation, total body irradiation

Introduction

Stem cell transplantation is a systemic therapy for hematological malignancies with rapid expansion during the last 30 years (more than 23,000 transplantations in 2001 all over the world), with remarkable results [1]. Nowadays the main indications for stem cell transplantation are acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), multiple myeloma, some malignant lymphomas, and some solid tumors.
TBI is an important technique, an integral part of the protocols of allogeneous or autologous stem cell transplantation and has 3 main purposes:

1. “Cleaning” the host marrow to allow repopulation with donor marrow cells;
2. Providing sufficient degree of immunosuppression to avoid allograft rejection by immunologically active cells of the host;
3. Destroying residual neoplastic cells; and these goals must be achieved with minimum side effects for the patients.

The selection of an optimal value of risk – benefit ratio, associated with local technical possibilities determined the development of a great variety of irradiation techniques and treatment schedules [2,3].

There is no ideal technique to irradiate the whole body homogeneously and precisely; AP/PA techniques are mostly used, with the patient sitting on the table or standing, or on a mobile table with speed controlled by computer, with adjacent fields or latero-lateral fields; each technique has its advantages and disadvantages regarding the dose distribution accuracy and the patient’s tolerance to the treatment as well [3].

As for the treatment schedule, reference doses of 5 to 16 Gy are delivered (6 - 15 Gy to the lung) in 1-13 fractions on days 1-6.

In this paper we present the experience and the results of the Institute of Oncology “Prof.Dr.Al.Trestioreanu” Bucharest with TBI as part of conditioning regimen to stem cell transplantation, a technique that was used for the first time in our country since the beginning of November 2003.

Patients and methods

Patients

Five patients (4 males and 1 female) were selected for TBI, aged between 13 and 48 years. In 4 cases allogeneous and in one patient autologous stem cell transplantation were carried out.

The patients were diagnosed with AML-M4 with central nervous system relapse, ALL also with central nervous system relapse, ALL and non-Hodgkin’s lymphoma.

Patients’ selection (Table 1) for allogeneous or autologous stem cell transplantation was performed in the Bone Marrow Transplantation Department of the Fundeni Clinical Institute, according to the protocol’s criteria. The current indications are high risk patients with leukemia or lymphoma in 1st complete remission and patients in 2nd complete remission. TBI + cyclophosphamide is the standard conditioning protocol for patients with acute leukemia below 50 years of age, without comorbidities. After selection, the patients were treated according to the chosen protocol.

Treatment protocol

We use the following treatment protocol:

- Day -9 → -4: TBI, total dose 12 Gy.
- Day -3 → -2: high dose chemotherapy - cyclophosphamide 120 mg/kg/day.
- Day 0: stem cell transplantation.
- GVHD prophylaxis: Day -1 → day +180: cyclosporine 1 mg/kg/day, and short term methotrexate p.o.: 15 mg/m² day+1, and 10 mg/m² day+3 and +6.

Irradiation technique

The radiotherapy equipment used was linear accelerator MEVATRON PRIMUS; photon-beam with nominal energy of 6 MV, with a dose rate in the isocentre of 200 cGy/min.

Initially, taking into account the need for a precise dose distribution correlated with minimal side effects allo-

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Total dose (Gy)</th>
<th>Median dose to the lung (Gy)</th>
<th>Current state</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Acute myeloid leukemia – AML-M4</td>
<td>12</td>
<td>8.0</td>
<td>Central nervous system relapse. Without signs of GVHD.</td>
</tr>
<tr>
<td>48</td>
<td>Acute lymphoblastic leukemia</td>
<td>12</td>
<td>9.6</td>
<td>Died on day +72 of acute GVHD</td>
</tr>
<tr>
<td>13</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>12</td>
<td>9.8</td>
<td>Complete remission.</td>
</tr>
<tr>
<td>20</td>
<td>Acute lymphoblastic leukemia</td>
<td>12</td>
<td>11.4</td>
<td>Complete remission. Without signs of GVHD.</td>
</tr>
</tbody>
</table>

GVHD: graft versus host disease
effects (especially interstitial pneumonitis), we chose an irradiation technique that allows the best control of the delivered dose to the entire target volume and especially to the lungs by using accurate positioning individualized blocks (Figures 1, 2).

The patients were placed in prone and supine position in a wooden case and covered with rice, including the lateral sides to obtain an equilibrium layer of 1 – 2 cm; with this approach we intended to move the maximal dose to the skin surface and eliminate dose inhomogeneities resulting from patient thickness variation (excepting the head), obtaining an inhomogeneity of maximum ±7 % (Figure 3) [4].

The source-skin distance (SSD) was 190 cm, and the beam orientation was vertical down.

The absorbed dose rate in the prescription point was approximately 50 cGy/min, depending on the AP diameter of the patient.

We used CT scans to calculate the lung correction factor and also to define the lung volume and position with regard to bony marks.

For the designing of the lung blocks we used SIMULIX simulator, with the same irradiation geometry as during the treatment.

For the last 2 patients we modified the irradiation technique and used two parallel opposed lateral fields, with the patient in supine position on a lateral table, with the knees immobilized; the accelerator’s head was rotated at 90°, collimator at 45° and the field size was 40 cm × 40 cm at 100 cm distance; in this manner the SSD was 320 cm and the variation of the dose was less than 10%. The dose rate at the treatment distance was 20.5 cGy/min.

Irradiation schedule

The total dose in the reference point was 12 Gy, delivered in 6 days, one fraction / day, 2 Gy/fraction (1 Gy on the AP and the PA field each) and right and left field respectively (for the last 2 patients, with lateral technique). The irradiation was performed during days -9 → - 4. The prescription point was on the middle line, at the umbilicus.

The dose delivered to the lungs was carefully evaluated; in order to reduce the risk of interstitial pneumonitis the average dose to the lung was 8 Gy in the first patient; for the remaining patients the dose to the lung was raised to 9.0 – 9.6 Gy and even to 11.4 Gy [5]. In the lateral technique the protection of the lung was realized by arms tightly flexed and immobilized with arm holder; the correct and the best position of the arms was verified at the simulator.

Two patients had central nervous system relapse and had already received whole brain irradiation with a total dose of 20 Gy; this previous dose did not cause

Figure 1. Patient’s alignment.

Figure 2. Marking the protection limits on the skin.

Figure 3. Irradiation of the patient in AP position.
a reduction of the dose delivered to the brain during the total body irradiation.

During the 6 days of irradiation the patients received prophylactic medication to reduce the incidence of acute side effects – for acute gastrointestinal toxicity (nausea, vomiting) they received granisetron 3 mg and dexamethasone 8 mg i.v. half an hour before and after irradiation; for increased intracranial pressure they received mannitol 100 ml half an hour before and after irradiation [6].

The patients were monitored for acute side effects and a blood count was performed every day during the 6-day duration of irradiation.

Dosimetry

Because of atypical irradiation geometry, to ensure an optimal control of the relative dose distribution into the body and especially of the absorbed dose at the prescription point and in other important points as well, our team performed specific dosimetric verification in the same geometry for both techniques (parallel opposed AP/PA and parallel opposed lateral technique).

Tissue maximum ratio measurement (Figure 4)

TMR was measured in a water phantom and in PMMA plates; we proved that this ratio does not depend on the distance source – measurement point and is dependent on the field size in the measurement point. The percentage depth dose in irradiation conditions was also measured.

Off Axis Ratio measurements (Figure 5)

OAR measurements were performed in water phantom and also in PMMA plates, for different depths.

Absolute dosimetry

The absolute dosimetry that allowed the monitor units calculation was performed with ionizing chamber type M 30001 PTW, connected to the electrometer UNIDOS; the chamber had been calibrated beforehand in absorbed dose in water with a gamma $^{60}$Co beam, according to the Secondary Standard Laboratory Dosimeter (SSLD Bucharest). The measurements were performed in water phantom and in PMMA plates under the exact irradiation conditions; the IAEA TRS 398 Code of Practices was applied [7].

Dosimeters’ calibration for in vivo dosimetry

For in vivo verification of the delivered dose to the patients we used Metal Oxide Semiconductor Field Effect Transistor (MOSFET) and semiconductor detectors (PTW, connected to a MULTIDOS electrometer) calibrated in operating conditions (SSD, field dimensions at the prescription point, beam energy); the detectors were calibrated with electronic equilibrium plate, according to the information given by the ionizing chamber placed in water, at the maximum dose point. The external influences (temperature at the detector’s level, field dimensions) were analyzed, and after each irradiation fraction the doses were measured in at least two points (one being the prescription point).

With the semiconductor detectors we were able to simultaneously determine in vivo doses in 12 points, including the doses at the entrance and exit points (Figure 6) [8].

Measurement of the individualized blocks coefficient

The correction coefficient for the absorbed dose to the lung was calculated based on the information

Figure 4. Typical tissue maximum ratio curves.

Figure 5. Typical percentage depth dose curves, horizontal geometry.
obtained from the CT scans. One of the most important side effects, with serious consequences for the patient, is interstitial pneumonitis after large doses. In order to reduce the dose to the lung at a desired value individualized blocks using the SIMULIX HP simulator were manufactured, with the patient in treatment position (the blocks were separately manufactured for AP and PA fields); the thickness of the block was relevant to the desired dose to the lung. For every block the attenuation coefficient in treatment position was measured using the phantom and the absolute dosimetry equipment. The median value of the attenuation coefficient was used to evaluate the real dose delivered to the lung.

Elaboration of the treatment planning

The treatment planning was individualized for every patient, using patient’s dimensions and the information acquired from the phantom under operating conditions.

For the reference prescribed dose (12 Gy) the absorbed doses in different points of interest (lung, mediastinum, head, neck, eye’s back, pelvis, legs etc.) were measured. Also the expected dose in the points of the in vivo detectors and the maximum dose in these points was calculated.

Verification with radiological films

KODAK X-omat radiological films placed under the patient during the irradiation session were used to confirm the correct positioning of the lung protection (in AP/PA technique) and to verify the correct positioning of the adjacent fields.

Reference dose verification

After each fraction of irradiation the reference dose rate and the dose by monitor unit were measured. The measurement was accomplished with the ionizing chamber placed in PMMA plates in the prescription point of the patient.

Results

Five patients (3 with the AP/PA technique and 2 with the lateral technique) were irradiated. The total dose delivered to the prescription point was 12 Gy and to the lung 8 - 11.4 Gy.

The absorbed doses calculated in other points than the prescription point were between 11.1 Gy and 13.0 Gy, leading to an inhomogeneity of ±8 % for the AP/PA technique, with rice as compensator material, and between 10.1 Gy to 15 Gy for the lateral technique.

The values measured with semiconductor detectors were about ±5 % from the calculated values.

From a dosimetric point of view, in Figures 4-7 represented are typical tissue – maximum dose curves and profiles that helped us achieve an individualized planning treatment.

All patients completed their irradiation in good clinical condition.

The acute side effects were minimal (WHO grade 1) and consisted in: nausea, vomiting - all patients, controlled with antiemetic agents; diarrhea - 1 patient; headache - 2 patients; controlled with corticosteroids and mannitol; photophobia and diplopia - 1 patient; controlled with corticosteroids and mannitol; skin erythema, especially to the head and neck - all patients.

As for late side effects it is too soon to have an evaluation because of the short period of follow-up (18 months, 11 months, and 10 months and 2 weeks respectively). During this period one patient developed a non-aggressive form of chronic liver GVHD and one patient died on day 72 due to acute GVHD.

Figure 6. Typical off axis ratio curves for vertical irradiation.

Figure 7. Typical off axis ratio curves for lateral technique.
Discussion

TBI is an important component of the stem cell transplantation protocols. Some trials showed an improvement of disease-free survival rates for the patients who underwent TBI for stem cell transplantation [9].

TBI offers several advantages: the delivered dose is homogenous to the entire body, independent of the blood supply; all cells in the body will be treated, including sanctuary sites (body compartments where effective anticancer drug levels cannot be achieved, such as the central nervous system or the testes); irradiation is not cross-reactive with any chemotherapeutic agent, the dose distribution can be modified by using blocks for organs at risk (e.g. lung) or the dose can be boosted to organs with high resistance to treatment (e.g. testes); TBI offers also a better immunosuppression.

There is no ideal technique for TBI. Literature review reveals that treatment methods for TBI are heterogeneous, with a large variety concerning fractionation (single dose, multiple fractions, highly fractionated regimens) and treatment planning (parallel opposed AP/PA, parallel opposed lateral fields or a combination of these techniques) [9,10].

Why did we choose a multiple fractions approach? Studies [11,12] suggest that fractionated TBI is better than single dose in reducing toxicity to normal tissues and the incidence of interstitial pneumonitis [13], without increasing the relapse rate. Interstitial pneumonitis is of great concern following TBI. It usually occurs within 90 days after transplantation and accounts for approximately 40% of transplantation-related deaths. Its incidence depends on total dose and fractionation, with increased incidence for single dose TBI rather than fractionated regimens [9].

Today the majority of the centers use fractionated regimens [3].

Vriesendorp et al. [14] created tables of surviving target cells (e.g. lung, intestine, bone marrow); they showed a dramatic sparing of lung and intestine with more fractionated regimens, probably due to their large shoulder on the survival curve and ability to repair sublethal damage.

Another advantage of fractionated regimens is the possibility to administer a larger total dose, with a better immunosuppressive effect (numerous experimental studies have demonstrated that the immunosuppressive effect is highly fractionation-sensitive) [14,15].

Why did we initially choose the parallel opposed AP/PA technique? Many centers prefer this technique to that with parallel opposed lateral fields because of better homogeneity of dose distribution (the dose variation to the various parts along the axis of the body ranges from ±7 - ±10%) [15,16]. Our patients had a dose inhomogeneity of ±8%.

For the parallel opposed lateral technique dose variation can range up to 50% in the head and neck and 10% in other parts of the body.

It must be mentioned that for the lateral technique it is easier to do individualized protection to organs at risk.

The lateral technique allows the irradiation of the whole body with two opposed fields, lowering the risk of overdosage by overlapping fields and offers better convenience for the patient during radiotherapy. It also makes things easier for the working team, by diminishing the treatment time up to 50% versus the AP/PA technique [15,17].

As for the results and side effects it is too soon to come to conclusions. Still, from comparative analysis of literature data it can be stated that a single dose of 9.9 Gy, which is equivalent with fractionated 12-13.5 Gy, can result in 7-year survival rate of 74% and in only 38% if the dose is lower than 9.9 Gy; increasing the single dose over 10 Gy (and of fractionated total dose over 12-13.5 Gy) it is not necessary correlated with a 7-year increased probability of survival [18,19].

As for the immunosuppressive effect, studies show that patients treated with fractionated irradiation with 12 Gy total dose have a higher probability of developing chronic GVHD than those treated with doses lower than 12 Gy [17,18]. In univariate and multivariate analysis GVHD was the main indicator of relapse prevention after stem cell transplantation for acute leukemia and it favors overall survival [20].

Conclusions

Four out of 5 patients that received TBI are alive at 18, 11, 10 months and 2 weeks, respectively, from the stem cell transplantation. One patient developed chronic and one acute GHD.

Total doses and fractionation schemes were according to internationally accepted protocols.

The performance status of the patients during and after treatment makes us consider this protocol acceptable, with good results.

The treatment technique has been chosen in a manner to achieve some important goals of TBI, such as the use of rice.

Homogenous dose distribution: Using rice as compensator material leads to irradiation geometry similar to phantom (used for absolute and relative dosimetry), minimizing the influence of patient thickness variation.
Accurate checking of personalized blocks positioning and of doses administered to the lung: Using this technique the protection blocks can be positioned with accuracy for every patient by using the same coordinates at the simulator and during irradiation; individualized measures of transmission for the personalized blocks offer a better control of the dose administered to the lung.

The main disadvantage of AP/PA technique is represented by the overlapping of adjacent fields, but with rigorous calculation of adjacent fields’ position the over- and underdosage can be eliminated. Use of radiologic films for high doses (X-omat) allows better visualization of adjacent fields; the calculus and the measurements show that dose inhomogeneities in adjacent areas are less than ±10 %.

To avoid overlapping of adjacent fields we introduced the lateral technique, with 2 parallel opposed fields, with the patient in prone position and with the accelerator’s head rotated at 90°, collimator at 45°; to assure an homogenous irradiation to the skin we used a PMMA plate placed between the patient and the radiation source, as close as possible to the patient; the SSD was 320 cm (Figures 7-9). The method has the advantage that the whole body is irradiated at the same time, without the risk of over- or underdosage; it is also better tolerated by the patient and the total time for total dose delivery is shorter than with AP/PA technique.

The disadvantage of the lateral technique is the high dose inhomogeneity. But the method has the essential advantage of in vivo dose measurement in 12 points simultaneously. The calibration of these 12 detectors was done simultaneously and they were given numbers – even numbers for exit points and odd numbers for enter points. Each pair (odd-even)
offers dosimetric information for an organ at risk or from the prescription point (umbilicus) (Figure 10). There are 6 points of interest for in vivo dosimetry, and the values indicated by the detectors are noted in a Table and compared with the expected values. The reproducibility of the detectors’ results over time as well as the accuracy of the measurements were according to international standards.

References