Acute and late toxicity after fractionated total body irradiation as conditioning for bone marrow transplantation

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During the past 40 years, *hematopoietic stem cell transplantation* has been accepted as routine treatment for many patients with neoplastic and hereditary diseases. The number of patients receiving transplants has increased exponentially to currently about 25,000 per year.
Total body irradiation followed by bone marrow transplantation is well established as a part of the conditioning regimen in high dose therapy.
During the last decades high-dose chemoradiotherapy including **TBI** has been considered to have a recognized therapeutic potential in acute high-risk **LEUKEMIAS** and in more than 20 other indications, including lympho- and myeloproliferative diseases and solid tumors.
It is just during the last decade that the Bulgarian oncological community has gained a deeper insight and knowledge in the field of HSCT.
In Bulgaria

the first *autologous BMT* was carried out in *1997*,

the first *TBI with allogeneic BMT* – in *2002*

and the first *allogeneic BMT* with nonmyeloablative conditioning regimen including *TBI of 2 Gy* – in *2005*. 
OBJECTIVE

- To report the acute and late toxicity investigated prospectively in patients with leukemias, treated at the Medical University of Sofia, who had conditioning regimes including fractionated TBI and chemotherapy.
Materials and methods

Between January 2002 and December 2007, 18 patients, 11 males and 7 females with median age 12 years (range 8-50), received TBI in our institution.
Materials and methods

INITIAL DIAGNOSIS

- ALL 11 (61%)
- AML 4 (22%)
- CML 3 (17%)
Materials and methods

DISEASE STATUS

REMISSION
11 (61%)

PROGRESSION
4 (22%)

CHRONIC PHASE
3 (17%)
Conditioning regimen

Myeloablative conditioning regimen

cyclophosphamide and TBI 10-12 Gy (10)

melphalan, fludarabine, ATG and TBI 10-12 Gy (2)

vipesid

cyclophosphamide and TBI 10-12 Gy (3)
Conditioning regimen

Nonmyeloablative conditioning regimen

- fludarabine
- and TBI of 2 Gy

(3)
Materials and methods

- Large fields treatment stationary technique, based on Cobalt-60 unit and specially designed patient table, movable above and below the floor level, was used.

- Field sizes up to 80x80 cm² at a SSD 300 cm were achieved.
Materials and methods

All the patients were conditioned with high-dose chemoradiotherapy regimen including a fractionated TBI delivering 10 - 12 Gy in 15 (73%) and 2 Gy in 3 (17%).
Materials and methods

FRACTIONATED TBI
10 – 12 Gy

10 Gy
5fr/5d
2 (11%)

10 Gy
6fr/3d
5 (28%)

12 Gy
6fr/3d
8 (44%)
Materials and methods

- The requirement for dose rate of 5 - 10 cGy/min was adhered to.
- Personalized lung shields were used to compensate different density and to reduce the lung dose to 8 Gy.
Materials and methods

The received radiation doses to various parts of the body are monitored by

**in vivo dosimetry**

using semiconductor detectors placed anteriorly and posteriorly on a number of specified body sites.
Materials and methods

In 13 (72%) patients transplantation was carried out from HLA-identical related donor and in 5 (28%) – from unrelated donor.

From the performed 18 allogeneic transplantations 17 were of peripheral blood stem cells and 1 – of bone marrow stem cells.
Materials and methods

Posttransplantation clinical, biologic, and functional evaluations were performed on days 30, 100, 180, year 1, and annually thereafter.
Materials and methods

Each evaluation included an assessment of the study end points:

- marrow chimerism,
- treatment-related toxicity,
- treatment related mortality,
- graft-versus-host-disease.
Materials and methods

The assessment of the early and late reactions was made using the adverse event severity scale of CTCAE v.3 NCI, USA.
RESULTS

Median follow-up from BMT was 27 months (range 3-52).
RESULTS

Premedication

was carried out in all patients including **antiemetics** (mainly serotonin receptor antagonists – ondansetron, granisetron, tropisetron) and **corticosteroids** (8 to 20 mg).
RESULTS

During the transplantation period on day 0 and +1 the realized transplantation of the donor cells pool passed without complications in 16 of the patients and was accompanied by allergic reactions in 2 patients.
RESULTS

✓ Induced bone-marrow aplasia was observed in all patients during the post-transplantation period.

✓ On day +14 to +24 "engraftment" was established in 16 patients.

✓ In 2 patients no symptoms of the grafting were observed, which imposed reinfusion of donor cells pool.
The most frequent reactions determining acute toxicity due to the conditioning regimens and the induced bone-marrow aplasia, are:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indisposition</td>
<td>93 %</td>
</tr>
<tr>
<td>Fatigue syndrome</td>
<td>68 %</td>
</tr>
<tr>
<td>Headache</td>
<td>16 %</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>58 %</td>
</tr>
<tr>
<td>Nausea</td>
<td>75 %</td>
</tr>
<tr>
<td>Emesis</td>
<td>58 %</td>
</tr>
<tr>
<td>Mucositis</td>
<td>50 %</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>8 %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50 %</td>
</tr>
<tr>
<td>Parotitis</td>
<td>8 %</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33 %</td>
</tr>
</tbody>
</table>
ACUTE TOXICITY

Acute organ toxicity was recorded in 11 patients during the 6-year period of clinical observation.
ACUTE TOXICITY

LIVER TOXICITY (1)

ACUTE GvHD (7)

IDIOPATHIC PHEUMONIA SYNDROME (2)

NEUROLOGICAL TOXICITY (1)
RESULTS

No development of cardiovascular, renal or other type of acute organ toxicity was established.
LATE TOXICITY

Late toxicity was recorded in 8 patients during the 6-year period of clinical observation.
LATE TOXICITY

Liver Toxicity (1) → Chronic GvHD (6) → Cataract (1)
LATE TOXICITY

In all the 6 patients
late GvHD was successfully controlled and it was not the reason for the fatal outcome in neither of these patients.
Fatal organ toxicity was found in 5 patients.
Fatal organ toxicity

- Acute GvHD (2)
- Idiopathic pneumonia syndrome (1)
- Neurological toxicity (1)
- Liver toxicity (1)
CONCLUSION

- FTBI is a well tolerated therapeutic regimen in high dose therapy.
- The observed acute and late toxicity in the 18 patients is similar to the cited in reference literature.
CONCLUSION

- The small number of cases precludes definitive conclusion of the efficacy of the regimens used and further evaluation is required.
THANK YOU FOR YOUR ATTENTION