Effect of Dose Fractionation on Pulmonary Complications during Total Body Irradiation

Hiromi IZAWA1*, Hisako HIROWATARI1, Yuriko YAHATA3, Yasuharu HAMANO3, Kana ITO1, Anneyuko I. SAIITO1, Hideo YAMAMOTO2, Kouhei MIURA2, Kumiko KARASAWA1 and Keisuke SASAI1

Total body irradiation/Pulmonary complications/Dose fractionation. Total body irradiation (TBI) is an important component of conditioning regimens for Allogeneic bone marrow transplantation (BMT). Interstitial pneumonitis (IP) and other pulmonary disorders are known regimen-related complications. The incidence of IP is related to the dose rate and dose fractionation; however, there is a paucity of clinical data regarding the optimal dose fractionation. This retrospective study evaluated patients to determine the influence of dose fractionation during TBI in preparation for allogeneic BMT on the subsequent development of IP and other pulmonary complications. Fifty-six patients were treated with TBI followed by BMT at our institute. All patients received a total TBI dose of 12 Gy given in 6 fractions over 3 days or in 4 fractions over 2 days. The prevalence of unrelated donors in the 4-fraction group was higher than that in the 6-fraction group. The overall and freedom from progression rates for patients in the 4-fraction group were better than those for patients in the 6-fraction group, but the difference did not reach significance. Clinically significant lung complications occurred in 19 (10: infectious and 9: non-infectious diseases) of 33 patients in the 6-fraction group and 12 (7: infectious and 5: non-infectious diseases) of 23 in the 4-fraction group. There was no significant difference between the two groups. There was no significant difference in pulmonary complications between patients treated with a TBI dose of 12 Gy in 6 fractions over 3 days and patients treated with a TBI dose of 12 Gy in 4 fractions over 2 days.

INTRODUCTION

Allogeneic bone marrow transplantation (BMT) is a leading treatment modality for malignant hematopoietic diseases, such as acute lymphoid leukemia and acute myeloid leukemia.1) Although BMT conditioning regimens not combined with total body irradiation (TBI) are sometimes used, TBI still plays an important role in the conditioning regimens. Interstitial pneumonitis (IP) and other pulmonary complications are well known regimen-related adverse events for TBI. The incidence of IP is related to the total lung dose, dose rate, size of fraction, and fractionation interval.2,3) There are many reports concerning IP incidence between a single dose and dose fractionation. Cosset et al. demonstrated in their review that fractionated schemes are superior to the conventional single dose TBI in terms of pulmonary toxicity;4) therefore, TBI is generally delivered with a fractionated or hyperfractionated regimen in an attempt to increase the therapeutic ratio between disease cell killing and normal tissue toxicity.5)

However, there has been a paucity of clinical data concerning the fractionation schedule, and therefore, the optimal dose fractionation regimen is still unclear. Currently, each institute uses a once to 3 times a day fractionation scheme over 3 to 4 days to deliver a total dose of 12 to 15 Gy.1–29) This retrospective study evaluated patients to determine the influence of dose fractionation during TBI in preparation for allogeneic BMT on the subsequent development of IP and other pulmonary complications. This study was approved by the ethics board of our institution.

The etiology of lung toxicity after TBI/BMT may be multifactorial. Radiation-induced IP, viral or fungal infection, and graft-versus-host disease (GVHD) are major causes of TBI/BMT-related lung complications.5) It was not practical to distinguish between complications that were strictly related to TBI and those due to other causes. Moreover, sub-
clinical lung damage secondary to TBI can cause pulmonary infections; therefore, we included all pulmonary diseases, such as pneumonitis, pneumonia, and other disorders, in pulmonary complications (PC) in this study, as did other investigators.8)

PATIENTS AND METHODS

Patients

Between May 1994 and December 2009, 56 consecutive patients were treated with a total dose of 12 Gy TBI followed by allogenic BMT at Juntendo University Hospital. Twenty-one other patients received less intensive, non-myeloablative low-dose TBI (4 to 6 Gy) and were excluded from this analysis. The 56 patients received the total dose in 6 fractions over 3 days (before March 2005, 33 patients) or in 4 fractions over 2 days (after March 2005, 23 patients).

Table 1 shows the characteristics of the patients. The prevalence of unrelated donors in the 4-fraction group (15 of 23 donors) was higher than in the 6-fraction group (1 of 32 donors). The primary diseases were acute myeloid leukemia in 19 patients, acute lymphoid leukemia in 16, non-Hodgkin’s lymphoma in 12, chronic myeloid leukemia in 5, and other hematopoietic diseases in 4.

There were no significant differences in other factors such as gender, age, and ECOG performance status30) between 2 groups.

Baseline pulmonary function tests (PFT) including forced expiratory volume at 1 s (FEV1.0) and forced vital capacity (%VC) were performed for all patients, but 10 before BMT. Twenty-three of 33 patients showed normal PFT in the 6-fraction group (8 patients did not receive PFT before BMT), whereas 17 of 23 showed normal PFT (2 did not receive PFT) in the 4-fraction group.

The last follow-up was performed in August, 2010. Complete follow-up was obtained in all but 4 patients. These patients were lost to follow-up with no evidence of recurrent disease at 14, 47, 55 and 130 months, respectively. Twenty-nine patients died of disease or treatment-related diseases. The follow-up period for the 23 survivors ranged from 9 to 166 months (median, 58 months).

TBI regimen

All patients received a total TBI dose of 12 Gy given in 6 fractions over 3 days or 4 fractions over 2 days. TBI was delivered by a linear accelerator (Mevatron KDX77; Siemens AG, Erlangen, Germany or Clinac 21EX; Varian Medical Systems, Palo Alto, CA, USA) using horizontal 6 or 10 MV x-ray beams by the long source-to-axis distance (SAD) method, as reported previously.31)

Patients were irradiated in a supine position with lateral opposing beams. Arms were folded and positioned on the chest. Three pairs of opposing fields were used, 1 pair of whole body open fields and 2 pairs of subfields (Fig. 1). One pair of subfields covered from the chest to pelvis, and another pair of subfields covered the pelvis. Multileaf collimators were used for the former subfields to cover the lung. The SAD was 470 cm. The dose rate ranged between 13 and 17 cGy/min. The maximum lung dose of each patient was limited up to 12 Gy. And the mean lung dose was 10.2 Gy. The lens dose was reduced to 6 Gy with a lead shield. The interval between any 2 consecutive fractions was greater than 6.5 hours.

Chemotherapy and transplantation

TBI was followed by chemotherapy with cytarabine (AraC) and cyclophosphamide (CY). On each of the second and third days after TBI, 60 or 50 mg/kg CY was administered intravenously. AraC (2–3 g/m²) was injected intravenously twice a day to a total dose of 8–24 g/m². Bone marrow hematopoietic stem cells were infused 1 to 3 days after the administration of CY, and granulocyte colony-stimulating factor was given after BMT. Some patients received almost the same chemotherapy before TBI, and therefore, bone marrow hematopoietic stem cells were transplanted after TBI.

Immunosuppression and prophylactic use of drugs

All recipients received a series of peritransplant treatments to prevent GVHD and various BMT-related complications. Most patients received a combination dose of either cyclosporin A (3 mg/kg) and methotrexate (MTX) in the cases of sibling donors or tacrolimus (FK506) (0.03 mg/kg) and MTX when donors were non-related for GVHD prophylaxis starting 1 day before BMT.

Patients received ganciclovir or acyclovir, combination tablets or granules of sulfamethoxazole and trimethoprim, fluconazole, and ciprofloxacin hydrochloride according to

<table>
<thead>
<tr>
<th>Table 1. Patients’ characteristics</th>
<th>12Gy/4 fx/2 days</th>
<th>12Gy/6 fx/3 days</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>23</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Gender: male/female</td>
<td>14/9</td>
<td>18/15</td>
<td>0.78</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>33 (17–53)</td>
<td>33 (1–53)</td>
<td></td>
</tr>
<tr>
<td>Performance status*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&gt; 1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HLA mismatch</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td></td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Related</td>
<td>8</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Non-related</td>
<td>15</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* ECOG performance status (ref. 29)
Prospectively controlled regimens to prevent the occurrence of various infectious diseases.

Pulmonary and other regimen-related complications
There are various definitions of IP,\textsuperscript{22} and the radiological findings are not very specific;\textsuperscript{14} therefore, we combined all pulmonary disorders, including IP, infectious diseases, and even pulmonary bleeding, as pulmonary complications. Infectious lung disease was defined when it was diagnosed immunologically and/or bacteriologically.

Adverse effects were scored according to the National Cancer Institute Common Toxicity Criteria v 3.0.\textsuperscript{32} Acute parotitis was defined as either an elevation of the serum amylase level beyond the normal upper limit designated by our institute (124 IU/L) or parotid pain greater than grade 1 within a week after commencing TBI treatment.\textsuperscript{6} The grade of GVHD was scored using the guidelines of the Japan Society for Hematopoietic Cell Transplantation Association.\textsuperscript{33}

Statistical evaluation
The overall survival rate (OS), freedom from progression rate (FFP), and the cumulative incidence of PC were evaluated in relation to various potential indicators of pulmonary complications. These rates and the cumulative incidence of PC were calculated from the first day of TBI using the Kaplan-Meier method. Differences between curves were analyzed by the log-rank test. Differences between 2 groups in the incidence of factors were compared using Fisher’s t test or the Mann-Whitney U test. These analyses were carried out using Excel (Microsoft corporation, USA) and Excel Tokei (SSRI, Tokyo Japan).

RESULTS
Survival
Figure 2 shows OS and FFP curves for all patients. The
5-year OS and FFP rates were 47% and 46%, respectively. Figure 3 demonstrates the survival curves for patients in each treatment group. The OS and FFP for patients in the 4-fraction group seemed better than those for patients in the 6-fraction group, but the difference did not reach significance (p = 0.14, 0.20, respectively).

**Treatment-related complications and GVHD**

Pulmonary complications

Clinically significant PCs occurred in 19 (10: infectious and 9: non-infectious diseases) of 33 patients in the 6-fraction group and 12 (7: infectious and 5: non-infectious diseases) of 23 in the 4-fraction group. Median time to the onset of PC was 6 months (range 1–83 months) in the 6-fraction group and 6 months (range 2–21 months) in the 4-fraction group. There was no significant difference in the time to the onset of PC between the 2 groups. Seven (21%) of 33 patients in the 6-fraction group died of PC, whereas 4 (17%) of 23 in the 4-fraction group. There was no significant relationship between FEV1.0 or %VC and the frequency of PC.

**Other adverse effects**

Table 2 shows the number of patients who suffered from each radiation-related acute toxicity and acute GVHD according to the treatment group. There was a tendency for the incidence of acute parotitis in the 4-fraction group to be higher than that in the 6-fraction group (p = 0.12): 22 patients (67%) in the 6-fraction group vs. 20 (87%) in the 4-fraction group. There was no significant difference in the frequency of other radiation-related toxicities between 2 groups. Only one patient developed veno-occlusive disease in the liver.

**Acute GVHD**

Twelve patients (36%) in the 6-fraction group developed grade 1 or severe acute GVHD, whereas 13 (57%) in the 4-fraction group. Eight patients showed grade 1, 2 grade 2 and 2 grade 3 GVHD in the 6-fraction group, and 6 grade1, 5 grade 2 and 2 grade3 in the 4-fraction group. The difference did not reach significance (p = 0.18).

**DISCUSSION**

TBI plays an important role in the conditioning regimen for BMT. Lethal PC, particularly IP, is a serious problem for patients who receive TBI of a myeloablative dose before BMT. TBI is generally delivered with a fractionated or a hyperfractionated regimen to reduce such complications; however, the optimal regimen of TBI with regard to the total dose, number and type of fractionation remains controversial. In this retrospective study, we compared 2 fractionation regimens of TBI. There was no significant difference in pulmonary complications between patients treated with a...
TBI dose of 12 Gy in 6 fractions over 3 days and patients treated with a TBI dose of 12 Gy in 4 fractions over 2 days. Although the former regimen is often used in the clinic, the latter is not so common. Some investigators treated their patients with a total dose of 12 Gy in 4 once-a-day fractions. Soejima and his colleague treated their patients with a total TBI dose of 12 Gy in 4 to 5 once-daily fractions over 4 to 5 days or in 6 twice-daily fractions over 3 days. In their study, the total lung dose was limited to 9 Gy by individualized shields. They found 15 patients with PC out of 86; however, there were no significant differences between the 2 groups in OS, FFP or the incidence of PC. Petersen et al. suggested from their dose escalation study on TBI that a 6-hour interval between fractions was sufficient to repair acute injury to the same extent as observed with 24-hour intervals. Although it is of course difficult to draw a conclusion from these results, it is suspected that the TBI dose of 12 Gy/4 fractions/2 days has an almost identical effect to that of 12 Gy in 4 fractions over 4 days.

The incidence of PC (infectious PC: 17 (30%), non-infectious PC: 14 (25%)) in this study was relatively high in comparison with other reports. It has been reported that IP morbidity after standard TBI/BMT ranged from 10% to 32%. One possible cause of this high incidence of PC in our study is the relatively higher radiation dose. The total dose to the lung is an important factor in the incidence of PC. Some authors have demonstrated the influence of total dose on the incidence of IP. Schneider et al. treated 257 patients with different hematologic malignancies with TBI in 6 fractions to a total dose of 12 Gy within 3 consecutive days (212 with lung dose of 11 Gy). They found that the IP incidence with the 12 Gy lung dose was 22%, whereas it was 8.5% when the dose was 11 Gy; therefore, they concluded that a total radiation dose to the lung up to 11 Gy is much safer and more effective than 12 Gy. Volpe et al. treated their patients with TBI of 10 Gy (3.33 Gy/fraction, 1 fraction/day, 0.055 Gy/min), which was delivered using a lateral-opposed beam technique with lung shielding by the arms. The median lung dose was 9.4 Gy. PCs were observed in 2 (3.8%) of the 52 patients who had received a mean lung dose of less than 9.4 Gy and in 7 (14.3%) of the 49 patients who had received a higher dose. Sampath et al. reviewed 20 articles to show the parameters in the TBI conditioning regimen that were significantly associated with IP. Lung dose, cyclophosphamide dose, and the addition of busulfan were significantly associated with IP.

However, Oya et al. reported their clinical experience of TBI, especially regarding pulmonary complications when the total lung dose and dose rate were changed. They concluded that there was no significant difference in the incidence of IP between the 2 total lung dose groups (12 Gy vs 8 Gy) or 2 dose rate groups (8 cGy/min vs 18 cGy/min). Lohr et al. analyzed the dose-effect relationship in the crude incidence of lethal IP versus the lung dose for fractionated TBI. There was no significant difference in the incidence between 9 Gy and 12 Gy. This finding is compatible with the observation by Oya et al. Other authors also demonstrated that there was no relationship between the lung dose and the incidence of interstitial pneumonitis if the lung dose was limited to 10.9 Gy in 6 fractions over 3 days. Roberts et al. described that within the range of conventional fraction sizes of 1.5 to 2 Gy given once or twice daily, no significant increase in the incidence of interstitial pneumonitis was noted up to total doses as high as 15 Gy.

We did not use any shield to reduce the total dose to the lung; however, our recent study demonstrated that the lung dose in our method was generally reduced about 10% because of using both arms as compensators. Others also used arms to shield the lungs. This approach, of course, is associated with individual variability of the lung dose; however, Mangili et al. revealed that the lung dose was generally reduced to 5 to 10% using almost the same technique as ours.

Generally, it is hard to compare the PC rate among different institutions due to the different criteria for judging lung toxicity. As described above we included all pulmonary disorders of any degree after BMT into PC; thus, our criteria for PC may be different from others. The prevalence of unrelated donors in the 4-fraction group (15 of 23 donors) was higher than that in the 6-fraction group (1 of 32 donors) in this study. This may be associated with a high incidence of GVHD. Corvo et al. reported that a transplant from unrelated donors was associated with a higher incidence of GVHD, morbidity and mortality than from sibling donors. One of the main causes of IP is GVHD after allogeneic transplantation; therefore, more lung complications should occur in patients with GVHD disease. However, there was no significant difference in the morbidity of PC between the 2 groups in this study. One explanation for this is the advance of treatment modalities. Harden et al. also observed no significant difference in the proportion of respiratory deaths between recipients from a sibling donor and those from unrelated donors. The treatment period in their study was long and they suggested that improved supportive care accounted for the overall incidence of severe PC.

In this study, the OS of patients in the 4-fraction group was slightly better than the others. One possible cause of this improved survival is the effect of graft versus leukemia (GVL). With non-related donors, the grade of GVHD and GVL may be higher than with sibling donors. This reflected the low recurrence rate of the primary malignant disease.
the TBI regimens of 12 Gy/6 fractions/3 days and 9.90 Gy/3 fractions/3 days, and found that the former was more effective for leukemia eradication and was associated with better OS than the lower dose regimen.5)

Bieri et al. retrospectively compared 3 groups of patients sequentially treated with different TBI doses but with a similar fractionation schedule, a similar interval between the two daily fractions, and a similar dose rate ranging between 0.12 and 0.2 Gy/min.13) TBI dose correlated negatively with survival; that is, 5-year survival was 62% for patients conditioned with 10 Gy, 55% for patients conditioned with 12 Gy, and 46% for patients conditioned with 13.5 Gy.

A Dutch group recently published the results of autologous and allogeneic BMT after high-dose conditioning in 1,032 patients.42) They introduced the BED to normalize the radiation dose. There was a significant influence on relapse incidence and non-relapse mortality; the group with the highest BED had a significantly lower probability of relapsing than those with lower BED regimens; however, the rate of complications was significantly greater.

We could not find any relationship between PFTs before TBI and PC morbidity; however, Soule et al. recommended that patients with lower pulmonary function should receive TBI with a reduced pulmonary dose.43) In our study, only 6 out of 46 patients showed low pulmonary function; therefore, it was very difficult to draw any conclusions from such a small number of patients.

Oya et al. demonstrated that the incidence of IP was significantly higher in patients with acute parotitis.6) In this study, we could not find any such relationship between the incidence of this adverse effect and PC. The reason for this difference is not clear; however, no other investigators have demonstrated a relation between radiation parotitis and PC; further investigation may be necessary. Other factors, such as age and performance status, might be related to the incidence of PC.

The treatment period of this study was more than 15 years, and during this period several changes in the treatment methods occurred: almost all donors were siblings in the early period, whereas in the late period the prevalence of non-related donors increased. The supportive care methods for BMT/TBI related complications also changed. Because of such changes, it may be difficult to draw conclusions regarding which fraction is better; however, although the 4-fraction group included more recipients from unrelated donors and, therefore, was more susceptible to treatment-related PCs, as mentioned above, there was no significant difference in morbidity between 2 groups or in the incidence of PCs. Thus, we can conclude that this retrospective study demonstrated the lower inferiority of the TBI regimen of a total dose of 12 Gy/4 fractions/2 days over the regimen with the same dose in 6 fractions.

Patients must stay in the treatment room alone for a long time, and could suffer from nausea and other acute complications during TBI. The 4 twice-daily fraction regimen seems feasible and may have the benefit of reducing the complexity of TBI because of fewer fractions.

CONCLUSION

There was no significant difference in PCs between patients treated with a TBI dose of 12 Gy in 6 fractions over 3 days and patients treated with a TBI dose of 12 Gy in 4 fractions over 2 days.

ACKNOWLEDGEMENT

Part of this manuscript was presented at the Radiological Society of North America 96th Scientific Assembly and Annual Meeting, November 29, 2010, Chicago, Illinois, USA and at the 69th Annual Meeting of Japan Radiological Society, April 8–11, 2010, Yokohama, Japan.

REFERENCES


Received on December 4, 2010
Revision received on February 17, 2011
Accepted on February 19, 2011
J-STAGE Advance Publication Date: April 12, 2011