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Comparison of Total Body Irradiation Before and After Chemotherapy in Pretreatment for Hematopoietic Stem Cell Transplantation

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Abstract

Objective: To explore the best time to carry out total body irradiation (TBI) in hematopoietic stem cell transplantation (HSCT) pretreatment.
Methods: Retrospective analysis was applied in 88 cases of HSCT using TBI as pretreatment from March 2001 to June 2009 in our hospital. Using 8 MV X-ray, all the patients were irradiated by linear accelerator in 2 consecutive days, with a total dose of 7–11 Gy and an instantaneous dose rate ranging between 4.0 and 5.0 cGy/min. Of the 88 cases, 40 cases were given traditional high-dose chemotherapy before TBI (Group CT/TBI), and 48 cases were given TBI before chemotherapy (Group TBI/CT) instead.
Results: Eighty-seven cases of transplantation were successful, with no serious complications, including radiation pneumonia. Compared with Group CT/TBI, Group TBI/CT showed similar incidence of complications ($p = 0.08$), similar recent chemotherapy toxicity ($p = 0.833$), and significantly lower recent radiation toxicity ($p = 0.000$).
Conclusions: TBI in the pretreatment of HSCT is safe and effective. Using TBI before the high-dose chemotherapy can maintain the same pretreatment effect, effectively reduce apparent immediate reaction/discomfort during TBI, reduce preparation workload of radiotherapy, and lower radiation side-effects. Further research is needed to expand its clinical application.

Key words: hematologic malignancies, hematopoietic stem cell transplantation, TBI

Introduction

High-dose chemotherapy combined with total body irradiation (TBI) is one of the classic pretreatment regimens for hematopoietic stem cell transplantation (HSCT) and/or peripheral blood stem cell transplantation (PBSCT).[1] TBI has always been delivered after conditioning chemotherapy.[2,3] With the increasing use of bone marrow transplantation for hematologic malignancies, TBI is becoming a more commonplace procedure in many of the larger cancer centers in P.R. China.[4,5] The goal of using TBI on the preparation regimens for HSCT is threefold: destroying residual neoplastic cells, clearing the host marrow to allow repopulation with donor marrow cells, and providing sufficient immunosuppression to avoid allograft rejection by immunologically active cells in the host.[6,7] In addition, techniques must be used to safely and efficiently deal with patients who are usually very ill and require long-term treatment. Historically, TBI regimens differed widely in total dose, fractionation schedule, dose rate, patient positioning, and beam modifiers. In the 1970s, the most commonly used TBI schedule was a single fraction of about 10 Gy administered at a low-dose rate. In the 1980s, some authors recommended fractionating the dose once daily or twice daily with the goal of improving the therapeutic ratio, particularly of reducing treatment mortality.[8] Although it has been carried out for decades clinically, there is no uniform

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standard on some main problems such as the optimal dosage of TBI, segmentation, and the relationship between TBI dosage and individual differences during the operation. In the currently used high-dose chemotherapy before TBI (CT/TBI) classical programs, it is conventional to take high-dose chemotherapy first and then TBI. Patients are in poor physical condition after high-dose chemotherapy. To prevent infection, patients need strict isolation protection before and during the treatment, meanwhile strict disinfection of the radiotherapy room, which increases the workload.[9] This work summarizes all the cases using TBI for pretreatment of HSCT in our hospital during the past 9 years. Control study was applied to compare high-dose chemotherapy before TBI (Group CT/TBI) with TBI first (Group TBI/CT).

Patients and Methods

Patients

From March 2001 to June 2009, 88 patients with hematological malignancies were enrolled in our department, who were pretreated with TBI/CT or CT/TBI in HSCT. Of the 88 patients, 67 were men and 21 were women; they age from 6 to 64 years old, with 11 patients younger than 16 years old (33.4 years in median). Among them, 43 had acute lymphoblastic leukemia, 21 had chronic myeloid leukemia, 15 had acute mixed leukemia, and 9 had malignant lymphoma. Fifty-nine patients received autologous peripheral blood stem cell transplantation (APBSCT) and 29 received allogeneic HSCT (Allo-HSCT). All of them provided signed consent for the transplant regimen. Forty patients were pretreated with high-dose chemotherapy before TBI (Group CT/TBI) from March 2001 to June 2006, and the other 48 patients were pretreated with TBI before chemotherapy (Group TBI/CT) from July 2006 to June 2009. Patient characteristics of these two groups are listed in Table 1. The TBI dose was given in 2 fractions for 2 consecutive days (one fraction per day) before HSCT. The total dose was 7–9 Gy in 11 patients, and 9–11 Gy in 77 patients.

Pretreatment regimen

All the patients were pretreated with TBI/CT or CT/TBI. Chemotherapeutic drugs were used: cyclophosphamide (CTX) alone or CTX combined with cytosine arabinoside (Ara-C) and antithymocyte/antilymphocyte alobulin (ATG). Chemotherapy regimen was as follows: CTX 60 mg/kg ×2 days, Ara-C 3 g/m^2 ×2 days, ATG 2.5 mg/kg ×4 days. In Group CT/TBI, 23 patients received CTX alone, and 17 received CTX/Ara-C/ATG regimen; whereas in Group TBI/CT, 21 patients used CTX alone, and 27 used CTX/Ara-C/ATG regimen. TBI was administered using SLi linear accelerator (Philips) and an 8-MV photon beam was used. TBI regimen was as follows: Adults older than 18 years were pretreated with TBI of 9–11 Gy in 2 consecutive days, and teenagers younger than 16 years were pretreated with TBI of 7–9 Gy in 2 consecutive days. In Group CT/TBI, TBI was carried out on the next day after chemotherapy. In Group TBI/CT, high-dose chemotherapy was adopted on the next day after TBI.

Mobilization and collection of hematopoietic stem cell

In Allo-HSCT, healthy donors were given granulocyte colony-stimulating factor (G-CSF) ($5\,\mu g\cdot kg^{-1}\cdot day^{-1}$) with subcutaneous injection alone for mobilization of HSCs. In autologous HSCT (Auto-HSCT), chemotherapy plus G-CSF were used to mobilize HSCs. G-CSF ($5–10\,\mu g\cdot kg^{-1}\cdot day^{-1}$) was subcutaneously injected when leukocytes (WBC) began to rise from the lowest point after chemotherapy. In Group CT/TBI, 3 patients received Allo-HSCT, and 37 received Auto-HSCT. In Group TBI/CT, 26 patients underwent Allo-HSCT, and 22 underwent Auto-HSCT. The mobilized hematopoietic stem cells were collected when WBC was raised to 5.0×10^9 L^{-1}. Blood cell separator is Baxter CS 3000plus. Circulating blood volume is 2–4 times capacity of blood circulation. Sufficient quantities of stem cells were collected in 2–4 cycles to obtain mononuclear cells (MNCs) $>5.0\times10^8$ kg^{-1} and CD34$^+$ cells $>2.0\times10^6$ kg^{-1}.

Treatment position and equipment condition in TBI

An Elekta SLi linear accelerator and 8-MV photon beam were used in TBI, applying the maximal field size of 40×40 cm^2. Parallel opposed beams were used by delivering each fractional dose in two equal setups and switching the patient's position between the two fields. Patients lay on their side on a radiotherapy couch with knees bent slightly. Radiation fields included two opposed fields, anterior-posterior field (face toward the gantry) and posterior-anterior field (back toward the gantry) with the collimator being rotated 45°. By positioning the gantry at 270° and the couch alongside the treatment room wall, a distance between the source and the center of human body should reach 380 cm to cover the patient's entire body with the radiation field.

Radiation dosimetry

The dose of a TBI is usually prescribed to a dose prescription point inside the body in the pelvic region at the height of the umbilicus. And the depth of prescription point is the half of the average thickness of a patient's head, neck, chest, abdomen (umbilicus), thigh, and ankle. For other vital organs, such as lung, eye lens, and brain, the dose is calculated. The absorbed dose rate in dose prescription point is 4.0–5.0 cGy/min. The total absorbed dose is calculated according to tissue maximum ratio method with the half of depth and thickness of body in umbilical plane. The

Table 1. Patient Characteristics Between Group CT/TBI and TBI/CT

Group	*Cases*	*Men/women*	*Age: 6–16*	*Age: 17–64*	*ALL*	*CML*	*AML*	*NHL*	*APBSCT*	*Allo-HSCT*
CT/TBI	40	30/10	5	35	15	11	10	4	36	4
TBI/CT	48	37/11	6	42	28	10	5	5	23	25

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; APBSCT, autologous peripheral blood stem cell transplantation; CT, chemotherapy, TBI, total body irradiation.

radiation dose is 7–11 Gy, given in 2 days altogether. Radiation dose was verified by Farmer2570 dosimeter and 0.6 cc ionization chamber. Plexiglass plates that are 1.2-cm thick were used as flattening filters to realize dose uniformity within 5% at 380 cm position within a size of 160 cm × 160 cm, and to meet the dose homogeneity requirements in radiotherapy. A 1.5-cm-thick PMMA screen was positioned between the source and the patient to raise the surface dose to ≥90% of the prescribed TBI dose.

Shielding of vital organs

Vital organs were shielded by 5 half-value layer lead blocks. During irradiation, eyes, lens, oral cavity, and parotid were blocked in anterior-posterior position, but not in posterior-anterior position because of the natural shield provided by the head. Lead block of both lungs were made individually according to radiographic location. Both lungs were shielded for some certain time in posterior-anterior position to ensure that irradiation dose of total lung was less than 7.5 Gy.

Follow-up treatment after transplantation

In conventional methods, preventive measures of graft versus host disease (GVHD) are combined with Cyclosporin A with short-term Mycophenolate mofetil and methotrexate (MTX). The acute GVHD maybe treated using methylprednisolone pulse therapy, which can be changed to the Solae or CD3 monoclonal antibody when invalid. After autologous stem cell transplantation, consolidation chemotherapy is given when appropriate. And induction chemotherapy is needed again for recurrence after transplantation. In principle, chemotherapy uses standard dose joint programs. After transplantation, residual lesions receive additional local irradiation of 30–40 Gy.

Evidence of hematopoietic reconstitution

Hematopoietic reconstitution is considered successful, if the following indicators are fulfilled. After transplantation, neutrophils and platelet count are more than 0.5×10^9 L^{-1} and 20×10^9 L^{-1}, respectively, for consecutive 3 days without depending on blood transfusion. For allogeneic peripheral blood stem cell transplant, the evidence of engraftment is that the blood group of recipient transforms into the donor's blood group or bone marrow cells into donor's sex chromosome in ABO blood group or gender subtransplant. If the blood group or gender is consistent, the evidence of engraftment is that the recipient STR test transforms into donor's type. For APBSCT, the evidence of engraftment is short-term recovery of blood and lasting stability of bone marrow hematopoiesis.

Statistical analysis

Event rates were calculated as discrete data. Analysis was performed by SPSS 13.0 (Chicago, IL). The statistical significance of differences between Group CT/TBI and TBI/CT was examined by chi-square test. $p<0.05$ was defined to be statistically significant.

Results

Hematopoietic reconstitution

In Group CT/TBI, one patient failed to achieve hematopoietic reconstitution; for the other patients, their WBC dropped to 0 at about 4 (4.6 ± 3.2) days after transplantation, and PLT dropped to less than 10×10^9 L^{-1} at about 6 (6.8 ± 3.4) days later. In Group TBI/CT, all the patients finished pretreatment and achieved hematopoietic reconstitution. The mean days for hematopoietic reconstitution (ANC $>0.5\times10^9$ L^{-1}, PLT $>20\times10^9$ L^{-1}) were 10 ± 3 days and 15 ± 5 days in all the patients, respectively, without transplantation-related death. The median days for hematopoietic reconstitution were 9 ± 2 days for ANC and 13 ± 3 days for PLT in Group CT/TBI and 13 ± 2 days for ANC and 17 ± 4 days for PLT in Group TBI/CT. Shorter hematopoietic reconstitution time in Group CT/TBI was because APBSCT patients in Group CT/TBI were more than those in Group CT/TBI. As for APBSCT patients, the median days for hematopoietic reconstitution were 9.25 ± 1.5 days for ANC and 13.17 ± 2.57 days for PLT in Group CT/TBI and 9.913 ± 1.730 days for ANC and 14.17 ± 2.93 days for PLT in Group TBI/CT. There was no statistical significance in the difference for hematopoietic reconstitution time between the two groups by only comparing the APBSCT patients (for ANC, $p=0.124$; for PLT, $p=0.170$).

Complications

Of the 88 patients, 41 (51.1%) had infection when WBC dropped to less than 1.0×10^9 L^{-1}. The clinical manifestation was fever. Most patients showed no obvious symptoms of system infection. Blood culture showed no bacterium or fungus growth in any patient with fever. The fever could be effectively controlled with third-generation cephalosporin or carbapenem antibiotics. Three patients had cytomegalovirus infection at 1–3 weeks after transplantation, who were treated using ganciclovir ($5\,mg\cdot kg^{-1}\cdot 12\,hour^{-1}$) and high-dose γ globulin for 3 weeks until etiology disappeared. No hepatic veno-occlusive disease was observed. Twenty-two patients suffered from acute GVHD of different degrees; methylprednisolone ($2\,mg\cdot kg^{-1}\cdot d^{-1}$) shock treatment was used for 3–5 days and all got cured. Three patients had chronic GVHD, who recovered using Cyclosporine and prednisone. The two groups showed no significant difference in

Table 2. Comparative Analysis of Complication Rate Between Group CT/TBI and TBI/CT

Group	*Cases*	*Bacterial infection*	*Cytomegalovirus infection*	*Hepatic veno-occlusive disease*	*Acute GVHD*	*Chronic GVHD*	*Complication*
CT/TBI	40	21	2	0	12	2	37
TBI/CT	48	20	1	0	10	1	32
p-Value		0.424	0.872	—	0.458	0.872	0.08

GVHD, graft versus host disease.

Table 3. Comparative Analysis of Recent Radiation Toxicity Between Group CT/TBI and TBI/CT

Group	*Cases*	*Nausea and vomiting*	*Sweating*	*Dizziness*	*Oral parotid response*	*Interstitial pneumonia*	*Cystitis*	*Recent radiation reaction*
CT/TBI	40	11	6	5	1	0	0	23
TBI/CT	48	1	1	1	0	0	0	3
p-Value		0.002	0.067	0.132	0.927	—	—	0.000

complication rate after combined chemo and TBI treatment ($p = 0.08$, Table 2).

Bleeding

Four patients exhibited nasal bleeding (1 in Group CT/TBI and 3 in Group TBI/CT) and 2 patients had scattered subcutaneous bleeding (both in Group CT/TBI). Prophylactic blood platelet suspensions were transfused routinely. Nobody showed internal organ bleeding or intracranial hemorrhage. The average amount of platelet transfusion was 20 units (10–40 units), 10 units once.

Recent radiation toxicity

Twenty-six patients had different degrees of gastrointestinal symptoms like nausea, vomiting, sweating, and dizziness, during radiotherapy. Of them, each could complete the treatment after about 10 minutes of rest, and two underwent symptomatic treatment with phenergan injections. One patient experienced parotid gland swelling the next day after treatment, but continued irradiation after symptomatic treatment, without obvious acute pain in throat and mouth, interstitial pneumonia, or bladder infection. Compared with Group CT/TBI, Group TBI/CT showed significantly reduced recent radiation toxicity ($p = 0.000$, Table 3).

Recent chemotherapy toxicity

Forty-five patients had different degrees of uncomfortable symptoms, like nausea, vomiting, fever, constipation, diarrhea, mucositis, skin rash, and so on, during chemotherapy. Each of these patients could complete the treatment with granisetron or phenergan injections. Compared with Group CT/TBI, Group TBI/CT showed no significantly increased recent chemotherapy toxicity ($p = 0.833$, Table 4).

Follow-up

One patient in Group CT/TBI died of secondary infection 2 months after allogeneic transplantation. Seven patients suffered a relapse at 4 months (2 in Group CT/TBI), 6 months (1 in Group TBI/CT), 9 months (2 in Group TBI/CT), or 10 months (2 in Group CT/TBI) after transplantation, and died of invalid induction chemotherapy. The rest had survived for 13–46 months free from any diseases. By July 1, 2010, all the patients in Group CT/TBI suffered a relapse, and 7 patients survived free from any diseases in Group TBI/CT. In Group CT/TBI, the survival time free from any diseases was 13–42 months with a median of 32.7 months. In Group TBI/CT, the survival time free from any diseases was 15–46 months with a median of 34.1 months. No significant difference existed between the two groups ($p = 0.627$).

Discussion

TBI is a complex radiotherapeutic technique used for treating certain hematologic, oncologic, and immunologic diseases. TBI-containing regimens have been demonstrated to create better outcomes than non-TBI regimens for treating pediatric acute or adult leukemia.[10–12] The role of TBI is to destroy the recipient's bone marrow and tumor cells and to immunosuppress the patient sufficiently to avoid rejection of the donor's bone marrow transplant.[13,14] In the pretreatment program of HSCT, the primary mechanism of TBI is as follows: to make implantation easier by maximally inhibiting the immune responses, to facilitate survival of the implanted hematopoietic stem cells by emptying bone marrow, to maximally kill residual tumor cells, and to significantly increase the death rate of bone marrow tumor cells that are sensitive to radiotherapy.[15]

TBI combined with high-dose chemotherapy is widely used as a pretreatment regimen of HSCT in hematologic disorders. Over the past several years, there have been few changes in the pretreatment and chemotherapy regimen for HSCT. The major chemotherapy drugs were CTX, Ara-C, and ATG. From July in 2006, we began to take TBI/CT program instead of CT/TBI. The chemotherapy regimens for the two groups were also the same. Thus, TBI/CT and CT/TBI are still comparable although the research has lasted 8–9 years. As patients in Group TBI/CT are in relatively good condition without high-dose chemotherapy, they can enter the radiotherapy room after its routine cleaning, use of disinfection sheet, and ultraviolet air disinfection. Pretreatment effect of this program is exactly the same as before. But it can significantly simplify the radiation room disinfection and patient pretreatment preparation, and reduce immediate reactions in radiotherapy.

The number or frequency of recent toxicity was evaluated during the course of radiotherapy by the therapist staff and during the course of chemotherapy by the nursing staff. Compared with Group CT/TBI, Group TBI/CT showed no

Table 4. Comparative Analysis of Recent Chemotherapy Toxicity Between Group CT/TBI and TBI/CT

Group	*Cases*	*Nausea and vomiting*	*Fever*	*Constipation*	*Diarrhea*	*Mucositis*	*Skin rash*	*Recent chemotherapy reaction*
CT/TBI	40	32	22	8	7	14	5	38
TBI/CT	48	36	25	10	9	17	6	45
p-Value		0.762	0.953	0.854	0.866	0.900	0.746	0.833

significantly increased recent chemotherapy toxicity. However, compared with Group CT/TBI, Group TBI/CT showed significantly reduced recent radiation toxicity.

Because TBI treatment time is long, patients need to maintain a relatively fixed body posture. In the treatment they easily present nausea, vomiting, and other acute radiation reactions to interrupt the treatment. Actually, recent radiation toxicity or chemotherapy toxicity was a component symptom during TBI in Group CT/TBI or during CT in Group TBI/CT. But we only analyzed the recent toxicity during radiotherapy or chemotherapy and then explored the effect of recent radiation toxicity on radiotherapy itself. During the course of radiotherapy, we paid special attention to conformability, compliance, and time consumption, which can improve treatment quality, patient safeness, and protective measure during the course of radiotherapy. In the Group CT/TBI, more patients present fatigue, sweating, and dizziness; more treatment interruption occurs. The treatment compliance of Group TBI/CT is better. There is more successful completion of the whole irradiation. To overcome these problems, the daily dose is divided into 3 sections during treatment, 1.5–2.0 Gy per section, so the patients have time to rest in treatment; this can improve patients' tolerance of a fixed position, and reduce treatment shift or errors.

Clinically, TBI program is usually used in lymphoblastic leukemia.[16] Before HSCT, TBI needs to be adjusted to consist with the previous treatment and patients' general condition. For children or the patients who were weak or have received irradiation of whole brain and spinal cord or intrathecal injection of MTX, TBI dose should be reduced and other chemotherapy drugs should be added. For malignant lymphoma patients with huge mass in early onset, it is expected to improve the efficacy to do complementary radical irradiation to the large tumor location.

In summary, in HSCT of hematological malignancies, the pretreatment regimen of TBI before high-dose chemotherapy has the same pretreatment effect as the CT/TBI regimen. However, it effectively reduces apparent immediate reaction/discomfort during radiotherapy and reduces preparation workload of radiotherapy. Therefore, TBI/CT regimen is more convenient in clinical application. It may decrease the incidence of infection and increase the chances of successful transplantation. It is worth clinical application and popularization.

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Disclosure Statement

No competing financial interests exist.

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