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Study on Fractionated Total Body Irradiation before Hematopoietic Stem Cell Transplantation

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OBJECTIVE To observe the dose and the complications from total body irradiation before hematopoietic stem cell transplantation.
METHODS This study involved 312 patients with total body irradiation before hematopoietic stem cell transplantation. They were entered into the treated research from May 1999 to October 2005. All patients had received the irradiation from ^{60}Co of an absorbed dose rate of (5.2 ± 1.13) cGy/min. The total dose of TBI was 7~12 Gy, 1 f/d × 2 d. A high-dose rate group (≥ 10 Gy) included 139 cases and a low-dose rate group (< 10 Gy) included 173 cases.
RESULTS The probability of acute gastrointestinal reactions in the high-dose rate group was more compared with that in the low-dose rate group. The differences for other reactions, such as hematopoietic reconstitution and graft survival rate, between the two groups were insignificant.
CONCLUSION Using fractional total body irradiation at a dose rate of 5 cGy/min, with a total dose of 7~12 Gy, 1 f/d × 2 d , with the lung receiving under 7.5 Gy is a safe and effective pretreatment for hematopoietic stem cell transplantation.

KEY WORDS: hematopoietic stem cell, transplantation, pretreatment, total body irradiation, absorbed dose rate.

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Introduction

At present, hematopoietic stem cell transplantation (HSCT) is an important and effective method for treating some malignant hematological system diseases and some solid tumors. HSCT also is a single method for treating some hematopathies. High-dose chemotherapy combined with total body irradiation (TBI) has been a classic pretreatment for hematopoietic stem cell transplantation. Pretreatment is an important part of transplantation. For many years, the dose and treatment model of TBI has not reached a consensus. This problem is due to differences in equipment used and the irradiation technique among all the clinics. Moreover, every radiotherapy centre lacks sufficient cases to review the past results. Since 1999, our hospital has treated a great number of patients by TBI cooperating with many other blood transplantation centers. In this report we have summarized the clinical TBI results.

Materials and Methods

Clinical data

From May 1999 to October 2005, 312 patients were treated with total

body irradiation, among which 229 were males and 83 females. The median age was 34 years (range, 16 to 56 years). Disease types and transplanting types are shown in Table 1.

Tab1e 1. General patients data.

Disease	Cases	Transplant type	Cases
ALL	52	ABMT	33
AML	89	APBSCT	61
CML	61	Allo-BMT	94
CLL	38	Allo-PBSCT	124
ML	40		
MM	15		
MDS	13		
SAA	4		

Pretreatment program

All of patients were treated with a TBI/CY pretreatment program. Radiation dose was 7~12 Gy (< 10 Gy for 39 patients; > 10 Gy for 173 patients). Chemotherapy: cyclophosphamide (CTX) qua basis, CTX 50~60 mg/kg on each of 2 days, and combined with cytarabine (Ara-C), etoposide (VP-16) and daunorubicin (DAM), respectively.

Total body irradiation

Radiation body position

The patients were treated by T-780 ^{60}Co sources correspondence radiation from AP-PA. The gantry revolved 235° and the coll revolved 35°, with a beam of horizontal irradiation. The distance of the radioactive source to the wall was 350 cm and utility of diagonal length was 160 cm. The body position of patient was lateral decubitus and bent knees. The reference point for calculation of the dose was the umbilical plane.

Irradiation dose

The calculation of the dose thickness was the average thickness from the frontal region, angle of the stemum and umbilical plane of the patients. The calculated depth of therapeutic prescription dose was a half of the dose calculation thickness. The absorbed dose rate was (5.2 ± 1.13) cGy/min. The calculated total dose was based on the patient's umbilical plane dose. The total irradiation dose was 7~12 Gy, 1 f/d × 2 d.

Dose calculation

Nominal standard dose elected umbilical plane when total body irradiation. The midpoint dose (D_m) was calculated according to the tissue phantom rate (TPR).

Equation: $D_m = D_f \times TPR$

D_f was the point of reference dose; TPR was the tissue phantom rate of this thickness. Dose calculation of the lung was as follows:

Equation: $D_{lung} = [(D_{total}-D_{screen})+D_{leakage}]\times$Frevise

D_{screen}: screen dose; $D_{leakage}$: leakage dose during screening; $F_{correct}$: heterogenicity revise of tissue (Table 2).

Table 2. Lung tissue correction factor.

Thickness (cm)	Lung tissue correction factor	
	^{60}Co γ-ray	6MV X-ray
12	1.04	1.04
16	1.09	1.09
20	1.14	1.13
24	1.19	1.17
28	1.24	1.24

Measurement checking

We measured the beam uniformity to make use of Farmer 2570 and 0.6CC ion chamber. The filter was made of 1.5 mm organic glass, providing a dose uniformity of ± 5% in 160 cm ×160 cm limit.

Methods of screening critical organs

Make two blocks by Lipowitz (3 cm × 7 cm × 20 cm) and screen lens and parotid gland when the patient used the AP position; erect blocks in front of the eyes and keep 30 cm distance, and then dislodge the blocks when the patient used the PA position. Blocks for screening lungs were used according to the localization film.

Evaluation target of extramedullary toxicity

The toxicity reaction from pretreatment was classed as 0-IV level by Bearman et al.[1] from Seattle, USA. Absence of a reaction was considered be 0 level, and a lethal reaction was IV level. Hematopoiesis rebuilding: after transplantation, absolute neutrophil count (ANC) > 0.5 × 10^9/L, platelet count (PLT) > 20 × 10^9/L, moreover, keep the hematopoiesis rebuild continual more than 3 days without blood transfusion. We observed the required time for hematopoietic rebuilding. Successful evidence of transplantation are: if donee and donor were not the same blood type or sex, select the donor's blood type or sex as successful evidence. Otherwise we would make judgment according to the hemogram quick recovery and the continual hematopoietic ability of marrow.

Statistical analysis

The SPSS 13.0 statistical package was used to compare percentages by the χ^2 tests, and to analyze the mean.

Results

Absorbed dose of critical organ or tissue

The TBI dose rate was (5.2 ± 1.13) cGy/min with a total dose of 7~12 Gy (range 312, < 10 Gy, 139 cases; ≥ 10 Gy, 173 cases). The dosage to the lung was 6~8 Gy (mean, 7.5 Gy). The lens dose was (3.9 ± 0.7) Gy and the parotid dose was (4.6 ± 1.5) Gy.

Early adverse reactions

The early toxicity reactions included nausea, vomiting, diarrhea, oral mucositis, swollen parotids and pain, fever (≥ 38.5°C) etc. The difference in the incidence rate between gastrointestinal reaction and oral mucositis was significant. The difference in the incidence rate between hemorrhagic cystitis and cirrhosis of the lungs were insignificant (Table 3).

Table 3. The early toxicity reactions of TBI in different dosage groups.

Symptom	< 10 Gy (n = 139)	≥ 10 Gy (n = 173)	P
Fever	62	49	> 0.05
Parotid swollen	111	148	> 0.05
Gastrointestinal reaction	78	125	< 0.05
Oral mucositis	82	123	< 0.05
Hemorrhagic cystitis	17	31	> 0.05
Cirrhosis of lung	12	19	> 0.05

Hematopoiesis rebuilding and the graft achievement rate after transplantation, see Table 4.

Discussion

TBI is an important part of pretreatment for hematopoietic stem cell transplantation. Its main effects include the followings: *i*) immunosuppression used in order that the new cells can be accepted by the donee[2]; *ii*) removing the malignant tumor cells, which have escaped from chemotherapy[3]; *iii*) killing bone marrow cells so that transplant may be accepted; *iv*) to destroy tumor cell multidrug resistance of the primary tumor, and *v*) significantly increase to the radiation sensitive of leukemia and lymphoma cells of destruction.

TBI is a special radiotherapy technology that produces many questions related to clinical medicine, radiation biology, physics etc. Although it has been in practice more than 50 years, there are still many questions. To increase the survival rate and reduce the recurrence rate as well as the incidence of interstitial pneumonitis (IP), staff from many blood transplant centers have studied the use of the single and fractionated-dose TBI treatments, and then once more the single and fractionated TBI treatment models and dose fractions[4,5]. Now, at the international level, there is no unified standard for TBI dosage. Experimental studies and clinical data have confirmed that the incidences of IP with single-dose TBI (STBI) is higher than with fractionated (FTBI)[6,7]. The purpose of FTBI is to decrease normal tissue damage and complications, especially to reduce the incidence of IP. The FTBI may allow an increase in the total dose and improve the therapeutic ratio.

Clinical research has confirmed the cataract incidence of 80% in long-term survivors of STBI to 10 Gy and obviously incidence of FTBI about 10%~20%. FTBI treatment time was short and the patients keeping the body position was easy. The general model of FTBI were 2 Gy/f, 2 f/d, interval 6 to 8 h, TBI total dose was 12 to 14 Gy and 3 Gy/f, 4 f/d or 1.2 Gy/f, 3 f/d, interval 5 h, total dose was 13.2 Gy and 4 Gy/f or 2.5 Gy/f, total dose was 12 Gy[8]. Our fractional model is total dose is 7~12 Gy, once per day in 2 days. The result indicated that the patients have excellent survivability and gastrointestinal reaction is mildness and hematopoietic reconstitution recovered quickly. The incidence of IP was decreased and graft survival rate was above 70%.

So we think that the FTBI have an advantage contrast with the STBI. The dose of FTBI could be added to 10~12 Gy. Radiobiology research indicated that FTBI could produce a different effect between tumor cells and normal tissue. It conduced to repair the normal tissue and make the treatment effect better than STBI. The model (1 f/d × 2 d) was reasonably. Using the multiple fraction models could not improve incidence of IP, and that increase infection. Besides, it may increase many difficult in the schedule of the radiotherapy department. Devergie et al.[9] introduced that with the FTBI, the recurrence rate is higher contrast with the STBI about leukemia.

Instantly response of TBI is a serious toxicity including nausea, emeses and dizziness since TBI beginning. Some studies[10-13] reported that the instantly response occurrence after irradiation 2 to 4 h. The response became seriously accompany irradiation dose increase. Treatment time of STBI was longer and proceeding serious gastrointestinal reaction.

In our study the high dose group was significantly contrast with the low dose group ($P < 0.05$) of the rate of acute gastrointestinal reaction and oral mucositis. The other reactions were insignificant difference. Several patients were received some antiemetics and sedatives in the first half hour of TBI and the treatment was successfully.

Now people generally recognize this relation between the IP and the total dose and the absorbed dose rate of

Table 4. Hematopoiesis rebuilding and graft survival evidence compared with the dose.

Group	Cases	Graft achievement rate (%)	Hematopoietic rebuilding time (days)	
			ANC > 0.5×10^9/L	PLT > 20×10^9/L
< 10 Gy	139	70.5	15.2 ± 4.8	17.8 ± 9.2
≥ 10 Gy	173	75.7	14.3 ± 6.1	19.6 ± 10.3
P		> 0.05	> 0.05	> 0.05

TBI[13,14]. With low dose rate irradiation, the treatment would spend more time that the patient is hard to keep position. On the other hand, the TBI may be intermitted because of the acute reaction of nausea and vomiting, etc. Although the high dose rate irradiation would spend less time, the incidence rate of complications were obviously increased, for instance IP.

It is not a linear correlation that between the lungs injury and the reception dose, and exist a critical value between them. Keane[15] proved a fact that the threshold dose of IP is 7.5 Gy when absorbed dose rate is 0.5~4 Gy/min and the incidence rate of IP add up to 50% when 9.3 Gy. In the low dose rate (1~5 cGY/min) instance, the threshold of IP could be increased to 9 Gy. When Barrett[16] using the ultra-low dose rate (2.5 cGy/min), the threshold dose could be increased to 9.5 cGy and the IP won't occurred. In our research the incidence rate for the two groups have not the distinct difference with the same dose rate. It explains that the dose rate is important factor of IP. It is safe and effective when the value of absorbed dose rate is 5 cGy/min and the total dose is 7 Gy~12 Gy. This time the incidence rate of IP is 10%. The difference about the hematopoiesis rebuild and the graft achievement rate between the high dose group and low dose group are insignificantly, and the graft achievement rate is 70%, it is satisfying.

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