Research Article

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The Dose per Fraction May be correlated with Late Kidney Toxicity after Total Body Irradiation: a Single Institution Experience

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Abstract

Background: *The purpose of the present study was to retrospectively evaluate the subacute or late toxicities in the kidney, lung, and liver after two total body irradiation regimens, 12 Gy in 6 fractions (group A) and 12 Gy in 4 fractions (group B).*

Methods: *Forty-two patients who underwent total body irradiation (group A, n=32; group B, n=10) between June 1997 and June 2013 were included in the present study. The median follow up period was 60 months (range: 3–219 months) for the patients in group A and 143 months (range: 5–220 months) for the patients in group B. We evaluated the renal, pulmonary, and hepatic toxicities using the Common Terminology Criteria for Adverse Events version 4.0.*

Results: *There were 4 cases of chronic kidney disease (group A, n=1; group B, n=3). Although the cumulative incidence of chronic kidney disease differed significantly between the two total body irradiation regimens (p=0.014), the pulmonary and hepatic toxicities did not differ to a statistically significant extent.*

Conclusion: *The present study suggests that a higher dose per fraction caused a higher incidence of chronic kidney disease.*

Keywords: Whole-body Irradiation, Renal Insufficiency, Chronic Pneumonia, Dose Fractionation, Hematopoietic Stem Cell Transplantation

Introduction

Although hematopoietic stem cell transplantation (HSCT) is primarily used for the treatment of hematological and lymphoid cancers, it is also used in the treatment of many other diseases. Worldwide, more than 45,000 HSCTs are performed each year, mostly for leukemia and lymphoma [1].

Total body irradiation (TBI) and chemotherapy have been used as components of the conditioning regimen for HSCT since Thomas et al. first treated advanced leukemia with HSCT after TBI and chemotherapy, and TBI is widely used throughout the world at the present time [2,3].

Various adverse events occur after HSCT, including graft versus host disease. As TBI is radiotherapy of the entire body, every organ can be affected by adverse events. The sub-acute and late toxicities that occur after TBI in preparation for HSCT, include (but are not limited to) chronic kidney disease, pneumonitis and veno-occlusive disease of the liver [4]. Although severe adverse events, including death, are known to occur, only a few reports have investigated the adverse events that occur after TBI in preparation for HSCT over a long-term follow-up period. Furthermore, few reports have compared the effects of different doses per fraction with respect to the incidence of chronic kidney disease.

In the present study, we retrospectively evaluated the sub-acute or late adverse events in the kidney, lung, and liver of adult patients after TBI in preparation for HSCT, and investigated the correlations between the dose per fraction and adverse events.

Methods

Ethics statement

Institutional review board of Yamagata University Faculty of Medicine approved the present study (S-14). It was conducted in accordance with the Declaration of Helsinki.

Patients

Patients who underwent TBI treatment in preparation for HSCT at our hospital between June 1997 and June 2013 were recruited retrospectively from Yamagata University Hospital database. Fifty-eight patients received TBI in this period. The inclusion criteria were as follows: age ≥16 years; a TBI regimen of 12 Gy in 6 fractions (group A) or 12 Gy in 4 fractions (group B); and a follow up time of ≥3 months.

In total, 42 eligible patients who underwent TBI were included in the present study. The characteristics of the patients are summarized in Table 1. Group A included 13 men and 19 women, with a median age of 42 years (range: 17–62 years); the median follow-up time was 60 months (range: 3–219 months). In contrast, the patients in group B consisted of 9 men and 1 woman, with a median age of 34 years (range: 17–54 years); the median follow up time was 143 months (range: 5–220 months). The median follow up time of the patients in group B was longer than that of the patients in group A because all of the former patients were treated before 2008. The chemotherapy regimens included, cyclophosphamide alone (n=32), cyclophosphamide and cytarabine (n=7), and cyclophosphamide and etoposide (n=3). There were no statistically significant differences between the chemotherapy regimens (p=0.059).

Table 1: Patient characteristics

	12 Gy in 6 fractions (n=32)	12 Gy in 4 fractions (n=10)	P value
Age			
Median	42	34	0.248
Range	17 – 62	17 – 54	
Gender			
Male	13	9	
Female	19	1	
Follow up time (months)			
Median	34.5	131	0.002
Range	3 – 198	5 – 189	
Diagnosis			
Acute myeloid leukemia	15	7	0.703
Acute lymphocytic leukemia	8	1	
Myelodysplastic syndrome	3	1	
Chronic myeloid leukemia	2	1	
Malignant lymphoma	3	0	
Chronic lymphocytic leukemia	1	0	
Hematopoietic stem cell transplantation			
Bone marrow transplantation	21	7	0.844
Peripheral stem cell transplantation	10	3	
Umbilical cord blood transplant	1	0	
Chemotherapy			
Cyclophosphamide alone	26	6	0.059
Cyclophosphamide and cytarabine	3	4	
Cyclophosphamide and etoposide	3	0	

Total body irradiation

The patients lay in a supine position with their legs bent on a couch (a stretcher before 2009, and a couch for TBI only [ORP-TBI-MN, Oriden, Japan] after 2010) when they received TBI. All of the patients received a total dose of 12 Gy in 6 fractions or 4 fractions with lateral opposing portal 4 MV X-ray irradiation twice daily over consecutive days. The interval between fractionated irradiation was at least 6 hours. Patients were irradiated with eye shields with a dose rate of less than 0.1 Gy/min. The compensation of the lung was adjusted for each patient to reduce the lung dose (which was ≤ 80% of the dose); lung and kidney shields were not used. The source-target distance was 400 cm before 2009, and 500 cm after 2010 with a single square X-ray field.

The evaluation of toxicities

We examined the patients' medical records and extracted cases of subacute and late (one or more months after TBI) renal, pulmonary, and hepatic toxicities for which there was no apparent cause (such as infections or drugs). These cases were then evaluated based on the Common Terminology Criteria for Adverse Events version 4.0 [5].

Statistical analysis

All of the statistical analyses were performed using the IBM SPSS Statistics software program (version 22 SPSS Inc., Chicago, IL, USA). The group categories were compared using the chi-squared test or the Mann–Whitney U-test. The probabilities of chronic kidney disease, pneumonitis, and "hepatobiliary disorders, other specify" were estimated based on the cumulative incidence, and their cumulative incidence was compared by a log-rank test. A univariate analysis was performed using the log-rank test. The P values were two-sided. The follow up time was defined as the time between the initiation of TBI and the final follow-up examination, or the patient's death.

Results

Chronic kidney disease

The serum creatinine levels of all of the patients were with in normal range before they underwent TBI. The 2-year cumulative incidence of chronic kidney disease was 10.1% (95% confidence interval [CI]: 0.7–19.5%) (Figure 1a). In all but 4 patients, the renal dysfunction was temporary. The severity of the renal dysfunction was classified as grade 1 in one patient and grade 2 in three patients. Their estimated glomerular filtration rate decreased 2-7 months after TBI, continued to decrease gradually without recovering normal range. Three of these patients were in group B and one patient was in group A

(Figure 2). Although their renal function did not improve, they lived without any treatment. A univariate analysis revealed that the only significant difference between the two dosing regimens seemed to be the cumulative incidence of chronic kidney disease (p=0.014) (Table 2).

Pneumonitis

The 2-year cumulative incidence of pneumonitis was 5.9% (95% CI: 0–13.7%) (Figure 1b). One patient in group A developed dyspnea at 1 year after TBI treatment and died of pneumonitis at 2 years after TBI, despite receiving oxygenation and steroid therapy (grade5). One patient in group B had a cough and was diagnosed with pneumonitis based on the computed tomography findings at 9 months after TBI treatment, and was treated with steroids (grade2). Both patients received peripheral stem cell transplantation, and had no comorbidities affecting respiratory system (such as chronic obstructive pulmonary disease, interstitial pneumonia, and other respiratory conditions). There was no statistically significant difference in the cumulative incidence of pneumonitis between groups A and B (p=0.424). There was no statistically significant difference in the cumulative incidence of pneumonitis between the patients who received cyclophosphamide alone and those who received cyclophosphamide plus another drug (p=0.387) (Table 2).

Hepatobiliary disorders, other specify

The 2 year cumulative incidence of "hepatobiliary disorders, other specify" including one liver cirrhosis patient was 63.0% (95% CI: 47.0%–79.0%) (Figure 1c). There was no statistically significant difference in the cumulative incidence of "hepatobiliary disorders, other specify" between groups A and B (p=0.244). Furthermore, there was no statistically significant difference in the cumulative incidence of "hepatobiliary disorders, other specify" between the patients who received cyclophosphamide alone and those who received cyclophosphamide plus another drug (p=0.408) (Table 2).

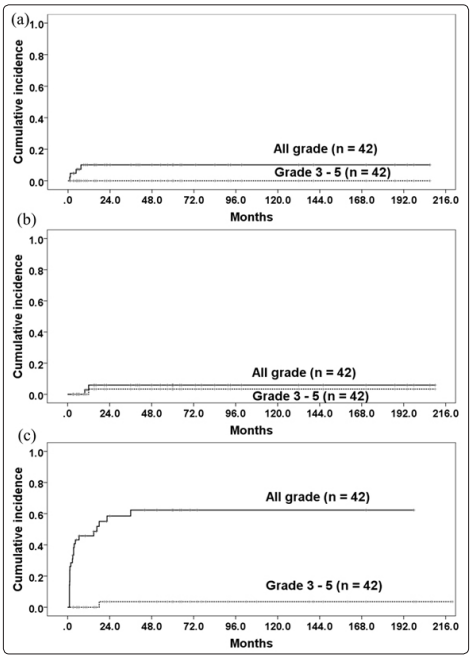

Figure 1: The cumulative incidence of toxicities. (a) The cumulative incidence of chronic kidney disease. The 2-year cumulative incidence of chronic kidney disease (all grades) was 10.1%. (b) The cumulative incidence of pneumonitis. There were 2 patients with pneumonitis. The 2-year cumulative incidence (all grades) was 5.9%. (c) The cumulative incidence of "hepatobiliary disorders, other specify". The 2 year cumulative incidence (all grades) was 63.0%. In some patients the "hepatobiliary disorders, other specify" were still present at 2 years after the TBI treatment.

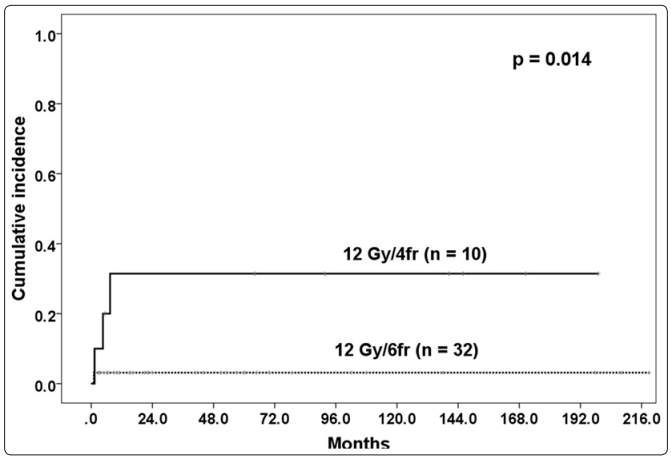

Figure 2: The cumulative incidence of chronic kidney disease in the 12 Gy in 4 fractions group and the 12 Gy in 6 fractions group. There was a statistically significant difference between the 2 groups (p=0.014).

Table 2: The univariate analysis for risk factors of adverse events after hematopoietic stem cell transplantation (n = 42)

	Number of chronic kidney disease	P value	Number of pneumonitis	P value	Number of hepatobiliary disorders	P value
Age						
≤ 41 (n = 23)	3 (13.0%)	0.394	0	0.140	15 (65.2%)	0.246
> 41 (n = 19)	1 (5.3%)		2 (10.5%)		11 (57.9%)	
Gender						
Male (n = 22)	3 (13.6%)	0.382	0	0.150	16 (72.7%)	0.120
Female (n = 20)	1 (5.0%)		2 (10.0%)		11 (55.0%)	
Diagnosis						
Acute myeloid leukemia (n = 22)	3 (13.6%)	0.358	0	0.150	13 (59.1%)	0.745
Other diseases (n = 20)	1 (5.0%)		2 (10.0%)		12 (60.0%)	
Chemotherapy						
Cyclophosphamide alone (n = 32)	3 (9.4%)	0.935	1 (3.1%)	0.387	17 (53.1%)	0.408
Cyclophosphamide plus another drug (n = 10)	1 (10.0%)		1 (10.0%)		8 (80.0%)	
Dose per fraction						
12 Gy in 6 fractions (n = 32)	1 (3.1%)	0.015	1 (3.1%)	0.424	17 (53.1%)	0.244
12 Gy in 4 fractions (n = 10)	3 (30.0%)		1 (10.0%)		8 (80.0%)	

Discussion

Table 3 shows that the previously reported incidence rates of chronic kidney disease of adult patients after TBI without kidney shields was 6.8–29% [6-9]. The incidence rate of chronic kidney disease was

9.5% for all of the patients in the present study, which was not as high as that reported in previous studies. In the univariate analysis of the present study, the only statistically significant difference was in the dose per fraction. In fact, the incidence of chronic kidney disease among the patients in group B was higher than that noted in previous reports; in contrast, the incidence of group A was lower than that of previous reports.

Table 3: The previous reports of incidence of chronic kidney disease after total body irradiation without kidney shields

Authors	Number of patients	Dose per fractions (Gy)	Total dose (Gy)	Incidence rate (%)
Borg et al. (6)	59	2	12	6.8
Igaki et al. (7)	70	2	12	20
Lawton et al. (8)	72	1.56	14	29
Abboud et al. (9)	91	2	12	12
Present study	32	2	12	3.1
Present study	10	3	12	30

To the best of our knowledge, there are no reports that directly compare different doses per fraction with an equal total dose in relation to their correlation with the incidence of chronic kidney disease. Kal et al. reported a relationship between the biologically effective dose (BED) and the development of chronic kidney disease from 11 case reports [10]. This study suggested that a high BED to the kidney was associated with a high incidence of chronic kidney disease (kidney $\alpha/\beta = 2.5$). In the present study, although the total dose was equal, the patients undergoing TBI treatment in group B (BED = 26.4) had a higher rate of chronic kidney disease than the patients in group A (BED = 21.6). Regarding the pathological findings, Inomata et al. reported that a hyperfraction regimen (1.0 Gy irradiation, twice daily; total 80 Gy) was associated with a lower rate of renal atrophy than a conventional fraction (2.0 Gy irradiation, once daily; total 80 Gy) in guinea pigs [11]. These findings suggest that a high dose per fraction is associated with a high incidence of chronic kidney disease when the total dose is equal.

Some reports have suggested that renal shielding was useful for reducing the incidence of chronic kidney disease [6,7]. Igaki et al. reported that there were no cases of chronic kidney disease in patients with renal shielding restricted to a renal dose of 10 Gy, in contrast to the findings in patients without shielding [6]. Lawton et al. similarly reported that patients with renal shielding of 30% had a lower incidence of chronic kidney disease than patients with renal shielding of 15% or no shielding [7]. In both reports, the dose rate for kidneys was also reduced, so a low dose rate may have contributed to these outcomes. In the present study, we did not use renal shield, so using renal shielding reduce incidence rate of chronic kidney disease in addition to deceasing the dose per fraction.

Previous studies have reported the incidence rate of pneumonitis (Grade ≥ 2; excluding infections) to be 0–23%; the incidence rate in the present study was 4.8%, which was not inferior to previous studies [12-15]. The present study suggested that the dose per fraction may be related to chronic kidney disease, but not to pneumonitis. Gopal et al. also reported that the incidence of pneumonitis did not differ significantly between patients who were treated with two regimens (12 Gy in 4 fractions and 10.2 Gy in 6 fractions) [16]. Thus, the incidence of pneumonitis may not decrease if the dose per fraction is reduced, and the impact of the dose per fraction, with regard to lung toxicities, may differ from the impact in relation to renal toxicities. On the other hand, Beyzadeouglu et al. reported that low-dose rate ($\leq$0.04 Gy/min) TBI reduced the incidence of pneumonitis [14]. Abugideiri et al. also reported that TBI dose rate was significantly associated lung toxicity, but total dose and dose per fraction did not [17]. Thus, a lower dose rate may reduce the incidence of pneumonitis.

Regarding liver dysfunction, the liver is injured after TBI, because the entire liver is irradiated. Although there are reports indicating that chemotherapy is a risk factor, there have been no reports to indicate that TBI is a risk factor for liver dysfunction after HSCT [18,19]. Hogan et al. reported that pretransplantation factors that were associated with liver dysfunction included a diagnosis of an aggressive malignancy, and fludarabin use [18]. Cutler et al. reported that sirolimus use was associated with veno-occlusive disease after a TBI based transplantation regimen [19]. However more than half of the patients in the present study experienced some kind of liver dysfunction; thus, we should pay attention to the liver function.

Undoubtedly, multiple factors, including chemotherapy are relevant to the occurrence of renal adverse events after preparation for HSCT. Furthermore, these factors cannot be completely avoided. Abbound et al. reported on the factors associated with chronic kidney disease, including the conditioning regimen, and noted that TBI was significantly associated with chronic kidney disease, while the conditioning regimen was not [20]. Mirabell et al. also reported that TBI was associated with chronic kidney disease, while drug treatments were not [21]. These findings suggest that chronic kidney disease is strongly associated with TBI. The present study also revealed radiotherapy was associated with chronic kidney disease and radiotherapy, but that the cyclophosphamide-based conditioning regimen was not (Table 2). Thus, radiotherapy may have a major influence on the incidence of chronic kidney disease.

The present study suggests that a high dose per fraction without kidney shields leads to a higher rate of chronic kidney disease, and that we should consider the use of kidney shields when performing TBI.

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