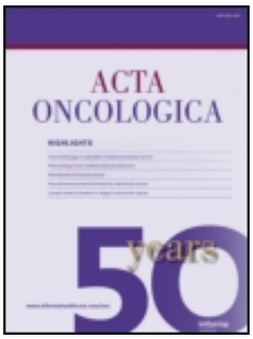

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Sanghyuk Song, Hyeon Jin Park, Jong Hyung Yoon, Dae Woong Kim, Jeonghoon Park, Dongho Shin, Sang Hoon Shin, Hyoung Jin Kang, Seung-Ki Kim, Ji Hoon Phi & Joo-Young Kim (2014) Proton beam therapy reduces the incidence of acute haematological and gastrointestinal toxicities associated with craniospinal irradiation in pediatric brain tumors, Acta Oncologica, 53:9, 1158-1164, DOI: 10.3109/0284186X.2014.887225

To link to this article: https://doi.org/10.3109/0284186X.2014.887225

Published online: 10 Mar 2014.

Acta Oncologica, 2014; 53: 1158–1164

informa
healthcare

ORIGINAL ARTICLE

Proton beam therapy reduces the incidence of acute haematological and gastrointestinal toxicities associated with craniospinal irradiation in pediatric brain tumors

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ABSTRACT

Background. The benefits of proton beam craniospinal irradiation (PrBCSI) in children have been extensively reported in dosimetric studies. However, there is limited clinical evidence supporting the use of PrBCSI. We compared the acute toxicity of PrBCSI relative to that of conventional photon beam CSI (PhBCSI) in children with brain tumours.

Material and methods. We prospectively evaluated the haematological and gastrointestinal toxicities in 30 patients who underwent PrBCSI between April 2008 and December 2012. As a reference group, we retrospectively evaluated the medical records of 13 patients who underwent PhBCSI between April 2003 and April 2012. The median follow-up time from starting CSI was 22 months (range 2–118 months). The mean irradiation dose was 32.1 Gy (range 23.4–39.6 Gy) and 29.4 CGE (cobalt grey equivalents; range 19.8–39.6), in the PrBCSI and PhBCSI groups, respectively ($p = 0.236$).

Results. There was no craniospinal fluid space relapse after curative therapy in either group of patients. Thrombocytopenia was less severe in the PrBCSI group than in the PhBCSI group ($p = 0.012$). The recovery rates of leukocyte and platelet counts measured one month after treatment were significantly greater in the PrBCSI group than in the PhBCSI group ($p = 0.003$ and $p = 0.010$, respectively). Diarrhoea was reported by 23% of patients in the PhBCSI group versus none in the PrBCSI group ($p = 0.023$).

Conclusions. The incidence rates of thrombocytopenia and diarrhoea were lower in the PrBCSI group than in the PhBCSI group. One month after completing treatment, the recovery from leukopenia and thrombocytopenia was better in patients treated with PrBCSI than in those treated with PhBCSI.

Craniospinal irradiation (CSI) is an essential component of the treatment of paediatric central nervous tumours that show a tendency to spread to the leptomeninges. However, the inevitable inclusion of normal tissue and organs in the radiation field frequently causes acute side effects. Several radiation techniques have been introduced to reduce the adverse effects of CSI. The main advantage of proton beam therapy (PrBT) over conventional photon beam therapy (PhBT) in CSI is that PrBT lacks an exit dose. In addition, dosimetric and modeling studies have demonstrated that PrBT is associated with fewer acute and late toxicities than PhBT [1,2]. Another report demonstrated the dosimetric benefit of PrBCSI using a spot beam scanning proton plan of a single representative patient [3]. However, very few studies have determined whether the dosimetric benefits of PrBT translate into improved clinical outcomes. Therefore, we conducted a study to determine whether PrBCSI reduces the incidence of acute

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(Received 15 October 2013; accepted 18 January 2014)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2014.887225

side effects and improves clinical outcomes of paediatric patients undergoing treatment for central nervous system tumours. As a reference group, we also evaluated the historical data for patients who underwent conventional photon beam CSI (PhBCSI) at our institution.

Material and methods

Study population

The clinical outcomes and toxicities were prospectively recorded for 39 patients aged < 18 years who underwent PrBCSI at National Cancer Center, Korea, between April 2008 and December 2012. Collection of patient data and blood samples were approved by our Institutional Review Board at National Cancer Center, Korea. Five patients who received concurrent chemotherapy and four patients who received PhBCSI as part of the PrBCSI protocol were excluded from the analysis; therefore, 30 patients who underwent PrBCSI were analysed. As a reference group, we retrospectively evaluated the medical records of patients aged < 18 years of age who were diagnosed with a malignant brain tumour and treated at the National Cancer Center, Korea, between January 2003 and December 2012. A total of 13 patients who received conventional PhBCSI were identified and were included in this study. The characteristics of both groups of patients are summarised in Table I. The median age at diagnosis was 10 years (range 2–18 years). The diagnosis varied, but medulloblastoma was the most common tumour type. Eighty-four percent of the patients received chemotherapy before CSI. Seventy-two percent of the patients underwent CSI with a curative (prophylactic) intent. The median follow-up time from the start of CSI was 22 months (range 2–118 months). Two patients died; one was being treated for recurrent disease and the other had leptomeningeal seeding.

CSI techniques

For simulation, computed tomographic (CT) scans (3.7–5.0 mm slices) were obtained in the prone position with a homemade CSI frame for the head or in the supine position with a dedicated CSI board. For PhBCSI, it was necessary to tilt the chin upwards to prevent beam divergence into the mandible. The planning target volume (PTV) for CSI consisted of a brain PTV, which included the entire cranial meninges with a 2 mm margin, and a spinal PTV, which included the entire vertebral body. The inferior limit of the spinal PTV was usually the S2 bone, but it was occasionally extended to the S3 bone.

For PrBT and PhBT, the brain PTV was treated with bilateral fields and the spinal PTV was covered with two or more abutting posterior–anterior (PA)

Table I. Patient characteristics.

Characteristic	PhBCSI (n = 13)	PrBCSI (n = 30)	p-value
Age (years)	11 (3–18)	10 (2–18)	0.254
Sex			0.619
Male	8 (62)	16 (53)	
Female	5 (39)	14 (47)	
Histology			
Medulloblastoma	4 (31)	9 (30)	
Mixed germ cell tumours	3 (23)	5 (17)	
Germinoma	1 (8)	6 (20)	
Non-germinomatous germ cell tumours	1 (8)	3 (10)	
Other histology	2 (15)	6 (20)	
Treatment aim			1.000
Prophylactic	9 (69)	22 (73)	
Leptomeningeal seeding or recurrent tumour	4 (31)	8 (27)	
Chemotherapy before CSI	10 (77)	26 (87)	0.655
CSI dose (CGE or Gy)	32.1 (23.4–39.6)	29.4 (19.8–39.6)	0.236
≤ 23.4	4 (31)	13 (43)	
> 23.4–≤ 33	2 (15)	5 (17)	
> 33–36	2 (15)	9 (30)	
> 36–≤ 39	4 (31)	0 (0)	
> 39	1 (8)	3 (10)	
Dose per fraction (CGE or Gy)			0.023
1.5	3 (23)	0 (0)	
1.8	10 (77)	30 (100)	
Dose applied to the primary site (CGE or Gy)	53.2 (39.6–60.6)	51.8 (30.6–61.2)	0.858

Values are presented as the mean (range) or number (per cent).
CGE, cobalt grey equivalent; CSI, craniospinal irradiation; PhBCSI, photon beam craniospinal irradiation; PrBCSI, proton beam craniospinal irradiation.

fields. Field matching was done for the brain and spinal fields or for two adjacent spinal fields, taking into account beam divergence. The field junctions were alternated daily between three junction positions with a 1 cm gap to reduce inhomogeneity between the junctions. To protect normal tissue, brass blocks were manufactured for PrBT, and multi-leaf collimators were used for PhBT. Margins of 1.2 cm from the brain PTV and 0.8 cm from the spine PTV were allowed for making custom blocks or shaping multi-leaf collimator. Range compensators made of polymethyl methacrylate were used for PrBCSI to create the distal PTV shape. The entire vertebral bodies were included in the spinal PTV for both PhBCSI and PrBCSI. The spinal PTV was pulled back by 3–4 mm from the anterior border of the vertebrae to reduce the radiation dose applied to the oesophagus and lung at the levels of the cervical and thoracic vertebrae. The daily setup was verified by diagnostic orthogonal x-rays, which were compared with digitally reconstructed radiographic images. Figure 1 shows examples of the PrBCSI and PhBCSI plans, together with their dose-volume histograms (DVH). All treatment plans were developed using the Eclipse® treatment planning system (External Beam Planning 8.1; Varian Medical Systems, Palo Alto, CA, USA).

The proton dose is presented in cobalt grey equivalents (CGE). The monitor units for PrBT were calculated using a proton radiobiological effectiveness value of 1.1. The mean irradiation doses were 32.1 Gy and 29.5 CGE in the PhBCSI and PhBCSI groups, respectively, and were not significantly different between the two groups ($p = 0.236$). The dose per fraction was 1.8 CGE for all patients in the PrBCSI group; however, three patients in the PhBCSI group received 1.5 Gy per fraction. This difference was statistically significant ($p = 0.023$). The prescribed doses in both groups are summarised in Table I.

Assessment of acute toxicities

The complete blood count, serum thrombopoietin (TPO), and coagulation profiles were determined before starting treatment. All the patients were seen by a radiation oncologist once a week during treatment. The first follow-up visit was scheduled one month after completing radiotherapy and then two months later. Acute toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).

The complete blood count was determined before radiotherapy, every week during treatment, and at the one-month follow-up. Our study population consisted of patients across a broad age range and with different types of brain tumours that were treated using different protocols. Therefore, the decreases in the white blood cell count, haemoglobin level, and platelet count in each patient were calculated as the changes in each parameter from before starting CSI to one month after completing CSI. As haematological parameters might be affected by platelet and red blood cell transfusion, the transfusion-corrected blood count was calculated, standardised to units (U), and compared again. A standardised unit represents one pack of red blood cells or platelets in adults, adjusted for body weight. We assumed that transfusion of 1 U increased the haemoglobin level by 1 g/ml, and the platelet count by 12 000 cells/μl.

Thrombopoietin measurement

Blood samples were routinely collected to identify factors possibly associated with platelet formation and destruction. Therefore, we measured the levels of TPO (a humoral regulator of thrombopoiesis), which is derived from the bone marrow and liver [4–7]. From October 2010, 3 ml of serum was taken at the start and end of CSI from 10 patients in the PrBCSI group who agreed to provide blood samples for the measurement of TPO. Additional samples were obtained six weeks after CSI in five patients who did not undergo chemotherapy after CSI. Serum TPO levels were measured using a commercial Quantikine Human Thrombopoietin Immunoassay kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

Statistical analysis

Pearson's χ^2-test or Fisher's exact test were used to compare categorical variables between the two groups. Unpaired t-tests or the Mann-Whitney test were used to compare continuous variables between the two groups. Paired t-tests or Wilcoxon's signed rank test were used to comparing changes in parameters over time. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS software version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Acute toxicities

Table II summarises the acute toxicities graded according to CTCAE version 4.0. The PrBCSI group experienced fewer cases of severe haematological toxicities, especially thrombocytopenia. Platelet transfusion was done in significantly fewer patients in the PrBCSI group. Leukopenia was less severe in the PrBCSI group, although the difference was not statistically significant. The majority of non-haematological toxicities were classified as Grade 1 or 2. Two patients

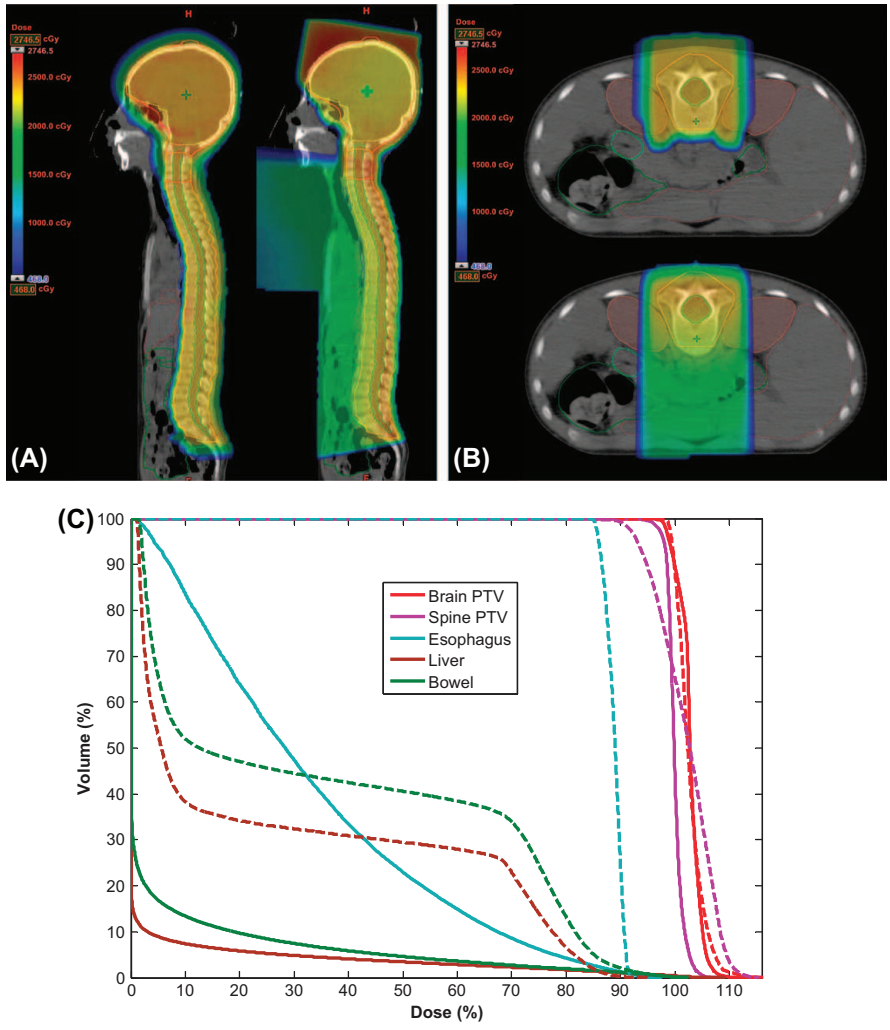

Figure 1. Representative examples of dose distribution for the craniospinal irradiation method. (A) Sagittal view (left: proton beam therapy; right: photon beam therapy). (B) Axial view (top: proton beam therapy, bottom: photon beam therapy). (C) Dose-volume histograms for the brain and spinal planning target volumes, and of specific tissues of interest (solid line: proton beam therapy, dashed line: photon beam therapy). PTV, planning target volume.

in the PrBCSI group and one in the PhBCSI group experienced Grade 3 non-haematological toxicities. Diarrhoea occurred in three patients in the PhBCSI group versus none in the PrBCSI group, which was statistically significant (Table II). Dysphagia was more frequent in the PrBCSI group, although the difference was not statistically significant. Grade 1 dysphagia occurred in one patient (8%) in the PhBCSI group versus 10 patients (33%) in the PrBCSI group.

Haematological profile and serum thrombopoietin levels

The decreases in the white blood cell and platelet counts were significantly greater in the PhBCSI group than in the PrBCSI group (Table III). After correcting the haemoglobin level and platelet counts for the transfusion volume, the decrease in the platelet count was still significantly greater in the PhBCSI group than in the PrBCSI group (Table III). The TPO level increased significantly after CSI in all 10 patients whose TPO levels were measured ($p = 0.005$; Figure 2A), while the platelet count decreased ($p = 0.007$; Figure 2B). In the five patients who did not undergo chemotherapy after CSI, the TPO level decreased at six weeks after treatment, while the platelet count recovered at this time in four patients (Figure 2C and D). However, there was some variation in the changes in both parameters over time in these five patients.

DVH analysis

DVH analysis was performed for the liver and bowel, which are the most important organs when assessing the acute haematological and gastrointestinal side effects of CSI. Two patients in the PhBCSI group were excluded from DVH analysis because of missing plan data. The irradiated volume was defined as an organ volume that received $>0.5\%$ of the pre-

Table II. Acute toxicities.

Toxicity	PhBCSI (n = 13)	PrBCSI (n = 30)	p-value
Leukopenia			0.069
Grade 3	6 (46)	14 (57)	
Grade 4	4 (31)	2 (7)	
G-CSF administration	4 (31)	12 (40)	0.655
Anaemia			0.493
Grade 3	2 (15)	0 (0)	
Grade 4	0 (0)	0 (0)	
RBC transfusion	5 (39)	15 (50)	0.486
Thrombocytopenia			0.012
Grade 3	4 (31)	6 (20)	
Grade 4	3 (23)	1 (3)	
Platelet transfusion	6 (46)	5 (17)	0.042
Nausea	6 (46)	10 (33)	0.424
Dysphagia	2 (15)	14 (47)	0.086
Anorexia	4 (31)	11 (37)*	1.000
Skin disorders	4 (31)	11 (37)	1.000
Vomiting	4 (31)	9 (30)*	1.000
Neurological disorders	3 (23)	4 (13)	0.655
Diarrhoea	3 (23)*	0 (0)	0.023
Ophthalmic disorders	1 (8)	2 (7)	1.000
Cough	1 (8)	2 (7)	1.000

Values are presented as number (percent).
G-CSF, granulocyte colony-stimulating factor; PhBCSI, photon beam craniospinal irradiation; PrBCSI, proton beam craniospinal irradiation; RBC, red blood cell.
*Non-haematological toxicities were classified as Grade 1 or 2, except in three grade 3 patients labelled with an asterisk.

scribed CSI dose. The irradiated volume and the mean dose applied to the liver and bowel were significantly lower in the PrBCSI group (all, $p < 0.001$). The irradiated volume and the mean dose applied to the liver were 61% (range 27–100%) and 9.7 Gy (range 5.2–14.2 Gy), respectively, in the PhBCSI group compared with 8% (range 1–16%) and 0.7 CGE (range 0.1–1.6 CGE), respectively, in the PrBCSI group. The irradiated volume and the mean dose applied to the bowel were 59% (range 37–100%) and 11.9 Gy (range 1–21.5 Gy), respectively, in the PhBCSI group compared with 14% (range 1–31%) and 1.1 CGE (range, 0–3.2 CGE), respectively, in the PrBCSI group.

Discussion

CSI is an important component of the treatment of paediatric central nervous system tumours. However, a major concern in CSI is the high risk of acute and late toxicity because of the large treatment volume. PrBT may reduce the risk of acute and late toxicity because of the weaker exit beam and the lower dose reaching normal tissues. Many dosimetric and model studies have demonstrated the benefits of PrBCSI [3,8–13]. In a dosimetric study, Howell et al. reported that PrBT had a sparing effect on the oesophagus, heart, liver, thyroid, kidneys, and lung [12]. In addition, the predicted risks of adverse events and secondary cancer were considered to be lower for PrBT than for PhBT [9,10,13]. Model studies revealed that the potential reduction in morbidity has benefits in terms of longer life span and reduced treatment cost [11,14]. Therefore, some groups have argued that PrBCSI is mandatory for paediatric patients [15]. To date, however, very few clinical reports have confirmed that PrBCSI actually reduces the incidence of adverse effects compared with PhBCSI. To our knowledge, only one study has been published in this field. In a study of adults with medulloblastoma, Brown et al. reported that PrBCSI was associated with fewer acute gastrointestinal and haematological toxicities compared with PhBCSI [16]. However, there are no reports of this nature in paediatric patients. Therefore, the present study is the first to prospectively investigate the incidence of acute toxicities in 30 paediatric patients undergoing PrBCSI.

We found that the incidence and severity of thrombocytopenia were lower in the PrBCSI group than in the PhBCSI group. Patients who received PrBT required fewer platelet transfusions. In addition, the extent of recovery from thrombocytopenia at one month after treatment was also better in the PrBCSI group. Prompt recoveries of the platelet and leukocyte counts after completing radiotherapy enable prompt administration of chemotherapy, and also allow patients to return to their normal daily activities

Table III. Changes in haematological parameters from before starting CSI to 1 month after treatment.

	PhBCSI (n = 13)	PrBCSI (n = 30)	p-value
White blood cell count (K/μl)	-2.61 ± 2.27	-0.57 ± 2.22	0.009
Haemoglobin (g/dl)			
Uncorrected	-0.70 ± 1.89	$+0.23 \pm 1.04$	0.115
Corrected for transfusion*	-1.16 ± 2.06	-0.57 ± 1.48	0.294
Platelet count ($\times 10^5$ cells/μl)			
Uncorrected	-1.37 ± 0.96	-0.49 ± 0.64	0.008
Corrected for transfusion*	-2.74 ± 2.28	-0.68 ± 0.72	0.007

Values are presented as the mean ± standard deviation change in each parameter from before starting CSI to 1 month after completing CSI.
PhBCSI, photon beam craniospinal irradiation; PrBCSI, proton beam craniospinal irradiation.
*A standardised unit represents one pack of red blood cells or platelets in adults, adjusted for body weight. We assumed that transfusion of 1 U increased the haemoglobin level by 1 g/ml, and the platelet count by 12 000 cells/μl.

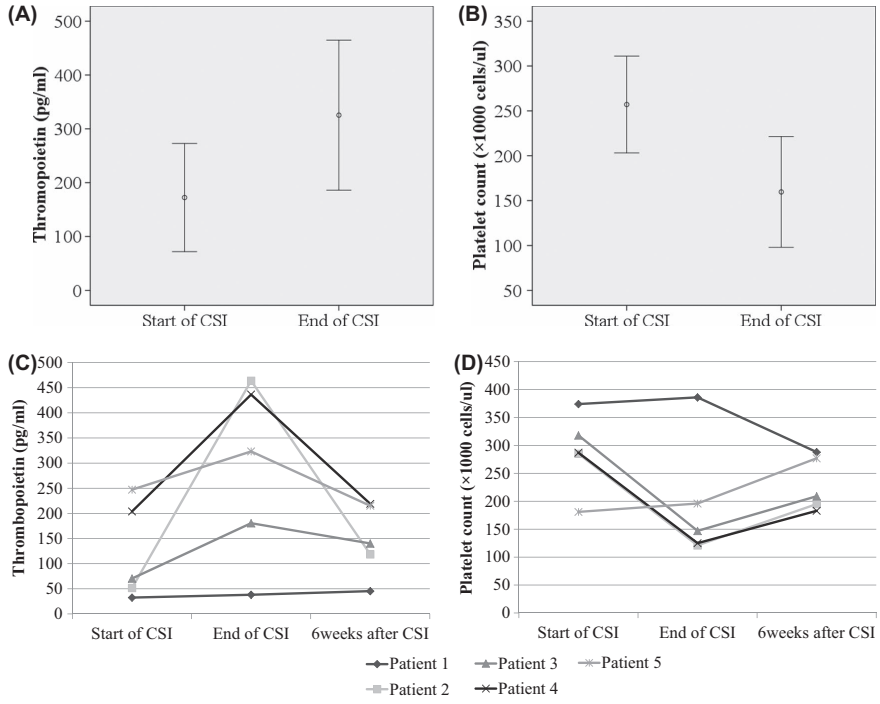

Figure 2. (A,B) Changes in thrombopoietin levels (A) and platelet counts (B) during craniospinal irradiation. (C,D) Changes in thrombopoietin (C) and platelet counts (D) in five patients who did not undergo chemotherapy after craniospinal irradiation. Values in A and B are means with 95% confidence intervals. Values in C and D are the actual values in each patient.

sooner than in patients with prolonged thrombocytopenia or leukopenia. The exact mechanisms underlying these findings have yet to be discovered. The volume of bone marrow subjected to CSI did not differ between the two groups in our study. The production of humoral factors, such as granulocyte colony stimulating factor, which is produced by endothelial and immune cells, might affect blood counts if a larger volume of normal tissue is included in the radiation field during PhBT, but not with PrBT. TPO, which is the principal humoral regulator of platelet production, is not used in clinical settings. Eltrombopag, an oral TPO receptor agonist, was recently shown to increase the platelet count in patients with aplastic anaemia [17]. The liver is the major source of endogenous TPO, and several studies have observed reduced TPO levels in patients with liver cirrhosis and thrombocytopenia [18–21]. In these patients, the TPO level increased after liver transplantation [5], suggesting that poor liver function is associated with a reduced TPO level.

It is widely thought that thrombocytopenia in patients with liver disease is due to passive platelet sequestration in the spleen. However, recent studies have suggested that decreased platelet production may be due to reduced TPO levels [16]. Therefore, PrBCSI, which spared the liver in dosimetric analyses, might be useful in patients where large volumes of active bone marrow are included in the irradiation field. Although it could not be examined in this study, it is possible that a large volume of liver was irradiated by PhBCSI, compromising the liver's ability to secrete TPO. However, it is not clear whether the volume of the liver irradiated by during PhBT influenced TPO production, which may increase in response to suppressed bone marrow function. The present study could not address this issue because the TPO levels were not measured in the PhBCSI group.

PrBCSI may spare the bone marrow within the spinal column in adults, although it is not clear whether this also applies to paediatric patients. Brown et al. [16] reported that the reductions in the white blood cell count, haemoglobin level, and platelet count were significantly lower in the PrBCSI group. They also reported that the mean vertebral dose was associated with the reduction in blood counts. In our study of paediatric patients, although we did not observe clear differences in anaemia, unlike that reported in adult patients, we did observe a smaller reduction in the platelet count in the PrBCSI group than in the PhBCSI group.

In terms of non-haematological toxicities, only the incidence of diarrhoea was significantly different between the two groups, and it was only observed in the PhBCSI group. Dosimetric analysis showed that the bowel volume and irradiation dose were higher in the PhBCSI group than in the PrBCSI group. Based on these results, it can be inferred that the absence of bowel complications was due to the lower

irradiation dose applied to the bowel during PrBT. Although the dose applied to the bowel was lower in the PrBCSI group, the incidence rates of nausea and vomiting were similar in both groups. It is probably because both groups received similar dose at the nausea centre in the central nervous system. Although dysphagia was more frequent in the PrBCSI group, the difference was not statistically significant and most of the episodes of dysphagia were classified as Grade 1 (71%). This difference could be explained by the prospective assessment of toxicities in the PrBCSI group, as the physicians interviewed the patients to assess possible symptoms, whereas adverse events were retrospectively retrieved from the patients' medical records in the PhBCSI group.

Our study has several limitations. First, the number of patients included in the study was relatively small and there was a broad age range. Second, the number of patients in the control PhBCSI group was very small, and the data were retrospectively collected. Finally, the TPO levels could not be measured in the PhBCSI group.

In conclusion, this study compared the incidence of acute toxicities between PrBCSI and conventional PhBCSI in paediatric patients with brain tumours. PrBCSI was associated with less severe acute toxicities affecting the haematological and gastrointestinal systems. Therefore, PrBT should be considered as a treatment option for paediatric patients who need CSI at institutions where it is available.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This work was supported by a grant from the National Cancer Center, Korea (no. 1010480).

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