outcome would be worsened because the optimal chemotherapy for NB differs from that for LCH.

Therefore, we should consider an aggressive pathological diagnosis in cases of atypical localized tumor for LCH.

It remains to be confirmed whether the nature of LCH is neoplastic or due to inflammatory response. Supporters of the neoplastic theory have declared that LCH is a clonal disease in which an activating allele of an authentic oncogene is carried in the majority of cases.[1] In contrast, supporters of the inflammatory response theory have declared that some cases of LCH present a clinical course responding to the inflammatory state.[1] Although the pathological mechanism by which the tumors synchronously occur remains unclear, LCH may have occurred in the present case in response to hidden NB. A review of the literature on coexisting LCH and other neoplasms including malignant lymphoma, leukemia, and lung carcinoma supports this speculation.[7]

An initial attempt to diagnose the adrenal tumor on radiology and tumor markers was unsuccessful, and required tumor resection following pathological diagnosis. LCH frequently involves the skeleton (80%), skin (33%), and pituitary (25%), but other organs (lymph nodes, liver, spleen, lung, bone marrow, and central nervous system) are rarely affected.[8] To the best of our knowledge, there is currently no literature on LCH in the adrenal gland. Although LCH often spreads into multi-organ systems, an aggressive pathological diagnosis may be required in cases of atypical localization for LCH in consideration of the synchronous occurrence of other solid tumors. Tumor markers such as urine VMA and HVA have not always been effective in diagnosing these types of tumors.

The current patient presented with KD and cervical lymphadenopathy prior to the onset of LCH and NB. Cases of neoplasm following KD were previously reported and reviewed by Suzuki *et al.*[9] Neoplasms following KD include NB,[10,11] lymphoid malignancies, sarcomas, and schwannomas.[9] The interval from the onset of KD to the diagnosis of neoplasms varies widely from days to several years. Whether KD or the neoplasm was the fundamental cause remains unclear.

Previous reports have suggested that inflammatory cytokines and vascular endothelial growth substances in the acute phase of KD accelerate the progression of tumors. In terms of NB following KD, vascular endothelial growth factor (VEGF) was previously shown to be elevated in the plasma in the acute phase of KD.[12] VEGF has been reported to play a critical role in angiogenesis, cell growth, and metastasis of NB.[13] Inflammatory cytokines and vascular endothelial growth substances including VEGF may also have contributed to NB tumor growth in the present case.

In conclusion, we have described the case of a girl diagnosed with the synchronous occurrence of stage 1 NB during staging of LCH. We should consider the possibility of the synchronous occurrence of other solid tumors in cases of atypical localization for LCH.

Acknowledgment

There are no potential conflicts of interest.

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Original article

Preparation of pediatric patients for treatment with proton beam therapy

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ABSTRACT

Purpose: Anesthesia is often used in proton beam therapy (PBT) for pediatric patients and this may prolong the treatment time. The aim of the study was to examine preparation of pediatric patients to allow smooth performance of PBT.

Material and methods: Preparation was initiated 1–2 days before treatment planning CT and continued for 10 days. The patient first visited the facility to become familiar with the treatment room and staff. As the second step, the patient stayed in the treatment bed for a certain time with their mother, and then stayed on the treatment bed alone. Special fixtures painted with characters, music, and gifts were also prepared.

Results: From 2010 to 2014, 111 pediatric patients underwent PBT. These patients were divided into 3 groups: 40 who could follow instructions well (group A, median age: 13.6 years old), 60 who could communicate, but found it difficult to stay alone for a long time (group B, median age: 4.6 years old), and 11 who could not follow instructions (group C, median age: 1.6 years old). Preparation was used for patients in group B. The mean treatment times in groups A, B and C were 13.6, 17.1, and 15.6 min, respectively, on PBT treatment days 2–6, and 11.8, 13.0, and 16.9 min, respectively, for the last 5 days of PBT treatment. The time reduction was significant in group B ($p = 0.003$).

Conclusion: Preparation is useful for pediatric patients who can communicate. This approach allows PBT to be conducted more smoothly over a shorter treatment time.

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Radiotherapy is frequently used for pediatric tumors to improve disease control. However, many pediatric patients cannot remain still on the treatment bed during radiotherapy, and these patients often require sedatives or general anesthesia [1,2]. Proton beam therapy (PBT) is widely used in pediatric patients to reduce toxicities [3–5], but the treatment time for PBT can be longer than that for photon radiotherapy and similar sedatives or anesthesia are required. Buchsbaum et al. showed that anesthesia is safe and efficient in pediatric patients receiving PBT [6] and Owusu-Agyemang et al. showed that non-invasive anesthesia is effective and safe for pediatric patients, with a seizure/laryngospasm/bronchospasm rate of 0.05% [7]. However, daily sedation or anesthesia has several difficulties, including the need for specialized staff and an extension of the treatment time.

In our hospital, anesthesiologists are unavailable on a regular basis and there is no room to perform anesthesia near the PBT treatment room. A pediatric physician induces anesthesia or administers sedatives, accompanies the patient to the treatment room, observes the PBT, and remains with the patient on transfer back to the ward. Pediatric patients also receive PBT in the same treatment room as adult patients; therefore, we have to minimize anesthesia and shorten the occupancy time in the treatment room. It would be advantageous if the need for sedation could be reduced in pediatric patients who cannot remain still, but can communicate, and we have developed a preparation process for these patients that allow PBT to be conducted smoothly and rapidly. In this report, we retrospectively investigated the effect of this process on performance of PBT for pediatric patients.

Methods and materials

Patients

A total of 111 pediatric patients received PBT at our hospital from April 2010 to April 2014. Prior written informed consent was obtained from the parents of all patients. The patients

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comprised 55 boys and 56 girls, and had a median age of 6.2 years old (range: 0.7–19.6 years old). The sites of irradiation were the brain ($n = 40$), head and neck ($n = 33$), and body ($n = 38$). The diagnoses were rhabdomyosarcoma ($n = 23$), neuroblastoma ($n = 16$), Ewing sarcoma ($n = 13$), pons glioma ($n = 10$), ependymoma ($n = 8$), germ cell tumor ($n = 7$), retinoblastoma ($n = 4$), glioma ($n = 4$), arteriovenous malformation ($n = 3$), chordoma ($n = 3$), yolk sac tumor ($n = 3$), and other tumors ($n = 17$). The patient and tumor characteristics are shown in Table 1.

Patient groups

Of the 111 patients, 40 could follow instructions and did not require preparation for PBT (group A; median age 13.6 (range 7.1–19.6) years old); 60 had difficulty staying in the treatment bed for a long time, but could communicate (group B; median age 4.6 (range 2.0–12.6) years old); and 11 could not follow instructions and required anesthesia (group C; median age 1.6 (range 0.7–3.0) years old). The preparation process described below was performed for patients in group B. The number of preparation sessions was limited to 10.

Proton beam therapy

Computed tomography (CT) images were taken at 2- to 5-mm intervals for brain or head and neck tumors, and at 5-mm intervals for body trunk tumors. A respiratory gating system (Anzai Medical Co., Tokyo, Japan) was used as required [8]. The clinical target volume was defined based on the tumor diagnosis. An additional margin of 5–10 mm was added to cover the entire CTV by enlarging the multileaf collimator and adjusting the range shifter. Proton beams from 155 to 250 MeV generated through a linear accelerator and synchrotron were spread out and shaped with ridge filters, double-scattering sheets, multicollimators, and a custom-made bolus to ensure that the beams conformed to the treatment planning data. During each treatment session, the patient position was monitored using an orthogonal fluoroscopy unit attached to the treatment unit under direct vision. On the first treatment day, a therapeutic radiologist and a radiotherapy technologist both checked the fluoroscopy images, while in routine treatment only a radiotherapy technologist checked these images. The relative biological effectiveness (RBE) of the PBT was assumed to be 1.1 [9].

Table 1
Characteristics of patients.

Characteristics	Number	%
Age (years)	0.7–19.6	6.2 (median)
Gender		
Boy	55	50
Girl	56	50
Irradiated site		
Brain	40	36
Head and neck	33	30
Body	38	34
Diagnosis		
Rhabdomyosarcoma	23	21
Neuroblastoma	16	14
Ewing sarcoma	13	12
Pons glioma	10	9
Ependymoma	8	7
Germ cell tumor	7	6
Retinoblastoma	4	4
Glioma	4	4
Arteriovenous malformation	3	3
Chordoma	3	3
Yolk sac tumor	3	3
Others	17	15

Preparation

The purpose of the preparation process was to allow the patient to remain still while alone in the treatment bed during PBT. Preparation was scheduled and performed by a radiation technologist and a nurse who were in charge of the actual treatment. Preparation was performed using a step-by-step schedule (see Supplementary File-1). The first step was to become familiar with the treatment room and staff. This step mainly consisted of visiting the PBT facility and playing with the radiation technologist and nurse. The second step was to stay still in the treatment bed for a period of time with a well-known person (mother in most cases). The final step was to remain still on the treatment bed for the required treatment time while alone (see Supplementary File-2). An immobilization bed and mask (those actually used during PBT) were utilized during preparation to allow the patient to become used to fixation. A picture book was usually used from the first visit as an aid to preparation. In this book, well-known characters provide a simple explanation of PBT. To reduce anxiety, a special treatment area was prepared for pediatric patients. Favorite characters were painted on the treatment mask and the body fixture was decorated as the patient wished (Fig. 1). A favorite video or music CD was played during position adjustment and irradiation, and a sticker was placed on the treatment calendar on every treatment day as a gift.

Treatment planning CT was performed about 1 week before the first day of PBT and preparation was initiated on this day or 1–2 days earlier. The average time of preparation was about 15 min per day and was limited to a maximum of 30 min. Preparation was performed about 5–6 times before PBT. Some patients who could not remain still on the treatment bed alone on the first treatment day continued preparation during the treatment period up to a total of 10 times overall.

Statistical analysis

Two measurements were used to evaluate the efficacy of the preparation process: the daily occupancy time of the treatment room, and the number of patients who needed anesthesia during PBT. The occupancy time was defined as the time from patient entry into the treatment room until completion of irradiation. One-way analysis of variance (ANOVA) was performed to compare occupancy times among groups A, B and C. The numbers of patients who needed anesthesia during PBT were recorded for treatment planning CT, on the first day of PBT, and on the last day of PBT.

Results

Of the 60 patients who underwent the preparation process (group B), 36 needed anesthesia for treatment planning CT (essentially prior to preparation), 31 needed anesthesia on the first day of PBT (after the preparation process was initiated), and 17 needed anesthesia within the first 5 treatment days (after preparation was complete). The dose of anesthetic agent also decreased in 9 of these 17 patients. Changes in the number of patients who needed anesthesia in group B are shown in Fig. 2a.

In all 111 patients, 47 needed anesthesia for treatment planning CT (median age 3.4, range 0.7–8.7), 41 needed anesthesia on the first day of PBT (median age 3.0, range 0.7–8.7), and 27 needed anesthesia on the last day of PBT (median 2.5, range: 0.7–8.7). The dose of anesthetic agent was decreased in 9 of these 27 patients. Anesthesia was required in 41% of all patients for treatment planning CT (100%, 93%, 70% and 56% in 2-, 3-, 4-, and 5-year old patients, respectively), but only in 24% after preparation (75%, 57%, 10% and 0% in the respective age groups). Changes in the num-

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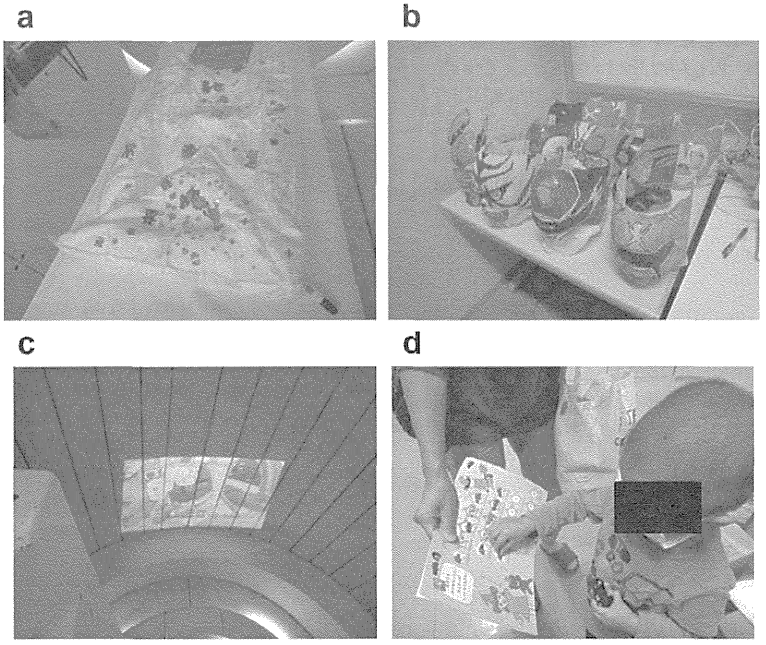

Fig. 1. (a) Decorated treatment bed. (b) Painted treatment mask. (c) A favorite video is shown on the ceiling or music is played during position adjustment and irradiation. (d) A sticker is placed on the calendar on every treatment day. All decorations and paintings are handmade at the patient's request.

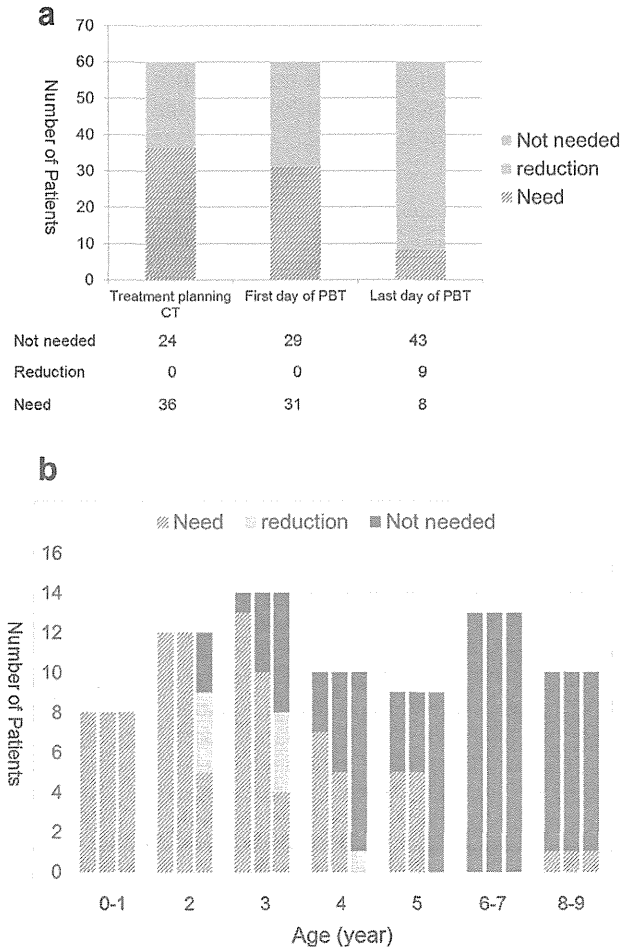

Fig. 2. (a) Process of anesthesia in group B ($n = 60$, underwent preparation). (b) Process of anesthesia in age groups in all patients. The age-grouped bar charts indicate (from left to right) the number of patients who required anesthesia for planning CT, on the first day of PBT, and on the last day of PBT, respectively. The number of patients requiring a reduced dose of anesthesia is also indicated.

ber of patients who needed anesthesia in each age group are shown in Fig. 2b.

The mean treatment times on the first day of PBT were 24.5 (range 8.5–80.2, 95% CI 21.7–27.3) min for all patients, and 20.9 (range 10.2–52.2, 95% CI 17.9–24.0), 26.5 (range 8.5–80.2, 95% CI 22.1–30.9) and 26.6 (range 12.4–72.5, 95% CI 15.5–37.8) min in groups A, B and C, respectively. These times are longer than those on subsequent days because of body adjustments performed on day 1 by the physician and radiation technologist. There were no significant differences among the three groups ($p = 0.161$ by ANOVA). The mean treatment times on all PBT days (localization by a radiation technologist only) were 14.6 (range 7.4–46.1, 95% CI 13.3–15.8) min for all patients, and 13.3 (range 7.4–35.3, 95% CI 11.3–15.4), 15.1 (range 8.4–46.1, 95% CI 13.4–16.9) and 16.0 (range 10.1–25.3, 95% CI 12.8–19.1) min in groups A, B and C, respectively, again with no significant difference among the groups ($p = 0.304$). Treatment times on the first and following days of PBT are shown in Supplementary File-3a and 3b.

A comparison of treatment times on days 2–6 and on the last 5 days of PBT was performed to evaluate the impact of familiarization with the PBT procedure. The mean treatment times on days 2–6 were 13.6, 17.1, and 15.6 min in groups A, B and C, respectively, with no significant differences among the groups ($p = 0.068$). In contrast, for the last 5 days, the mean treatment times were 11.8, 13.0, and 16.9 min, respectively, and there was a significant difference among the groups ($p = 0.03$). The changes in treatment times for the last 5 days compared to days 2–6 were −1.7 (range −11.1–5.3, 95% CI −2.9 to −0.4), −4.2 (range −27.1 to 4.1, 95% CI −5.7 to −2.7) and 1.4 (range −4.8 to 5.7, 95% CI −0.8 to 3.6) min in groups A, B and C, respectively (see Supplementary File-3c). ANOVA showed a significant difference among the groups ($p = 0.001$) and multiple comparison showed significant differences between groups A and B (p = 0.047) and between groups B and C ($p = 0.003$).

Discussion

PBT is performed for various malignancies [10–14] and PBT for pediatric patients may be particularly beneficial due to reduction

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of late toxicities such as disturbance of growth and second malignancies [15,16]. Brodin et al. found that PBT reduces the risk of a second malignancy in irradiation of the whole spine [15] and Sethi et al. showed a reduced risk of a second malignancy in patients with retinoblastoma who were treated with photon and proton radiotherapy, with 10-year actual cumulative incidences of radiotherapy-induced in-field second malignancy of 0% (proton) and 14% (photon) [16]. However, PBT requires accurate daily localization, and therefore has an equal or longer treatment time compared to photon radiotherapy. In an evaluation of radiotherapy and treatment planning CT, Bois et al. found that the mean time per person for routine irradiation from entering to leaving the treatment room was 19 min [19]. This is similar to our occupancy time of 15 min, particularly because our time did not include the time from the end of PBT to leaving the treatment room.

Anesthesia for pediatric patients during radiotherapy is commonly used and is considered to be safe and effective [1,2]. In a study of anesthesia in pediatric patients receiving PBT, Buchsbaum et al. found that the total time under anesthesia was about 50 min and that the average time from the start of anesthesia to the start of PBT was about 7 min [6]. These data indicate that anesthesia greatly lengthens the total treatment time, but does not have a major influence on the time of occupancy of the treatment room. However, in practice, there are problems with use of anesthesia. Staff resources may limit performance of anesthesia to a maximum of 2–3 patients each day. Also, anesthesia is performed by a pediatric doctor for all except high-risk patients, and this doctor remains with the patient throughout the anesthesia and pre- and post-PBT period, which may take more than 30 min. A treatment schedule is also required for anesthesia, including performance of anesthesia at least 3 h after lunch in our hospital. Ideally, PBT for all patients is finished earlier, but PBT for pediatric patients under anesthesia is performed later and some patients cannot eat dinner because of insufficient recovery from anesthesia. This causes a disruption in the rhythm of everyday life.

Given these problems, a strategy for smooth PBT for pediatric patients is required. In photon radiotherapy, Tsai et al. showed that play reduces the anxiety of pediatric patients with a brain tumor treated by radiotherapy [17]. Haederli et al. showed that a psycho-educational intervention reduced the need for anesthesia during radiotherapy for pediatric patients [18], with anesthesia required for most patients aged 3–4, but few aged 4–5, without the intervention, and in most patients aged 2–3, but few aged 3–4, with the intervention. For photon radiotherapy, Fortney et al. showed that anesthesia was required in 86% of patients aged 2–3, but in only 49% of those aged 3–4 [2].

In our study, anesthesia was required for all patients aged 2 or less, but only for about half of the patients aged 3 years old. Thus, we can perform PBT for pediatric patients with minimum use of anesthesia, even though the time for PBT is generally equal to or longer than that for photon radiotherapy. The treatment time on PBT days 1 and 2–6 was longer in patients in groups B and C than in group A (although without a significant difference), but this time was significantly reduced in group B (patients who underwent preparation) in the last 5 days of PBT. The mean time of 13.0 min for group B in this period was similar to that of 11.8 min in group A (patients who could communicate well). This indicates that patients in group A underwent PBT more smoothly in earlier sessions, but that preparation smoothened performance of PBT in group B in later sessions. These findings show that the preparation process described in this study is useful for reducing the need for anesthesia, allowing PBT to be performed in less time, and permitting regular daily life activities in pediatric patients who can communicate, but find it difficult to stay alone on the treatment bed.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.01.007.

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Tailor-made Treatment combined with Proton Beam Therapy for Children with Genitourinary/Pelvic Rhabdomyosarcoma.

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Abstract

Background: Rhabdomyosarcoma (RMS) is one of the most common soft tissue sarcomas among children. Patients who developed genitourinary/pelvic Rhabdomyosarcoma (GU/P-RMS) had a higher complication ratio and relatively poorer event free survival, with local therapy being very important. While proton beam therapy (PBT) is expected to reduce co-morbidity especially for children, this lacks firm evidences and analysis. We analyzed GU/P-RMS children who underwent multimodal therapy combined with PBT at a single institution. **Method:** We retrospectively reviewed charts of children with GU/P-RMS treated from January 2007 to May 2013 at the University of Tsukuba Hospital who underwent multimodal therapy with PBT. **Results:** There were 5 children and their median age at diagnosis was 2.8 years old (0.6 to 4.4 years). Primary sites were 2 at bladder and 3 at prostate. All received neo-adjuvant chemotherapy and 3 underwent chemotherapy during PBT (Group Cx). All patients of Group Cx developed leukocytopenia (WBC<1,000/uL). The median dose of PBT was 47.7 GyE (41.4 to 50.4 GyE). All patients had survived by their last hospital visit (median, 36 months). **Conclusions:** We analyzed multimodal treatment combined with PBT undergone for GU/P-RMS. PBT was well tolerated and could be a plausible choice instead of photon therapy for this population.

Key words; Rhabdomyosarcoma, Proton-beam therapy, genitourinary/pelvic tumor, childhood malignancy, multimodal therapy

Introduction

Rhabdomyosarcoma (RMS) is one of the most common soft tissue sarcomas among children[1]. Cure rates for RMS have reached up to 60 to 80% with multimodal treatment consisting of chemotherapy, surgery and radiotherapy[1-3]. While patients with genitourinary/pelvic Rhabdomyosarcoma (GU/P-RMS) account for around 25% of all patients with RMS, they have a higher complication ratio and relatively poorer event free survival[4-6]. Local control, particularly complete surgical resection and adequate radiotherapy, is very important among this population[7, 8]. While photon therapy has been used for this population for decades, adverse effects around genitourinary pelvic regions are of much concern due to the closely-packed vital organs such as the colon, hip joints, ovary and urinary tract.

Proton beam therapy (PBT) is a novel method of particle radiotherapy that is optimized to spare normal organs beyond the treatment target volume due to its sharp and narrow dose peak[9], but lacks firm evidences as a treatment of malignancy particularly among children[10]. Cotter et al. reported that PBT for prostate/bladder RMS spared doses to the normal structure of reproduction or skeleton and provided doses equally to target volumes compared with volumes generated for Intensity Modulated Radiation Therapy (IMRT)[11].

Since the feasibility of PBT concurrent with multimodal treatment had not been well explored, particularly for children, we analyzed feasibility and early outcome among GU/P-RMS children who underwent multimodal treatment with chemotherapy, surgery and PBT.

Method

Patients

Pathologically proven GU/P-RMS patients treated with multimodal treatment including multimodal chemotherapy and surgery combined with PBT at the University of Tsukuba Hospital between January 2007 and May 2013 were included in our study.

Charts review

Charts were reviewed retrospectively. Neo-adjuvant chemotherapy, chemotherapy during PBT and high-dose chemotherapy with autologous hematopoietic transplantation were reviewed. Adverse events during PBT including lowest white blood cell count, blood transfusions, infections, cessation of PBT, or any other events related to multimodal therapy combined with PBT were assessed. Patients' conditions and time at last follow-up were recorded as patients or their primary physicians contacted our institution.

Proton beam therapy

Before treatment, CT images for PBT planning were obtained at intervals of 2-5 mm in the treatment position. The interval was determined based on the patient's age, height and treatment site. Proton beams from 155 to 250 MeV generated through a linear accelerator and synchrotron were spread out and shaped with ridge filters, double-scattering sheets, multicollimators, and a custom-made bolus to ensure that the beams conformed to the treatment planning data. The clinical target volume was defined as the area of residual tumor. The margin for clinical target volume was 10 to 15 mm at

first. After 41.4 to 45 GyE, clinical target volume was reduced to the area of macroscopically residual tumor. The margin for clinical target volume was then reduced to 5 to 10 mm. The dose for whole bladder was limited to 41.4 GyE. After 41.4 GyE, we minimize the irradiated volume of small bowel. The treatment was provided 5 days in a week. The photon equivalent dose (GyE) was defined as the physical dose (Gy) × the relative biological effectiveness of the proton beam assigned a value of 1.1. Before each treatment, correct placement of the patient relative to the radiation field was confirmed fluoroscopically for all cases. Ultrasonography was conducted to confirm the bladder volume for selected sedated cases. A sedative was administered for 4 patients aged 1.3 to 3.7 years old for planning CT and treatment. Patients underwent physical examination every day and laboratory test were conducted more than once a week.

Results

We reviewed charts of children who were treated at our hospital. There were 5 patients with GU/P-RMS who underwent multimodal treatment combined with PBT between January 2007 and May 2013. Patient characteristics are shown in Table I and treatment summary and patient outcome are in Table II. The median age at diagnosis was 2.8 (0.6 to 4.4) years old and the median age at PBT was 2.9 (1.3 to 6.4) years old. There were 1 female and 4 males. The tumor was located at the bladder for 2 and the prostate for 3. All were diagnosed as having embryonal RMS, except for one patient whose histologic subtype was unknown.

All patients underwent VAC treatment, which consisted of Vincristine, Actinomycine-D and Cyclophosphamide according to the Intergroup rhabdomyosarcoma study-IV with minor institutional changes, as their first line therapy[3]. Then treatment protocol was changed for Cases 1, 2, 4 and 5 due to refractory clinical course.

At week 9, Case 1 was changed to VID treatment (VCR 1.0 mg/m^2 + IFO 1,200 mg/m^2 and DOX 25 mg/m^2) as a second line chemotherapy. After 2 courses of VID, he underwent third line chemotherapy of irinotecan. However, due to tumor status of no response, he underwent gross resection with PBT. Cases 2 received VAC with X-ray therapy as a first line therapy; however, with partial response clinical status, the treatment protocol was changed to irinotecan as a second line chemotherapy, and then cisplatin based chemotherapy as a third line therapy. Since residual disease was confirmed with a biopsy specimen, he received additional high dose chemotherapy (800 mg/m^2 of Thiotepa and 280 mg/m^2 of Melphalan) with autologous hematopoietic stem

cell transplantation. While viable tumor cells were confirmed, he underwent gross total resection and PBT. Case 4 received VAC regimen with PBT as a first line therapy. However, with no response clinical status, she received cisplatin-based therapy and then irinotecan-based therapy as a second/third line therapy. Finally, she received gross tumor resection. Following tumor resection, reduced VAC treatment was conducted as a consolidation therapy. Case 5 received VDS/IE treatment (consisting of Vincristine 1.5 mg/m^2 day 0, Doxorubicin 37.5mg/m^2 day 0,1, Cyclophosphamide 1,200 mg/m^2 day 0, Ifosphamide 1,800 mg/m^2 days 14 through 18 and Etoposide 100mg/m^2 days14 through 18) as a second line chemotherapy. After confirmation of complete response, he underwent VAC regimen and PBT.

There were 3 patients (Cases 3, 4 and 5) who underwent chemotherapy during PBT (Group Cx). All PBT-combined chemotherapy was VAC based treatment where Actinomycine-D was removed for 2 of 3 patients. The lowest leukocyte levels of patients who underwent chemotherapy during PBT were 100, 500 and 700 /uL. A pack of red blood cell was transfused to 2 patients and 2 of Group Cx developed fever. Severe cystitis caused a 17-day interruption of PBT for one patient undergoing VAC based chemotherapy. No patients other than one each from the non-Group Cx and Group Cx experienced PBT suspension.

Proton beam therapy was adapted during the planned course of chemotherapy for 3 children and after completion of chemotherapy and resection resulted in no assessable tumor for 2 children. The median dose of PBT was 47.7 GyE; Case1 received 41.4 GyE/23 Fr in 41 days; Case2 received 41.4 GyE/23 Fr in 35 days; Case3 received 50.4 GyE/28 Fr in 43 days; Case4 received 50.4 GyE/28 Fr in 56 days which was postponed momentarily due to cystitis; Case5 received 50.4 GyE/28 Fr in 42 days

(Table II).

All patients were biopsied at their first visit. Two out of 5 patients completely and 2 out of 5 grossly resected with microscopic residual disease after chemotherapy. At the end of the second/third line chemotherapy, pathological findings of the biopsy specimens showed viable tumor cells in two patients with bladder RMS (case 1 and 4; after third line chemotherapy) and in one patient with prostate RMS (case 2; after third line chemotherapy including high dose chemotherapy rescued with autologous hematopoietic stem cell transplantation and 45Gy of X-ray therapy for local field). Eventually, radical extirpation with continent urinary reservoir was undergone for 2 and sigmoid colon conduit for 1.

One girl (Case 2) developed vaginal infection and fistula within 1 month after surgical operation and 9 months after completion of PBT at the site of tissue expander, which is artificial tissue optimized to spare colons or other normal tissues from future radiation. She had a vaginal fistula, 2.5 cm in diameter, which was covered by a pedicled rectus abdominis musculocutaneous flap from the left[12]. After this vaginoplasty, she did not develop other infection nor complications at the time this article was submitted.

All patients survived in their first complete response, other than one boy with very good partial response and then stable disease, at their last hospital visit with a median time of 37 months (10 to 92 months). All of them remain well and all 3 with sigmoid colon conduit or continent urinary reservoir go to preschool or elementary school on a continuing basis.

Discussion

Rhabdomyosarcoma is one of the common tumors among children. While cure rates can reach up to 60 to 80%, geniurinary/pelveic RMS (GU/P-RMS) presents an inferior outcome[6, 11]. While local treatment for GU/P-RMS is very important, radiotherapy for the pelvis could cause severe impairment of reproductive organs, the intestine, bladder or skeleton, and second neoplasm particularly for children[7, 13, 14].

We assessed combined therapy including PBT for GU/P RMS. Since mean doses for normal organs will be reduced with PBT rather than with X-ray, it will lead to the reduced risk of secondary cancer and impairment of the normal organs, particularly among children[15].

Three out of 5 patients were administered chemotherapy during PBT. All of them developed a leukocyte count under 1,000 /uL and 2 had fever. However, any infections were fatal and an acceptable adverse event compared with combined therapy of X-ray therapy.

One girl developed vaginal fistula 9 months after completion of PBT. At the site of fistula, she underwent radical extirpation of the bladder and artificial tissue was inserted after PBT. The calculated radiation dose is 45 GyE at that site; normally the vagina can tolerate that amount of radiation[16]. However, radiation-induced vasinal fistula sometimes occurs in women who undergo pelvic radiation at 0.6 to 7%[17]. When radiation is terminated, fibrosis occurs and hyalinization of the connective tissues develops. Then the majority of fistulas become apparent 1.5 to 2 years after termination of radiotherapy[12, 17, 18]. Patient 2 developed her fistula within 9 months at the completion of PBT, which was earlier than has been reported. This may have been caused by invasive operation and the artificial tissue adapted to this case. We have since

changed the type of artificial tissue and no longer experienced vasinal fistula.

Though bone marrow suppression did not cause a fatal adverse event, we need to consider that chemotherapy-induced complications were probably exacerbated with radiotherapy, even treated with PBT which can greatly reduce the radiation field compared with other modality.

Four out of 5 patients who underwent multimodal treatment including PBT were in complete response and one patient whose follow-up time was relatively short was in very good partial response followed by stable disease.

No death or life-threatening event had occurred during PBT and no patient had experienced relapse as of the writing of this report. This clinical course led us to a conclusion that multimodal treatment combined with PBT is feasible and at least equal curability and less acute toxicity to X-ray.

Conclusion

We analyzed multimodal treatment combined with Proton beam therapy for genitourinary/pelvic Rhabdomyosarcoma. Although tumors were controlled well locally, infection and friability need to be considered the same as with X-ray therapy. PBT was well tolerated and could be a plausible choice instead of X-ray for this population.

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