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Original research article

Tailor-made treatment combined with proton beam therapy for children with genitourinary/pelvic rhabdomyosarcoma

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ARTICLE INFO

Article history:
Received 8 July 2014
Received in revised form
17 November 2014
Accepted 11 December 2014

Keywords:
Rhabdomyosarcoma
Proton-beam therapy
Genitourinary/pelvic tumor
Childhood malignancy
Multimodal therapy

ABSTRACT

Background: Rhabdomyosarcoma (RMS) is one of the most common soft tissue sarcomas among children. Patients who developed genitourinary/pelvic rhabdomyosarcoma (GU/P-RMS) have 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 evidence and analysis. We analyzed GU/P-RMS children who had undergone 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 had undergone multimodal therapy with PBT.

Results: There were 5 children and their median age at diagnosis was 2.8 years (0.6–4.4 years). Primary sites were the bladder (2) and the prostate (3). All received neo-adjuvant chemotherapy and 3 underwent chemotherapy during PBT (Group Cx). All patients of Group Cx developed leukocytopenia (WBC <1000/μL). The median dose of PBT was 47.7 GyE (41.4–50.4 GyE). All patients survived by their last hospital visit (median, 36 months).

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http://dx.doi.org/10.1016/j.rpor.2014.12.003

Conclusions: We analyzed multimodal treatment combined with PBT applied for GU/P-RMS. PBT was well tolerated and could be a plausible choice instead of photon therapy for this population.

1. Background

Rhabdomyosarcoma (RMS) is one of the most common soft tissue sarcomas among children.[1] Cure rates for RMS have reached up to 60–80% 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 the 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 evidence 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 had undergone multimodal treatment with chemotherapy, surgery and PBT.

2. Method

2.1. Patients

Included in our study were 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.

2.2. Chart 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 the 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.

2.3. 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 10–15 mm at first. After 41.4–45 GyE, clinical target volume was reduced to the area of macroscopically residual tumor. The margin for clinical target volume was then reduced to 5–10 mm. The dose for the whole bladder was limited to 41.4 GyE. After 41.4 GyE, we minimized the irradiated volume of the small bowel. The treatment was provided 5 days a week. The photon equivalent dose (GyE) was defined as the physical dose (Gy) × relative biological effectiveness of the proton beam assigned the 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 1.3–3.7 years old for planning CT and treatment. Patients underwent physical examination every day and laboratory tests were conducted more than once a week.

3. Results

We reviewed charts of children who had been treated at our hospital. There were 5 patients with GU/P-RMS who had undergone multimodal treatment combined with PBT between January 2007 and May 2013. Patient characteristics are shown in Table 1 and treatment summary and patient outcome are in Table 2. The median age at diagnosis was 2.8 (0.6–4.4) years and the median age at PBT was 2.9 (1.3–6.4) years. There were 1 female and 4 males. The tumor was located in the bladder in 2 patients and in the prostate in 3 patients. 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.

Table 1 – Patient characteristics.

	No.	Age (years)	Sex	Location	Pathology	Stage (TNM)	IRS-Group	Registered clinical study group
Group non-Cx	1	0.6	M	Bladder	Embryonal	2	III	JRSG
	2	4.4	M	Prostate	Embryonal	2	III	JRSG
Group Cx	3	0.9	M	Prostate	Unknown	3	III	None
	4	2.7	F	Bladder	Embryonal	3	III	None
	5	2.8	M	Prostate	Embryonal	3	III	JRSG

Abbreviations: IRS: intergroup rhabdomyosarcoma study group; M: male; F: female; JRSG: Japan Rhabdomyosarcoma Study Group.

At week 9, Case 1 was changed to VID treatment (VCR 1.0 mg/m^2 ± IFO 1200 mg/m^2 and DOX 25 mg/m^2) as a second line chemotherapy. After 2 courses of VID, he underwent a third line chemotherapy of irinotecan. However, due to tumor status of no response, he underwent gross resection with PBT. Case 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 37.5 mg/m^2 days 0 and 1, Cyclophosphamide 1200 mg/m^2 day 0, Ifosphamide 1800 mg/m^2 days 14–18 and Etoposide 100 mg/m^2 days 14–18) 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 the 3 patients. The lowest leukocyte levels of patients who underwent chemotherapy during PBT were 100, 500 and 700/μL. 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; Case 1 received 41.4 GyE/23 Fr in 41 days; Case 2 received 41.4 GyE/23 Fr in 35 days; Case 3 received 50.4 GyE/28 Fr in 43 days; Case 4 received 50.4 GyE/28 Fr in 56 days which was postponed momentarily due to cystitis; Case 5 received 50.4 GyE/28 Fr in 42 days (Table 2).

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 (cases 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 45 Gy of X-ray therapy for local field). Eventually, radical extirpation with continent urinary reservoir was performed 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 infections nor complications at the time this article was submitted.

All patients survived in their first complete response, other than one boy with a very good partial response and then stable disease, at their last hospital visit with a median time of 37 months (10–92 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 continuous basis.

4. Discussion

Rhabdomyosarcoma is one of the common tumors among children. While cure rates can reach up to 60–80%, genitourinary/pelvic 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 in 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 1000/μL and 2 had fever. However, no infections were fatal

Table 2 – Treatment summary and patient outcome.

	Pt no	Cx	PBT					Radiotherapy other than PBT	HDC ± Auto HST	Surgery	Outcome	Months to last f/u	Complications at last visit
			GyE (Fr)	Combined Cx	Lowest WBC (/μL)	BTF	Adverse event						
Group non-Cx	1	1st: VAC 2nd: VID	41.4 (23)	None	2100	None	None	No	No	RCP + SC[a]	1CR	37	None
	2	1st: VAC 2nd: irinotecan 3rd: CDDP-based	41.4 (23)	None	2400	None	Catheter related infection	Yes; X-ray 45 Gy local	Yes; Tepa 960 mg/m^2 Mel 224 mg/m^2	RCP + CUR	1CR	93	Hydronephrosis[b]
	3	1st: VAC	50.4 (28)	VC	500	RBC	Dermatitis	No	No	Gross total resection	1CR	10	None
Group Cx	4	1st: VAC 2nd: CDDP-based 3rd: irinotecan ± VCR 4th: reduced VAC	45 (25)	VAC	700	None	Cystitis, vaginal fistula	No	No	RC + CUR	1CR	56	Mild hydronephrosis
	5	1st: VAC 2nd: VDC/IE 3rd: back to VAC	50.4 (28)	VC	100	RBC	Local pain with phentanyl	No	No	Biopsy	VGPR ⇒SD	11	None

Abbreviations: Pt no: patients' number; BTF: blood transfusion; HST: hematopoietic stem cell transfusion; CR: complete response; VGPR: very good partial response; SD: stable disease; RCP: radical cystoprostatectomy; SC: sigmoid colon conduit; CUR: continent urinary reservoir; RC: radical cystectomy; PBT: proton beam therapy; Cx: chemotherapy; WBC: white blood cell count; VAC: consists of Vincristine 1.5 mg/m^2 days 0, 7, 14, Actinomycine-D 0.045 mg/kg day 0 and Cyclophosphamide 2200 mg/m^2 day 1; VC: consists of Vincristine 1.5 mg/m^2 days 0, 7, 14 and Cyclophosphamide 2200 mg/m^2 day 1; VID: consists of VCR 1.0 mg/m^2 + IFO 1200 mg/m^2 and DOX 25 mg/m^2; VDC/IE: consists of Vincristine 1.5 mg/m^2 day 0, Doxorubicin 37.5 mg/m^2 days 0, 1, Cyclophosphamide 1200 mg/m^2 day 0, Ifosphamide 1800 mg/m^2 days 14–18 and Etoposide 100 mg/m^2 days 14–18.

[a] Diversion to continent urinary reservoir being under consideration.

[b] Due to ureterointestinal anastomosis stricture.

and an acceptable adverse event was achieved 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 was 45 GyE at that site; normally, the vagina can tolerate that amount of radiation.[16] However, radiation-induced vaginal fistula sometimes occurs in women who undergo pelvic radiation at 0.6–7%.[17] When radiation is terminated, fibrosis occurs and hyalinization of the connective tissues develops. Then the majority of fistulas become apparent 1.5–2 years after the termination of radiotherapy.[12,17,18] Patient 2 developed her fistula within 9 months of the completion of PBT, which is earlier than has been reported. This may have been caused by the invasive operation and the artificial tissue adapted to this case. We have since changed the type of artificial tissue and no longer experienced vaginal fistula.

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

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

No death or life-threatening event 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 offers at least equal curability and less acute toxicity than X-ray.

5. 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.

Conflict of interest

We herein declare that there are no relationships that may pose a conflict of interest.

Financial disclosure

This work was supported in part by Grants-in-Aid for Scientific Research (B) (24390286); Challenging Exploratory Research (24659556); Young Scientists (B) (25861064); and Scientific Research (C) (24591832) from the Ministry of Education, Science, Sports and Culture of Japan; and Grant from the Ministry of Health, Labor and Welfare of Japan (26271201).

Acknowledgement

We would like to thank Mr. Charles N. Jones who provided scientific writing assistance.

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