REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 23 (2018) 442–450

Available online at www.sciencedirect.com

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journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Interinstitutional patient transfers between rapid chemotherapy cycles were feasible to utilize proton beam therapy for pediatric Ewing sarcoma family of tumors

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ARTICLE INFO

Article history:
Received 6 January 2018
Received in revised form 4 June 2018
Accepted 11 August 2018

ABSTRACT

Aim: To assess the feasibility of transferring to the University of Tsukuba Hospital for proton beam therapy (PBT) during intensive chemotherapy in children with Ewing sarcoma family of tumors (ESFT) who had been diagnosed and started their first-line treatment at prefectural or regional centers for pediatric oncology.

Abbreviations: PBT, proton beam therapy; ESFT, Ewing sarcoma family of tumors; VDC-IE, vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide; UTH, University of Tsukuba Hospital; EFS, event-free survival; OS, overall survival; DFS, disease-free survival.

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https://doi.org/10.1016/j.rpor.2018.08.006

Keywords:
Ewing sarcoma family of tumors (ESFT)
Proton beam therapy (PBT)
Multidisciplinary therapy
Multi-institutional
Pediatric

Background: The treatment of ESFT relies on a multidisciplinary approach using intensive neoadjuvant and adjuvant chemotherapies with surgery and radiotherapy. Multi-agent chemotherapy comprising vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) is widely used for ESFT, and the interval between each course is very important for maintaining the intensity and effect of chemotherapy.
Materials and methods: Clinical information of patients who received PBT and VDC-IE between April 2009 and May 2016 was collected retrospectively. The intervals between each course of VDC-IE and adverse events were assessed.
Results: Fifteen patients were evaluated. No delays in the intervals of chemotherapy due to transfer were observed. There were no adverse events caused during/just after transfer and no increases in adverse events. The estimated 4-year overall and event-free survival rates were 94.6% and 84.8%, respectively.
Discussion: Although the results of efficacy are preliminary, survival rates were comparable with past studies. More experience and follow-up are required to further assess the efficacy of PBT for patients with ESFT.
Conclusion: Multidisciplinary therapy for children with ESFT involving transfer to our hospital for PBT during VDC-IE was feasible without treatment delay or an increase in adverse events.

1. Introduction

Ewing sarcoma family of tumors (ESFT) is an aggressive sarcoma of bone or soft tissue with a peak incidence during adolescence and young adulthood. The treatment of ESFT relies on a multidisciplinary approach using intensive neoadjuvant and adjuvant chemotherapies together with surgery and radiotherapy. Multi-agent chemotherapy comprising vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) is widely used for ESFT, and the interval between each course is very important to maintain the intensity of chemotherapy. Womer et al. showed that VDC-IE administered every 2 weeks was more effective than that administered every 3 weeks, improving the 5-year event-free survival rate from 65% to 73% without increasing toxicities.[1] Although overall survival in patients with localized disease now approaches 65–75%, the acute and long-term toxicities of therapy are substantial. Reduction in quality of life due to retardation of growth and development and secondary cancer are also significant problems in pediatric patients.[2,3]

Particle therapy, including proton beam therapy (PBT), has unique physical properties that allow for the reduction or elimination of unnecessary radiation doses to normal tissues.[4] It is believed that reduced normal tissue exposure will translate into decreased rates of both early and late treatment-induced toxicities. Fukushima et al. reported that the quality of life of childhood brain/head and neck tumor survivors treated with PBT was similar to that of healthy controls and favorable compared to patients treated with photon beam therapy.[5]

In Japan, PBT for childhood malignant solid tumors has been approved by the public health insurance system since April 2016. Although 13 institutions can provide PBT in Japan, only four institutions have treated children. Most pediatric patients with malignant solid tumors, including ESFT, need to continue concurrent chemotherapy during radiotherapy. Since PBT facilities that treat pediatric cases are limited, most children with malignant tumors have to be transferred for PBT during intensive multimodal treatment without incurring any delays in chemotherapy or surgery. Rombi et al.[6] has reported 30 cases with ESFT receiving multidisciplinary treatment, including chemotherapy and PBT, at a single institution, although pediatric patients with ESFT receiving multimodal treatment involving interinstitutional transfer have not been reported. From 1984 to 2015, more than 200 pediatric patients with tumors were referred to the University of Tsukuba Hospital (UTH) for PBT, accounting for approximately 60% of all cases in Japan, which is the largest cohort; UTH is one of the most experienced PBT facilities in the world.[7–12]

Since the feasibility of PBT concurrent with multimodal treatment involving interinstitutional patient transfer has not been explored, we retrospectively analyzed the feasibility and early outcomes of the approach in the subset of children with ESFT who had undergone PBT, surgery and VDC-IE chemotherapy.

2. Materials and methods

Patients who were newly diagnosed with ESFT at age <20 years who had started their first-line treatment with VDC-IE at prefectural or regional institutions and who were referred to UTH for PBT with chemotherapy from April 2009 to May 2016 were included.

At UTH, patients are followed-up at least once a year after PBT.

Chemotherapy was performed according to the following protocol[13]: for VDC, patients received 1.5 mg of vincristine per square meter of body-surface area (maximal dose, 2 mg) and 1200 mg of cyclophosphamide per square meter, followed by mesna, given to prevent hemorrhagic cystitis caused by cyclophosphamide. At UTH, doxorubicin, normally given at 75 mg per square meter was omitted to prevent toxicity during irradiation (VC-IE). For the IE component, 1800 mg of ifosfamide per square meter per day was given for five days,