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Original Article

Combined chemotherapy and ^{125}I-particle implantation for treatment of children with head and neck soft tissue sarcomas improve the short-term efficacy: Beijing Children's Hospital experience over 2 years

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Abstract: Objective: To evaluate the efficacy of chemotherapy combined with ^{125}I seed implantation in treating pediatric head and neck soft tissue sarcomas. Methods: The clinical characteristics, overall survival rate, local control rate and event free survival rate of patients treated with chemotherapy and ^{125}I seed implantation were studied retrospectively. Results: There were 12 males and 2 female patients. Age at diagnosis ranged between 1.0-10.7 years, and the median age is 4.9 years. Only 3 of the patients had localized disease, the other 11 patients had metastatic disease. The follow up time ranged from 8 to 30.5 months, median follow up time was 12.3 months. The overall response rate (complete response, very good patial response and partial response; CR, VGPR and PR) for all 14 patients was 85%, including 6/14 patients with CR, 1/14 patient with VGPR, 5/14 patients with PR. 2/14 patients had progressive disease. The overall local control rate was 85%, with a median LC time 18.9 months (95% CI: 16.4 to 21.3 month). The overall survival rate in this group of patients was 100%. The overall survival time was 8 to 30.5 months. The event free survival rate was 85%, with a median EFS time 18.9 months (95% CI: 16.4 to 21.3 months). Hematological toxicity was the most common side effects of chemotherapy. 7 of 14 patients suffered from grade 1 or 2 skin reaction after seed implantation. Conclusions: Chemotherapy combined with ^{125}I seed implantation is a feasible treatment for children with head and neck sarcomas, with high local control rates and event free survival.

Keywords: ^{125}I seed implantation, head and neck sarcomas, children, chemotherapy

Introduction

Soft tissue sarcomas in children are a group of malignant tumors that originated from primitive mesenchymal tissue and accounted for 7% of all childhood tumors [1]. These tumors are subdivided into Rhabdomyosarcomas (RMS) and non-RMS soft tissue sarcomas (NRSTS). It is localized in the head and neck region in 40% of patients with RMS [2]. Outcomes have historically been worse in the head and neck soft tissue sarcomas, due to anatomic constraints leading to difficulty in completely excising tumors, with high rates of local recurrence.

The major therapeutic goals are long-term survival, avoidance of local recurrence, maximizing function and minimising morbidity. Multidisciplinary treatment that includes chemotherapy, surgery and radiation therapy (RT) has become the standard of care for head and neck soft tissue sarcomas. However, complete tumor resection is not generally advised if there is a significant risk for functional of cosmetic morbidity, especially for the head and neck sarcomas. Although the recent studies reinforced the necessity of RT in patients with head and neck soft-tissue sarcomas [3, 4], the late effects of RT in children, especially in very young children, is still of concern. Permanent implantation of ^{125}I seeds into the tumor has the major advantages of delivering a high dose of irradiation to the tumor with a very sharp fall-off outside the

Table 1. Characteristics of the patients

Characteristics	Number of patients	Percentage (%)
Totall Number of patient	14	
Gender		
Boy	12	85
Girl	2	15
Age (y)	1.0-10.7	
Median age	4.9	
Pathology		
Rhabdomyosarcoma (embryonal)	7	50
Rhabdomyosarcoma (alveolar)	3	21
Synovial cell sarcoma	1	7
Extraosseous Ewing sarcoma	1	7
Malignant rhabdoid tumor	2	15
Site		
Parameningeal	8	85
Orbital	1	
Other head site	3	
Neck	2	15
Size		
>5 cm	13	93
<5 cm	1	7
Stage		
T1N0M0	1	7
T1N0M1	1	7
T2N0M0	2	15
T2N1M0	1	7
T2N1M1	7	50
T2NxM1	2	15
Treatment before seed implantation		
Chemotherapy only	11	79
Surgery and chemotherapy	3	21

implanted volume. Since pediatric head and neck sarcomas are most sensitive to chemotherapy, we assume that combined chemotherapy and ^{125}I seed implantation might be a better choice for this group of patients.

Materials and methods

Patients

The medical records of all patients with head and neck sarcomas treated in hematology oncology center, Beijing Children's Hospital (BCH) between 2012 and 2014 were reviewed. The head and neck was defined as any site above the clavicles. Only patients whose diagnosis were confirmed by a pathology report and also have a rapid central review were included in this study. This retrospective study was approved by the hospital ethics committee, and all patients provided written informed consent.

Between 2012 and 2014, 14 patients with head and neck sarcomas were treated in our center. Age at diagnosis ranged between 1.0-10.7 years, and the median age is 4.9 year. There were 12 males and 2 female patients. All of these patients had no special past history. The pathology type of this group of patients included 7 rhabdomyosarcoma (embryonal), 3 rhabdomyosarcoma (alveolar), 2 malignant rhabdoid tumors, 1 synovial cell sarcoma, and 1 extraosseous Ewing sarcoma. The site of the primary tumors included parameningeal in 8 patients, orbital in 1 patient, other head site in 3 patients and neck in 2 patients. Only 3 of the patients had localized disease, the other 11 patients had metastasis to lymph node or had distant metastasis to bone, lung or central nerves system (**Table 1**).

Treatment regimens

Eleven patients received chemotherapy alone before ^{125}I-particle implantation, including 9 patients with rhabdomyosarcomas and 2 patients with malignant rhabdoid tumors. For patients with rhabdomyosarcoma, the chemotherapy before the seed implantation consisted of 2-6 cycles alternating of vincristine, actinomycin, and cyclophosphamide (VAC) and vincristine, topotecan, cyclophosphamide (VTC). After the seed implantation, the patients continue to give vincristine, doxorubicin, cyclophosphamide (VDC) and etoposide, ifosfamide (IE), alternating for 10 cycles.

For patients with malignant rhabdoid tumors, the chemotherapy consisted of vincristine, doxorubicin, cyclophosphamide (VDCPM1) and etoposide, carboplatin, cyclophosphamide (CPM5 + CE), alternating for 10 cycles, and the seed implantation was performed after 5-6 cycles of chemotherapy. For the patient with extraosseous Ewing sarcoma, the chemotherapy consisted of VDC and IE, alternating for 16 cycles, and the seed implantation was performed after the 5th cycle of chemotherapy.

Only 3 patients underwent extensive resection of tumor, and all of the 3 patients had different degrees of functional disorder and disfigure-

Table 2. Patients' response to the treatment

Characteristics	Number of patients	Percentage (%)
Follow up time	8-30.8 months	
Median follow up time	12.3 months	
Response to the treatment		
CR	6	43
VGPR	1	7
PR	5	36
PD	2	14

ment. The other 11 patients had tumor biopsy before chemotherapy.

The seed implantation technique

The brachytherapy treatment planning system (BTPS, Beijing Atom and High Technique Industries Inc., Beijing, China) software for Windows XP was used to read information from CT images and to construct the implantation plan. In the plan, needles were implanted from different directions to avoid bone, major blood vessels and important organs. The CT images, including planned information on number, position, and direction of the implant needles, were then exported and saved in DICOM format.

The Mimics 10.01 for windows (Materialise, Belgium) was used initially to read CT and needle information, and then used to reconstruct the three-dimensional (3-D) appearance of the head and neck region and implantation needles in the correct positions. The 3-D data was then exported to software Geomagic 8.0 (Geomagic Company, USA) in an STL format. The individual template was designed according to the 3-D appearance of the skin using Geomagic software. The thickness of the template and the diameter of the implantation needles (18 G interstitial needles in our treatment) were then determined, and the Boolean minus operation was applied to obtain an image of the individual template that contained the needle information. According to the digital model, the individual template was constructed from the medial light-cured resin using the rapid forming machine Eden250 (Objet Company, Israel).

Under general anesthesia, the needles were implanted using the individual template and CT guidance, to ensure that all needles were in the expected position and depth, which was calculated in BTPS. Following this, ^{125}I seeds were implanted in the tissues via the needles, in accordance with the implantation plan. Finally, a further CT examination was performed to verify and guarantee that the seeds were distributed in the correct position. CT images of the seeds were used to calculate the D90, V100, V150 and dosages at organs at risk after treatment by BTPS.

Follow up

Tumor responses were evaluated at two month and six month after seed implantation, and every three months thereafter. The status of the tumor was determined by means of imaging studies, such as CT scans and MRI. The follow up time was calculated from the beginning of the chemotherapy. Follow up time ranged from 8 to 30.5 months, median follow up time was 12.3 months.

Statistical methods

Event free survival time was calculated from the beginning of chemotherapy to the date of recurrence or to the last follow up. For calculation of survival, local recurrence or distant metastasis was scored as events. Local control was defined as lack of tumor progression. Tumor responses were monitored by CT or MRI, and assessed using WTO criteria. The data was analyzed by using SPSS16.0 software. The OS and EFS were calculated by using Kaplan-Meier method.

Results

Local control and survival

The follow up time ranged from 8 to 30.5 months, with a median follow up time of 12.3 months.

The overall response rate (complete response, very good patial response and partial response; CR, VGPR and PR) for all 14 patients was 85%, including 6/14 patients with CR, 1/14 patient with VGPR, 5/14 patients with PR. 2/14 patient had progressive disease (**Table 2**). The overall local control rate was 85%, with a median LC time of 18.9 months (95% CI: 16.4 to 21.3 months). One patient with malignant rhabdoid tumors had recurrence of the primary tumor 9 months after the onset of the disease. He was

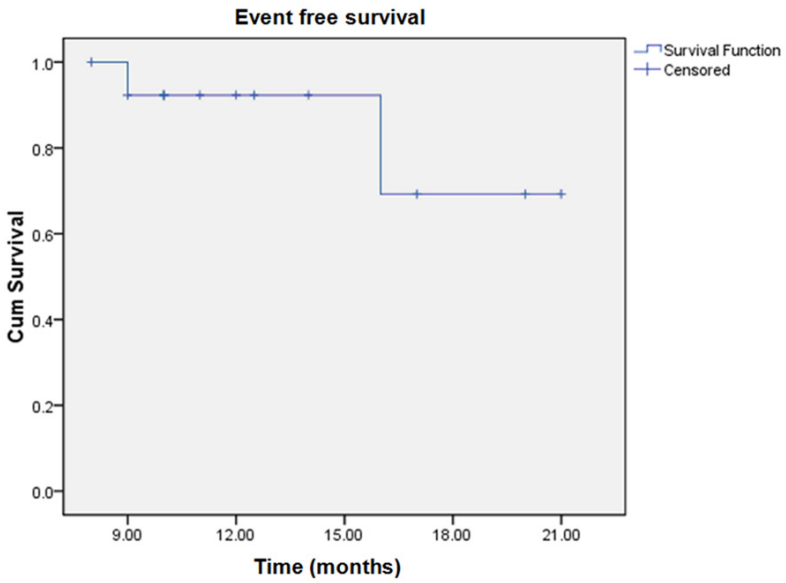

Figure 1. Kaplan-Meier estimate data showing event free survival for all patients after treatment.

carried on ^{125}I seed implantation and continued chemotherapy, and now he got completely response. Another patient with rhabdomyosarcoma (alveolar), who was initially given chemotherapy and ^{125}I seed implantation, had intracranial metastatic disease 16 months after the onset of the disease. He was given gamma knife radiosurgery, tumor resetion and continued to receive chemotherapy, and now the disease remained stable for 12 month.

The overall survival rate in this group of patients was 100%. The overall survival time was 8 to 30.5 months, with a median follow up time of 12.3 months. The event free survival rate was 85%, with a median EFS time of 18.9 months (95% CI: 16.4 to 21.3 months) (**Figure 1**).

Toxicity of chemotherapy

We followed the WHO anticancer drugs toxicity classification in acute and subacute phase to assess the grade of the toxicity. Hematological toxicity was the most common side effects. All of the patients had bone marrow suppression after chemotherapy. 10 of 14 patients had IV grade neutropenia, 4 of 14 patients had III grade neutropenia. 6 of 14 patients had III grade anemia, 7 of 14 patients had I-II grade anemia. Thrombocytopenia was mild in this group of patients. Only 5 of 14 patients had thrombocytopenia, 9 of 14 patients had normal platelet level after chemotherapy. No fatal infection occurred after chemotherapy. 1 of 14 patients had elevated transaminase during the treatment. The urinary system toxicity such as hematuria, proteinuria and elevated BUN or Cr levels were not seen in this group of patients. Cardiac toxicity including arrhythmia and cardiac dysfunction did not occur in this group of children. 1 of 14 patients had central nervous system toxicity, manifested as convulsions, and the MRI showed suspicious of demyelination disease. No sever skin and mucosal lesions were seen in this group of patients during chemotherapy.

Complications of seed implantation

We followed the RTOG (Radiation Therapy Oncology Group) grading criteria for acute radiation injury to assess the grade of the toxicity after seed implantation. 7 of 14 patients suffered from grade 1-2 skin reaction after seed implantation, manifested as erythema or mild edema of the local skin, which can be improved within 1-2 weeks. No soft tissue necrosis and other severe complications were observed in this group of patients. Bone marrow suppression was not observed after seed implantation, and the interval of chemotherapy was not affected by seed implantation.

Discussion

As the functional abilities and quality of life after treatment is becoming more and more important for cancer children, balancing the potential for cure with the possibility of incurring harmful late effects is one of the major challenges in treating children with malignancies. For patients with solid tumors, durable local control is critical to a favorable outcome. Because of anatomic constrains, head and neck sarcomas are nearly unable to completely resection. Consequently, chemotherapy and radiotherapy are the mainstays of treatment. Different from conventional radiotherapy, the image-guidance brachytherapy delivers a sufficiently high dose to the tumor target with a very

sharp fall-off outside the implanted volume, so it can greatly reduce the side effects of radiation therapy [5]. Our study has shown that chemotherapy combined with ^{125}I seed implantation is a safe and effective treatment for children with head and neck soft tissue sarcomas, with high short-term local control rates and event free survival.

Compare to traditional external radiation therapy, the ^{125}I seed implantation had relatively few side effects. The most common acute side effect of external radiation therapy is skin and mucous membrane damage. In addition to acute radiation injury, the late sequelae affected the majority of patients treated with RT for soft-tissue sarcomas of the head and neck, including failed to maintain their initial height velocity, hypolasia or asymmetry of tissue in the primary tumor site, poor dentition or malformed teeth, impaired vision and decreased hearing acuity [6]. Despite concerns about the late effects of its use in young children, cure of head and neck sarcomas remains unlikely without systematic use of RT. Defachelles AS, et al [7] showed that even in children younger than 3 years, patients who received RT had a significantly superior 5-year EFS rate compared with patients who did not receive RT (59% *vs*. 28%, respectively).

The parameningeal site (including nasopharynx, nasal cavity, parapharyngeal area, paranasal sinuses, infratemporal and pterygopalatin fossa, middle ear, or madtoid) has proven to be an unfavorable prognostic factor in recent prospective clinical trials [8-11]. Stephamie K, et al [12] showed that the 5-year failure-free survival for children with parameningeal rhabdomyosarcoma was only 52-67%. Isolated local recurrences accounted for more than one third of treatment failures, and local recurrence is a component of more than half of all failures. J. H. M. Merks, et al [3] showed that RT is an absolute need for children with parameningeal RMS. The 10-year EFS for those who did not receive RT as part of initial treatment was only 25.1% (versus 66.0% for those who did). The patient with orbital site RMS often has localized disease. Oberlin O et al [13] demonstrated in their research that the 10-year EFS to be significantly better for patients with orbital RMS receiving RT as part of their initial treatment compared to those who did not (82% versus 53%). These studies emphasized the importance of radiotherapy in the treatment protocol for children with head and neck soft tissue sarcomas.

Successful treatment of head and neck soft tissue sarcomas requires systemic chemotherapy. The histological types in this cohort include rhabdomyosarcoma, synovial cell sarcoma, extraosseous Ewing sarcoma and malignant rhabdoid tumor, which are all sensitive to chemotherapy [14]. Malignant rhabdoid tumor is one of the most aggressive and lethal malignancies in pediatric oncology [15]. This cohort includes two children with malignant rhabdoid tumor. They all underwent intensive chemotherapy and ^{125}I seed implantation, and have a relatively good short-term effect. Regular chemotherapy is the guarantee of a better prognosis. The acute radiation injury in this group was mild. Bone marrow suppression and other severe side-effect were not seen after seed implantation. The regular chemotherapy cycles was not affected by the seed implantation treatment.

Conclusions

Chemotherapy combined with ^{125}I seed implantation is a feasible treatment for children with head and neck sarcomas, with high local control rates and event free survival. To date, the follow-up is too short for definitive conclusions regarding these results. The long term prognosis of this group of patient still needs further investigation.

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Disclosure of conflict of interest

None.

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References

[1] Loeb DM, Thornton K, Shokek O. Pediatric Soft Tissue Sarcomas. Surg Clin North Am 2008; 88: 615-627, vii.

[2] Park K, van Rijin R, McHugh K. The role of radiology in paediatric soft tissue sarcomas. Cancer Imaging 2008; 8: 102-115.

[3] Merks JH, De Salvo GL, Bergeron C, Bisogno G, De Paoli A, Ferrari A, Rey A, Oberlin O, Stevens MC, Kelsey A, Michalski J, Hawkins DS, Anderson JR. Parameningeal rhabdomyosarcoma in pediatric age: results of a pooled analysis from North Ameican and European cooperative groups. Ann Oncol 2014; 25: 231-236.

[4] Radzikowska J, Kukwa W, Kukwa A, Czarnecka A, Krzeski A. Rhabdomyosarcoma of the head and neck in children. Contemp Oncol 2015; 19: 98-107.

[5] Daniela EB, Winston WH. Rhabdomyosarcoma in adolescent and young adult patients: current perspectives. Adolesc Health Med Ther 2014; 5: 115-125.

[6] Raney RB, Asmar L, Vassilopoulou-Sellin R, Klein MJ, Donaldson SS, Green J, Heyn R, Wharam M, Glicksman AS, Gehan EA, Anderson J, Maurer HM. Late complications of therapy in 213 children with localized, nonorbital soft-tissue sarcoma of the head and neck: a descriptive report from the Intergroup Rhabdomyosarcoma Studies (IRS)-II and -III. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. Med Pediatr Oncol 1999; 33: 362-371.

[7] Defachelles AS, Rey A, Oberlin O, Spooner D, Stevens MC. Treatment of nonmetastatic cranial parameningeal rhabdomyosarcoma in children younger than 3 years old: result from International Society of Pediatric Oncology studies MMT 89 and 95. J Clin Oncol 2009; 27: 1310-1315.

[8] Arndt CA, Stoner JA, Hawkin DS, Rodeberg DA, Hayes-Jordan AA, Paidas CN, Parham DM, Teot LA, Wharam MD, Breneman JC, Donaldson SS, Anderson JR, Meyer WH. Vincristine, actinomycin, and cyclcophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group study D9803. J Clin Oncol 2009; 27: 5182-5188.

[9] Dantonello TM, Int-Veen C, Harms D, Leuschner I, Schmidt BF, Herbst M, Juergens H, Scheel-Walter HG, Bielack SS, Klingebiel T, Dickerhoff R, Kirsch S, Brecht I, Schmelzle R, Greulich M, Gadner H, Greiner J, Marky I, Treuner J, Koscielniak E. Cooperative trail CWS-91 for localized soft tissue sarcoma in children, adolescents, and young adults. J Clin Oncol 2009; 27: 1446-1455.

[10] Oberlin O, Rey A, Sanchez de Toledo J, Martelli H, Jenney ME, Scopinaro M, Bergeron C, Merks JH, Bouvet N, Ellershaw C, Kelsey A, Spooner D, Stevens MC. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society of Pediatric Oncology MMT95 study. J Clin Oncol 2012; 30: 2457-2465.

[11] Buwalda J, Schouwenburg PF, Blank LE, Merks JH, Copper MP, Strackee SD, Voûte PA, Caron HN. A novel local treatment strategy for advanced stage head and neck rhabdomyosarcoma in children: results of the AMORE protocol. Eue J Cancer 2003; 39: 1594-1602.

[12] Childs SK, Kozak KR, Friedmann AM, Yeap BY, Adams J, MacDonald SM, Liebsch NJ, Tarbell NJ, Yock TI. Proton radiotherapy for parameningeal rhabdomyosarcoma: chinical outcomes and effects. Int J Radiat Oncol Biol Phys 2012; 82: 635-642.

[13] Oberlin O, Rey A, Anderson J, Carli M, Raney RB, Treuner J, Stevens MC; International Society of Paediatric Oncology Sarcoma Committee, Intergroup Rhabdomyosarcoma Study Group, Italian Cooperative Soft Tissue Sarcoma Group, German Collaborative Soft Tissue Sarcoma Group. Treatment of orbital rhabdomyosarcoma: survival and late effects of treatmen-result of an international workshop. J Clin Oncol 2001; 19: 197-204.

[14] Richard FR. Systemic therapy for advanced soft tissue sarcomas. Cancer 2012; 118: 1474-1485.

[15] Kreiger PA, Judkin AR, Russo PA, Biegel JA, Lestini BJ, Assanasen C, Pawel BR. Loss of INI 1 expression defines a unique subset of pediatric undifferentiated soft tissue sarcomas. Mod Pathol 2009; 52: 328-334.