ALK-positive cases. This finding is consistent with that of a previous report in which rhabdomyosarcoma cell lines were found not to harbor DNA copy number gain at the 2p23 locus, where the *ALK* gene is located.[39] Similarly, *ALK* was not found to be a differentially amplified gene when genomic imbalances were compared between primary rhabdomyosarcoma tissues and normal muscle.[39]

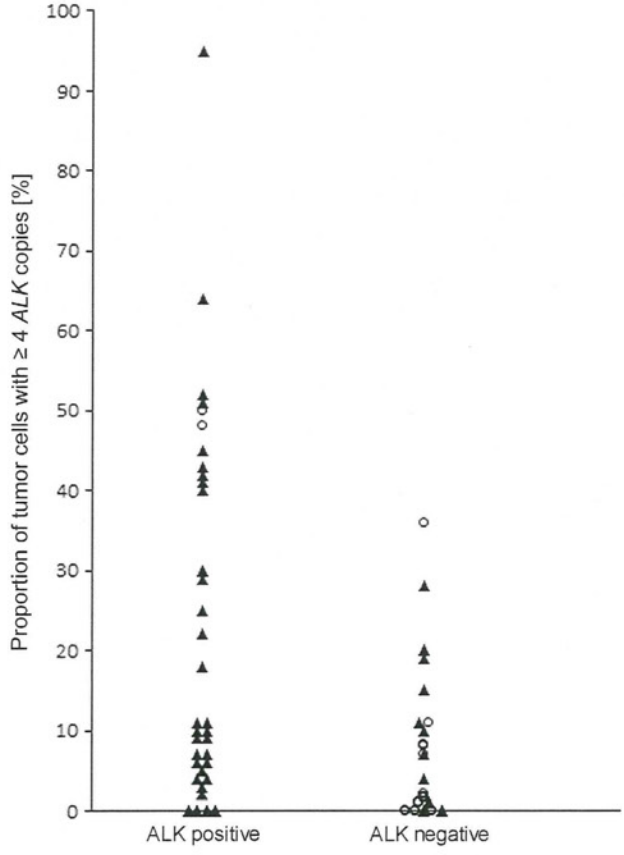

Figure 6 The percentage of tumor cells that harbored ≥4 copies of *ALK* gene determined by FISH in 37 ALK-positive and 23 ALK-negative rhabdomyosarcomas. ▲ indicates the alveolar subtype, and ○ indicates non-alveolar subtypes. ALK-positive tumors carried a significantly greater percentage of cells with ≥4 copies of the *ALK* gene than ALK-negative tumors did ($P=0.013$).

Our finding of a low incidence of increased *ALK* copy number in rhabdomyosarcoma was in contrast with the results of a recent large study by van Gaal *et al*[23] In their study, the absolute *ALK* copy number increased (>4 copies in >10% of cells) in 88% of alveolar rhabdomyosarcomas and 52% of embryonal tumors, and a selective *ALK* gain (average *ALK/LAF*>1.5) was seen in 45% of alveolar tumors and 61% of embryonal cases. The reason for this incongruence is unclear. Even when FISH interpretation criteria similar to theirs were applied, the *ALK* gain/amplification was uncommon in our cohort: tumors with >4 *ALK* copies in >10% of cells were observed in 23% of the alveolar tumors and 23% of the non-alveolar subtypes, and an average *ALK/CEN2p* of >1.5 was seen in 4% of the alveolar tumors and 15% of the non-alveolar cases. Other investigators also reported *ALK* gene gain/amplification in rhabdomyosarcoma (Table 4), but the number of cases studied was small, and the quantitative definition of gain/amplification was not provided.[19,20,22] Notably, these prior studies either did not use a reference probe[19,22] or separately examined the *ALK* gene and a reference gene,[20,23] whereas we simultaneously evaluated the *ALK* and reference genes using a dual-color approach that enabled precise determination of gene copy number at the cellular level.

ALK gene rearrangement and somatic mutation do not seem to have a major role in rhabdomyosarcoma. *ALK* rearrangement was not identified in any of the cases examined in this study, a finding similar to that of other studies.[20,22,23] Interestingly, one

Table 4 Published studies on the ALK status in rhabdomyosarcomas

	Cessna (2002)	*Pillay (2002)*	*Li (2004)*	*Corao (2009)*	*van Gaal (2012)*	*Present study (2012)*
Antigen retrieval	HIER (Citrate pH6)	HIER	HIER	HIER (TRS pH9)	HIER (Citrate pH6)	HIER (TRS pH9)
Antibody (dilution)	ALK1 (1:25)	p80 (1:100)	ALK1 (1:25) 5A4 (1:50)	ALK1 (1:50)	ALK1 (1:10)	5A4 (1:40)
Method	ABC	LSAB	Polymer	ABC	ABC	Polymer with Linker
Staining pattern	Cytoplasm	Nucleus	Cytoplasm	Cytoplasm	Cytoplasm/nucleus	Cytoplasm/membrane
Immunopositivity	4/16 ARMS 2/15 ERMS	15/35 ARMS 6/40 ERMS 2/8 Others	3/5 ARMS 1/2 ERMS	16/30 ARMS 9/37 ERMS 0/2 Others	47/58 ARMS 40/125 ERMS	42/61 ARMS 2/33 ERMS 0/22 Others
ALK rearrangement	Present (3/6)	NA	Absent (0/2)	Absent (0/6)	Absent (0/167)	Absent (0/24)
ALK copy number Change	3 copies (1/6) 3 – 6 copies (2/6)	NA	≥4 copies (1/2)	Loss of 1 copy (1/6) 2 – 6 copies (2/6) 30 – 40 copies (1/6)	>4 *ALK* in >10% (105/167) *ALK/LAF*>1.5 (31/56)	*ALK/CEN2p*≥2 (1/60) 1<*ALK/CEN2p*<2 (3/60) *ALK/CEN2p*=1 and≥4 copies in≥40% (7/60)
ALK mutation	NA	NA	NA	NA	1/43 (mutation) 7/43 (deletion)	1/19 (mutation)

Abbreviations: ABC, avidin-biotin complex; ALK anaplastic lymphoma kinase; ARMS, alveolar rhabdomyosarcoma; ERMS, embryonal rhabdomyosarcoma; HIER, heat-induced epitope retrieval; LSAB, labeled streptavidin biotin; NA, data not available; TRS, targeted retrieval solution (Dako).
Cessna *et al*[19] also separately evaluated p80 antibody, the results of which are not summarized here.

study[19] found *ALK* rearrangement in three of six rhabdomyosarcomas tested. We identified an *ALK* missense mutation (c.3830G>A, p.I1277T) in one embryonal rhabdomyosarcoma. However, this tumor was not immunopositive for ALK, indicating that the mutation may not be an activating one. This mutation was different from that (c.3673G>A, p.D1225N) reported previously in an embryonal rhabdomyosarcoma.[23] The same study[23] also identified frame-shift deletions in two alveolar and five embryonal rhabdomyosarcomas by cDNA sequencing, which probably represented alternative mRNA splicing;[23] we did not find any deletions in the genomic DNA.

The positive ALK immunoreactivity in a subset of rhabdomyosarcomas, some of which are associated with an *ALK* gene copy number increase, may suggest the potential clinical benefit of ALK inhibition. However, whether ALK expression without gene rearrangement has oncologic relevance remains controversial. Thus far, ALK-targeted therapy has been shown to be clinically effective only in *ALK*-rearranged tumors. Some researchers[40] argued that ALK expression in rhabdomyosarcoma may simply be physiological rather than oncogenic, by showing that the ALK-expressing Rh30 cell line lacked ALK autophosphorylation. In contrast, others[41–43] suggested that in neuroblastomas, ALK protein expression itself exerts oncogenic activity irrespective of genomic status and that it is a potential target of kinase inhibitors. Future clinical studies should investigate whether ALK inhibitors are beneficial for treating ALK-immunopositive tumors without gene rearrangement.

In summary, we clarified the subtype-specific incidence of ALK immunoreactivity in rhabdomyosarcomas and showed the association between ALK expression and several clinicopathologic/molecular parameters. This comprehensive analysis will serve as a basis for future investigations that aim to determine the indication, or lack thereof, of ALK-targeted therapy for patients with rhabdomyosarcoma.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

References

1 Montgomery E, Barr FG. Pleomorphic rhabdomyosarcoma, In: Fletcher CDM, Unni KK, Mertens F(eds) Pathology and genetics of tumours of soft tissue and bone. IARC Press: Lyon, France; 2002, pp 153–154.
2 Parham D, Barr FG. Embryonal rhabdomyosarcoma, In: Fletcher CDM, Unni KK, Mertens F (eds) Pathology and genetics of tumours of soft tissue and bone. IARC Press: Lyon, France; 2002, pp 146–149.
3 Parham D, Barr FG. Alveolar rhabdomyosarcoma, In: Fletcher CDM, Unni KK, Mertens F (eds) Pathology and genetics of tumours of soft tissue and bone. IARC Press: Lyon, France; 2002, pp 150–152.
4 Folpe AL, McKenney JK, Bridge JA, *et al.* Sclerosing rhabdomyosarcoma in adults: report of four cases of a hyalinizing, matrix-rich variant of rhabdomyosarcoma that may be confused with osteosarcoma, chondrosarcoma, or angiosarcoma. Am J Surg Pathol 2002;26:1175–1183.
5 Jo VY, Marino-Enriquez A, Fletcher CD. Epithelioid rhabdomyosarcoma: clinicopathologic analysis of 16 cases of a morphologically distinct variant of rhabdomyosarcoma. Am J Surg Pathol 2011;35:1523–1530.
6 Mentzel T, Katenkamp D. Sclerosing pseudovascular rhabdomyosarcoma in adults. Clinicopathological and immunohistochemical analysis of three cases. Virchows Arch 2000;436:305–311.
7 Nascimento AF, Fletcher CD. Spindle cell rhabdomyosarcoma in adults. Am J Surg Pathol 2005;29:1106–1113.
8 Morris SW, Kirstein MN, Valentine MB, *et al.* Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 1994;263:1281–1284.
9 Gascoyne RD, Lamant L, Martin-Subero JI, *et al.* ALK-positive diffuse large B-cell lymphoma is associated with Clathrin-ALK rearrangements: report of 6 cases. Blood 2003;102:2568–2573.
10 Lawrence B, Perez-Atayde A, Hibbard MK, *et al.* TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. Am J Pathol 2000;157:377–384.
11 Soda M, Choi YL, Enomoto M, *et al.* Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561–566.
12 Debelenko LV, Raimondi SC, Daw N, *et al.* Renal cell carcinoma with novel VCL-ALK fusion: new representative of ALK-associated tumor spectrum. Mod Pathol 2011;24:430–442.
13 Marino-Enriquez A, Ou WB, Weldon CB, *et al.* ALK rearrangement in sickle cell trait-associated renal medullary carcinoma. Genes Chromosomes Cancer 2011;50:146–153.
14 Chen Y, Takita J, Choi YL, *et al.* Oncogenic mutations of ALK kinase in neuroblastoma. Nature 2008;455:971–974.
15 Murugan AK, Xing M. Anaplastic thyroid cancers harbor novel oncogenic mutations of the ALK gene. Cancer Res 2011;71:4403–4411.
16 Kwak EL, Bang YJ, Camidge DR, *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693–1703.
17 Butrynski JE, D'Adamo DR, Hornick JL, *et al.* Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med 2010;363:1727–1733.

18 Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med 2011;364:775–776.
19 Cessna MH, Zhou H, Sanger WG, *et al.* Expression of ALK1 and p80 in inflammatory myofibroblastic tumor and its mesenchymal mimics: a study of 135 cases. Mod Pathol 2002;15:931–938.
20 Corao DA, Biegel JA, Coffin CM, *et al.* ALK expression in rhabdomyosarcomas: correlation with histologic subtype and fusion status. Pediatr Dev Pathol 2009;12:275–283.
21 Pillay K, Govender D, Chetty R. ALK protein expression in rhabdomyosarcomas. Histopathology 2002;41:461–467.
22 Li XQ, Hisaoka M, Shi DR, *et al.* Expression of anaplastic lymphoma kinase in soft tissue tumors: an immunohistochemical and molecular study of 249 cases. Hum Pathol 2004;35:711–721.
23 van Gaal JC, Flucke UE, Roeffen MH, *et al.* Anaplastic lymphoma kinase aberrations in rhabdomyosarcoma: clinical and prognostic implications. J Clin Oncol 2012;30:308–315.
24 Yoshida A, Tsuta K, Nakamura H, *et al.* Comprehensive histologic analysis of ALK-rearranged lung carcinomas. Am J Surg Pathol 2011;35:1226–1234.
25 Morotti RA, Nicol KK, Parham DM, *et al.* An immunohistochemical algorithm to facilitate diagnosis and subtyping of rhabdomyosarcoma: the Children's Oncology Group experience. Am J Surg Pathol 2006;30:962–968.
26 Cappuzzo F, Hirsch FR, Rossi E, *et al.* Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst 2005;97:643–655.
27 Kilpatrick SE, Teot LA, Geisinger KR, *et al.* Relationship of DNA ploidy to histology and prognosis in rhabdomyosarcoma. Comparison of flow cytometry and image analysis. Cancer 1994;74:3227–3233.
28 Shapiro DN, Parham DM, Douglass EC, *et al.* Relationship of tumor-cell ploidy to histologic subtype and treatment outcome in children and adolescents with unresectable rhabdomyosarcoma. J Clin Oncol 1991;9:159–166.
29 Mino-Kenudson M, Chirieac LR, Law K, *et al.* A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry. Clin Cancer Res 2010;16:1561–1571.
30 Takeuchi K, Choi YL, Togashi Y, *et al.* KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res 2009;15:3143–3149.
31 Takeuchi K, Soda M, Togashi Y, *et al.* Pulmonary inflammatory myofibroblastic tumor expressing a novel fusion, PPFIBP1-ALK: reappraisal of anti-ALK immunohistochemistry as a tool for novel ALK fusion identification. Clin Cancer Res 2011;17:3341–3348.
32 Parham DM, Qualman SJ, Teot L, *et al.* Correlation between histology and PAX/FKHR fusion status in alveolar rhabdomyosarcoma: a report from the Children's Oncology Group. Am J Surg Pathol 2007;31:895–901.
33 Dias P, Chen B, Dilday B, *et al.* Strong immunostaining for myogenin in rhabdomyosarcoma is significantly associated with tumors of the alveolar subclass. Am J Pathol 2000;156:399–408.
34 Williamson D, Missiaglia E, de Reynies A, *et al.* Fusion gene-negative alveolar rhabdomyosarcoma is clinically and molecularly indistinguishable from embryonal rhabdomyosarcoma. J Clin Oncol 2010;28:2151–2158.
35 Wachtel M, Dettling M, Koscielniak E, *et al.* Gene expression signatures identify rhabdomyosarcoma subtypes and detect a novel t(2;2)(q35;p23) translocation fusing PAX3 to NCOA1. Cancer Res 2004;64:5539–5545.
36 Davicioni E, Finckenstein FG, Shahbazian V, *et al.* Identification of a PAX-FKHR gene expression signature that defines molecular classes and determines the prognosis of alveolar rhabdomyosarcomas. Cancer Res 2006;66:6936–6946.
37 Lae M, Ahn EH, Mercado GE, *et al.* Global gene expression profiling of PAX-FKHR fusion-positive alveolar and PAX-FKHR fusion-negative embryonal rhabdomyosarcomas. J Pathol 2007;212:143–151.
38 Cao L, Yu Y, Bilke S, *et al.* Genome-wide identification of PAX3-FKHR binding sites in rhabdomyosarcoma reveals candidate target genes important for development and cancer. Cancer Res 2010;70:6497–6508.
39 Missiaglia E, Selfe J, Hamdi M, *et al.* Genomic imbalances in rhabdomyosarcoma cell lines affect expression of genes frequently altered in primary tumors: an approach to identify candidate genes involved in tumor development. Genes Chromosomes Cancer 2009;48:455–467.
40 Lamant L, Pulford K, Bischof D, *et al.* Expression of the ALK tyrosine kinase gene in neuroblastoma. Am J Pathol 2000;156:1711–1721.
41 Passoni L, Longo L, Collini P, *et al.* Mutation-independent anaplastic lymphoma kinase overexpression in poor prognosis neuroblastoma patients. Cancer Res 2009;69:7338–7346.
42 De Brouwer S, De Preter K, Kumps C, *et al.* Meta-analysis of neuroblastomas reveals a skewed ALK mutation spectrum in tumors with MYCN amplification. Clin Cancer Res 2010;16:4353–4362.
43 Duijkers FA, Gaal J, Meijerink JP, *et al.* Anaplastic lymphoma kinase (ALK) inhibitor response in neuroblastoma is highly correlated with ALK mutation status, ALK mRNA and protein levels. Cell Oncol 2011;34:409–417.

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ORIGINAL ARTICLE

Comparison of dose intensity of vincristine, *d*-actinomycin, and cyclophosphamide chemotherapy for child and adult rhabdomyosarcoma: a retrospective analysis

Yuki Kojima · Kenji Hashimoto · Masashi Ando · Kan Yonemori · Harukaze Yamamoto · Makoto Kodaira · Mayu Yunokawa · Chikako Shimizu · Kenji Tamura · Ako Hosono · Atsushi Makimoto · Yasuhiro Fujiwara

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Abstract
Purpose The prognosis of adult rhabdomyosarcoma (RMS) has been considered dismal. The question is raised that vincristine, *d*-actinomycin, and cyclophosphamide (VAC) chemotherapy may not be administered as per schedule for adult RMS; consequently, low dose intensity (DI) leads to poor prognosis. Herein, we examined whether the administration of VAC chemotherapy for adults and children with RMS is feasible with regard to the DIs of VAC.
Methods Chart review was retrospectively performed for all identified patients. The percentage of relative DI (RDI) was calculated according to the Children's Oncology Group D9803 protocol. Further, we examined the RDI in the first 6 cycles of VAC (induction phase) and the DI after the first 6 cycles of VAC (maintenance phase).
Results We identified a total of 27 adults and 18 children with RMS, respectively. The mean RDIs of vincristine in total phase were significantly lower in adults than that in children ($P = 0.04$). In induction phase, the mean RDIs of vincristine and cyclophosphamide were similar for both groups; however, they were dropped significantly in adults during maintenance phase ($P < 0.05$). Mean RDIs of vincristine in elderly patients tended to become low. Low RDI was mainly attributable to hematologic toxicity, infection, and peripheral neuropathy. The prognosis of low versus high RDI was similar.
Conclusions The RDIs of vincristine and cyclophosphamide in the maintenance phase were significantly lower than that in children. VAC chemotherapy for adults was not feasible; these patients require a different regimen.

Keywords Rhabdomyosarcoma · Adults · Children · Chemotherapy · Soft tissue sarcoma

Abbreviations

RMS	Rhabdomyosarcoma
VAC	Vincristine, *d*-actinomycin, and cyclophosphamide
DI	Dose intensity
RDI	Relative dose intensity
IRS	The International Rhabdomyosarcoma Study
PFS	Progression-free survival
OS	Overall survival
PCP	Pneumocystis jirovecci pneumonia

Introduction

Recent advances in the treatment for rhabdomyosarcoma have contributed to improve survival from 55 to 73 % [1–3]. Vincristine and *d*-actinomycin with or without cyclophosphamide (VAC) regimens for rhabdomyosarcoma are considered standard options according to the previous randomized trials [4–8]. However, these trials

Y. Kojima · K. Hashimoto (✉) · M. Ando · K. Yonemori · H. Yamamoto · M. Kodaira · M. Yunokawa · C. Shimizu · K. Tamura · Y. Fujiwara
Department of Medical Oncology and Breast Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: gonmusao@k6.dion.ne.jp

Y. Kojima
Department of Hematology and Medical Oncology, Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 460-0001, Japan

A. Hosono · A. Makimoto
Department of Pediatric Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

mainly focused on children or adolescents; therefore, the data of precious adult rhabdomyosarcoma patients were limited.

Sultan et al. [9] reported the prognosis of pediatric and adult rhabdomyosarcoma, and the data suggested that 5-year survival rate was significantly poor in adult rhabdomyosarcoma with 27 % compared to that of pediatrics with 61 %. Other facilities also reported small series of similar results [10–14]. Accordingly, the prognosis of adult rhabdomyosarcoma remained poor; however, the treatment strategy references along with childhood rhabdomyosarcoma.

There is no evidence available to uncover the reason for poor prognosis of adult rhabdomyosarcoma. The VAC chemotherapy was developed mainly for targeting pediatrics; therefore, adverse event may differ when we applied the regimen to adults. Accordingly, the VAC regimens may not be administered per schedule, which leads to poor prognosis due to low dose intensity. To our knowledge, there are no reports on dose intensity of VAC regimens in relation to prognosis. We launched this study to seek optimal treatment for adult rhabdomyosarcoma by comparing dose intensity to childhood or adolescent rhabdomyosarcoma.

Methods

Patients

All the patients included in this analysis meet the following criteria: histologically diagnosed with rhabdomyosarcoma, treated at the National Cancer Center Hospital in Tokyo between 1991 and 2010, and received VAC chemotherapy 6 cycles or over as a first-line treatment. The chart review was performed for all identified patients to obtain the following information: age, sex, primary tumor site, histopathology, tumor size, stage, group defined by the International Rhabdomyosarcoma Study (IRS) postsurgical grouping system [4], chemotherapy regimen, chemotherapy administration schedule, adverse event, date of radiotherapy, date of surgery, date of progression, and date of last follow-up.

Treatment

The details of VAC chemotherapy are shown as follows. VAC consisted of vincristine at a dose of 1.5 mg/m^2 (up to 2 mg/body), given intravenously on day 1, 8, 15, cyclophosphamide at a dose of 2.2 g/m^2, given intravenously on day 1, and *d*-actinomycin at a dose of 1.5 mg/m^2 (up to 2.5 mg/body), given intravenously on day 1. The treatment course was repeated every 3 weeks according to Children's Oncology Group Study D9803 [8]. *D*-actinomycin on day 1 and vincristine on day 8 and day 15 were omitted when radiotherapy was applicable.

Dose intensity calculation and definitions of terms

Dose intensity of vincristine and cyclophosphamide was calculated according to the following formula: Dose intensity (vincristine) = Total dose of vincristine (mg/m^2)/[(last date of injection − first date of injection) + 7]/7; Dose intensity (cyclophosphamide) = Total dose of cyclophosphamide (mg/m^2)/[(last date of injection − first date of injection) + 21]/7, respectively. The percentage of relative dose intensity (RDI) was calculated according to the Children's Oncology Group D9803 protocol [8]. We examined the RDI in induction phase and maintenance phase. Induction phase was defined as the first six cycles of VAC, and maintenance phase was defined as the latter cycles after induction phase. We defined cut-off points of RDI of vincristine and cyclophosphamide at 80 % and dichotomized into lower RDI (RDI $<$ 80 %) and higher RDI (RDI $\geq$ 80 %).

We defined adult as the patients aged greater than or equal to 21 years, and we used the term 'children' for the others. We attempted to retrospectively define the stage of disease according to the IRS staging system, which separates patients by site of the primary tumor, tumor size, and the presence or absence of tumor-involved regional lymph nodes and of distant metastases. Adverse events were retrospectively ranked by the National Cancer Institute Common Toxicity Criteria version 3.0. As a definition of febrile neutropenia, we used the guidelines established by the Infectious Disease Society of America [15]. Treatment delay was defined as more than a week of delay to start new cycle of VAC regimen.

Statistics

We used Student's *t* test to detect the difference of mean RDI. Progression-free survival (PFS) was defined as the time between the date of initial chemotherapy until the date of the recognition of local recurrence or distant metastases. Death was treated as an event, and the absence of disease progression was treated as a censored observation on the last day of follow-up. Overall survival (OS) was defined as the time from the date of initial chemotherapy until the date of death. Patients who were lost to follow up were treated as a censored observation on the last day of follow-up. We used the Kaplan–Meier method to draw survival curve, and significance was detected by the log-rank test. All statistical analyses were performed using SPSS ver. 19.0 (IBM Co. Inc, Okinawa, Japan).

Results

Patient characteristics

We identified 59 patients who received VAC regimen and of 45 patients met the eligibility criteria in the study period. Fourteen patients were excluded from this analysis by the following reasons: less than 6 cycles of VAC regimen in 12 patients, VAC chemotherapy of IRS II protocol in one, and clinical data unavailable in one. There were 27 adult patients and 18 were children.

The distribution of clinical and pathologic characteristics of these patients is listed in Table 1. The median age of adult was 28 years (range, 22–72) and that of children was 16 years (range, 2–19). Primary disease site, histopathology, and primary tumor size were similar among adult and children. Fourteen adults and 8 children had parameningeal primary site. Metastatic disease was somewhat high in adult.

Overall median follow-up period was 26 months (range, 6–114 months): 26 months in adults (range, 6–113 months) and 36 months in children (range, 6–114 months). We identified a total of 316 cycles of VAC chemotherapy in adults and a total of 209 cycles in children. The median number of chemotherapy cycles was 13 (range, 6–14) for adults and 12.5 (range, 6–14) for children.

Relative dose intensity of VAC chemotherapy

The mean RDIs of vincristine and cyclophosphamide in total phase for adults were 76.8 and 80.8 %, respectively, and those for children were 90.2 and 86.9 %, respectively. The mean RDI of vincristine in total phase was significantly lower in adults than that in children ($P < 0.05$) (Table 2).

In induction phase, the mean RDIs of vincristine and cyclophosphamide were similar for both groups; however, they were dropped significantly in adults during maintenance phase ($P < 0.05$) (Table 2). We examined the RDIs of vincristine and cyclophosphamide in relation to age. Mean RDIs of vincristine in elderly patients tended to become low (Fig. 1).

Chemotherapy efficacy by RDI

We analyzed the efficacy of RDI on PFS and OS. The PFS and OS were not statistically different in patients with high RDI and low RDI of vincristine and cyclophosphamide in total phase. For total phase of RDI for vincristine, median PFS was 28 months in patients with high RDI ($n = 15$) and 24 months in patients with low RDI ($n = 30$) ($P = 0.43$), and median OS was 60 months in patients with high RDI ($n = 15$) and 42 months in patients with low RDI ($n = 30$) ($P = 0.78$) (Fig. 2a). For total phase of RDI for cyclophosphamide, median PFS was 28 months in patients with high RDI ($n = 17$) and 24 months in patients with low RDI ($n = 28$) ($P = 0.78$), and median OS was 114 months in patients with high RDI ($n = 17$) and 60 months in patients with low RDI ($n = 28$) ($P = 0.67$) (Fig. 2b). We further analyzed induction phase and maintenance phase of RDIs for vincristine and cyclophosphamide or stratified them by adults and children on PFS and OS. None of the difference regarding RDI of both agents on PFS and OS was detected (Fig. 3).

Toxicity of VAC chemotherapy

Table 3 lists the worst degree of toxicity of VAC chemotherapy. Majority of patients experienced grade 3/4 neutropenia and anemia in both induction phase and maintenance phase. Grade 2–4 peripheral neuropathy was observed in 55.6 % of adult patients, while it was 33.3 % in children ($P = 0.37$). Approximately 80 % of patients needed granulocyte colony-stimulating factor, and 73.3 % of patients received trimethoprim-sulfamethoxazole for prevention of pneumocystis jirovecci pneumonia (PCP). Two patients who did not receive trimethoprim-sulfamethoxazole developed PCP; one experienced PCP in 4th cycle of VAC, and the other did in 14 the cycle of VAC.

Cause of dose reduction, skip, and delayed cycles

In induction phase, three of adults (11.1 %) and one of children (5.6 %) required dose reduction of vincristine due to peripheral neuropathy and myelosuppression. Eight of the patients (29.6 %) in adults and 4 of the patients (22.2 %) in children required dose reduction of cyclophosphamide, due to myelosuppression, febrile neutropenia, and liver dysfunction. In maintenance phase, four adults (16.0 %) and 2 children (11.8 %) required dose reduction of vincristine, due to peripheral neurotoxicity and myelosuppression. Nine adults (36.0 %) and 5 children (18.5 %) required dose reduction of cyclophosphamide, due to myelosuppression and febrile neutropenia.

Adult patients needed discontinuance of vincristine in total of 126 times out of 713 times (17.7 %) due to the following reasons: peripheral neurotoxicity in 75 times, myelosuppression in 35 times, and febrile neutropenia in 14 times. For these child patients, it was 55 times out of 483 times of vincristine administration (11.4 %) due to peripheral neurotoxicity in 16 times, myelosuppression in 16 times, and febrile neutropenia in 9 times.

In induction phase, 14 adult patients (51.9 %) and 9 child patients (50.0 %) experienced cycle delay. In maintenance phase, 17 adult patients (68.0 %) and 9 child patients (52.9 %) required cycle delay. The major causes of

Table 1 Patient characteristics

	Adults ($N = 27$)	Children ($N = 18$)
Age, median (range)	28 (22–72)	16 (2–19)
Gender		
Female	8 (29.6 %)	9 (50.0 %)
Male	19 (70.4 %)	9 (50.0 %)
Primary tumor site		
Head-neck	3 (11.1 %)	3 (16.7 %)
Parameningeal primary site	14 (51.9 %)	8 (44.4 %)
Unfavorable other	5 (18.5 %)	1 (5.6 %)
Extremity	3 (11.1 %)	5 (27.8 %)
Genitourinary primary site	2 (7.4 %)	1 (5.6 %)
Histopathology		
Alveolar	15 (55.6 %)	10 (55.6 %)
Embryonal	10 (37.0 %)	7 (38.9 %)
Others	2 (7.4 %)	1 (5.6 %)
Tumor size		
≥5 cm	10 (37.0 %)	8 (44.4 %)
<5 cm	15 (55.6 %)	9 (50.0 %)
Not available	2 (7.4 %)	1 (5.6 %)
IRS group		
I	3 (11.1 %)	2 (11.1 %)
II	3 (11.1 %)	1 (5.6 %)
III	12 (44.4 %)	12 (66.7 %)
IV	9 (33.3 %)	3 (16.7 %)
IRS pre-treatment stage		
Stage 1	4 (14.8 %)	4 (22.2 %)
Stage 2	4 (14.8 %)	1 (5.6 %)
Stage 3	10 (37.0 %)	10 (55.6 %)
Stage 4	9 (33.3 %)	3 (16.7 %)
Complete surgical resection		
Pre-chemotherapy	7 (25.9 %)	4 (22.2 %)
Post-chemotherapy	4 (14.8 %)	6 (33.3 %)
No surgery	16 (59.3 %)	8 (44.4 %)
Radiation therapy		
Pre-chemotherapy	2 (7.4 %)	2 (11.1 %)
Post-chemotherapy	20 (74.1 %)	14 (77.8 %)
No radiation therapy	5 (18.5 %)	2 (11.1 %)

IRS Intergroup Rhabdomyosarcoma Study

cycle delay were myelosuppression, febrile neutropenia, and patient preferences.

Discussion

In our analyses, 27 adults and 18 children of rhabdomyosarcoma who received VAC chemotherapy at a single institution were evaluated for RDIs of VAC chemotherapy. Adult patients had significantly lower RDIs of vincristine and cyclophosphamide in the maintenance phase compared

Table 2 Mean relative dose intensity in patients with adult and child rhabdomyosarcoma

	Adult (%)	Child (%)	*P* value
Vincristine			
Induction phase	77.7	86.4	0.109
Maintenance phase	71.9	100.1	0.042
Total phase	76.8	90.2	0.040
Cyclophosphamide			
Induction phase	87.1	88.2	0.820
Maintenance phase	69.7	86.4	0.011
Total phase	80.8	86.9	0.156

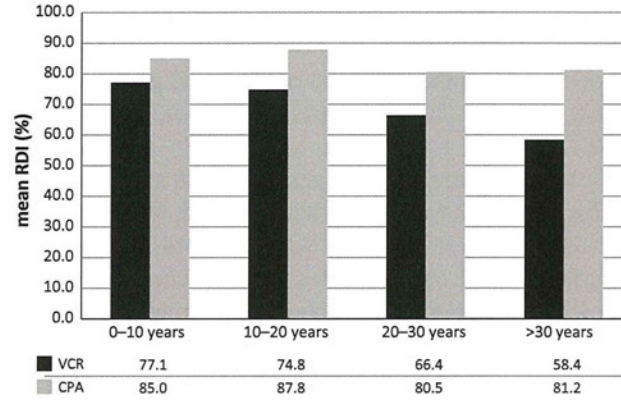

Fig. 1 Relative dose intensity of vincristine and cyclophosphamide in relation to age. *VCR* vincristine, *CPA* cyclophosphamide

to those of children. Further, the mean RDIs of vincristine tended to become low depending on patients' ages. The reasons for dose reduction, discontinuance, and treatment delay of vincristine and cyclophosphamide were generally due to myelosuppression, infection, and peripheral neurotoxicity. We revealed that the adult rhabdomyosarcoma patients significantly received lower RDIs of vincristine and cyclophosphamide than those of children; however, the PFS and the OS were not statistically different in patients with high RDI and low RDI in total phase and maintenance phase.

The prognosis of adult rhabdomyosarcoma remains poor, with approximately 30 % at 5-year survival [9–14, 16]. The reason for the poor outcome of adults remains unclear. Sultan et al. [9] reported the comparison of pediatric and adult rhabdomyosarcoma; they reported that the typical pediatric rhabdomyosarcoma variants (embryonal and alveolar subtypes) occurred less frequently in adult rhabdomyosarcoma and that the most common primary sites in adult were extremities and unfavorable sites and that radiation therapy was performed less frequently in adult rhabdomyosarcoma than in pediatric patients. In our study, adult rhabdomyosarcoma patients had lower RDIs in

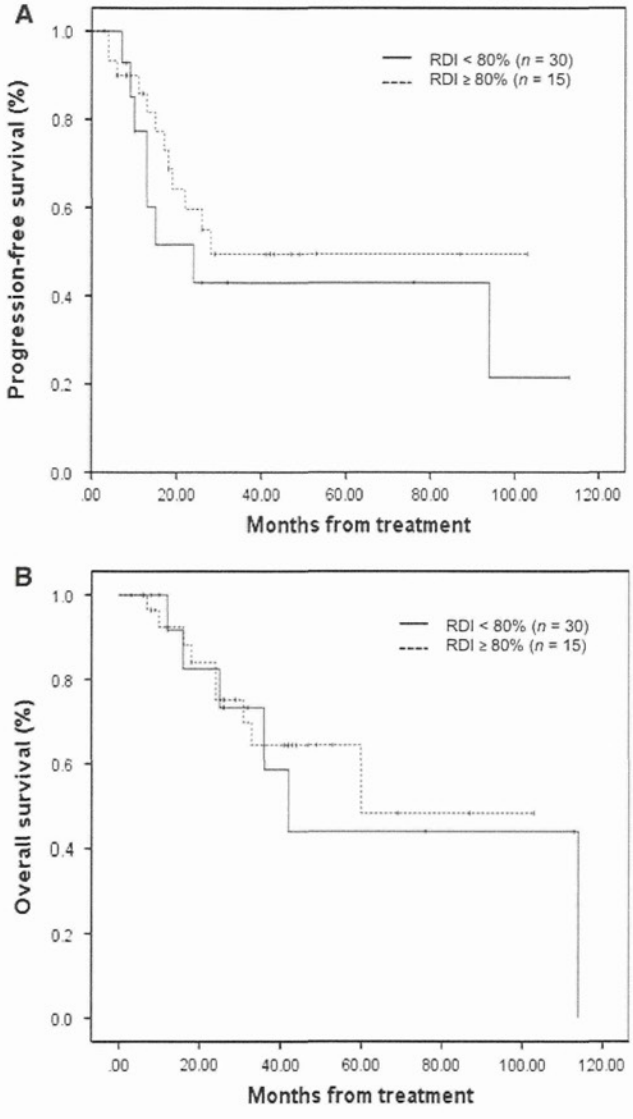

Fig. 2 **a** Kaplan–Meier curve of progression-free survival in patients with high relative dose intensity of vincristine (*dash line*) and low relative dose intensity of vincristine (*black line*). **b** Kaplan–Meier curve of overall survival in patients with high relative dose intensity of vincristine (*dash line*) and low relative dose intensity of vincristine (*black line*)

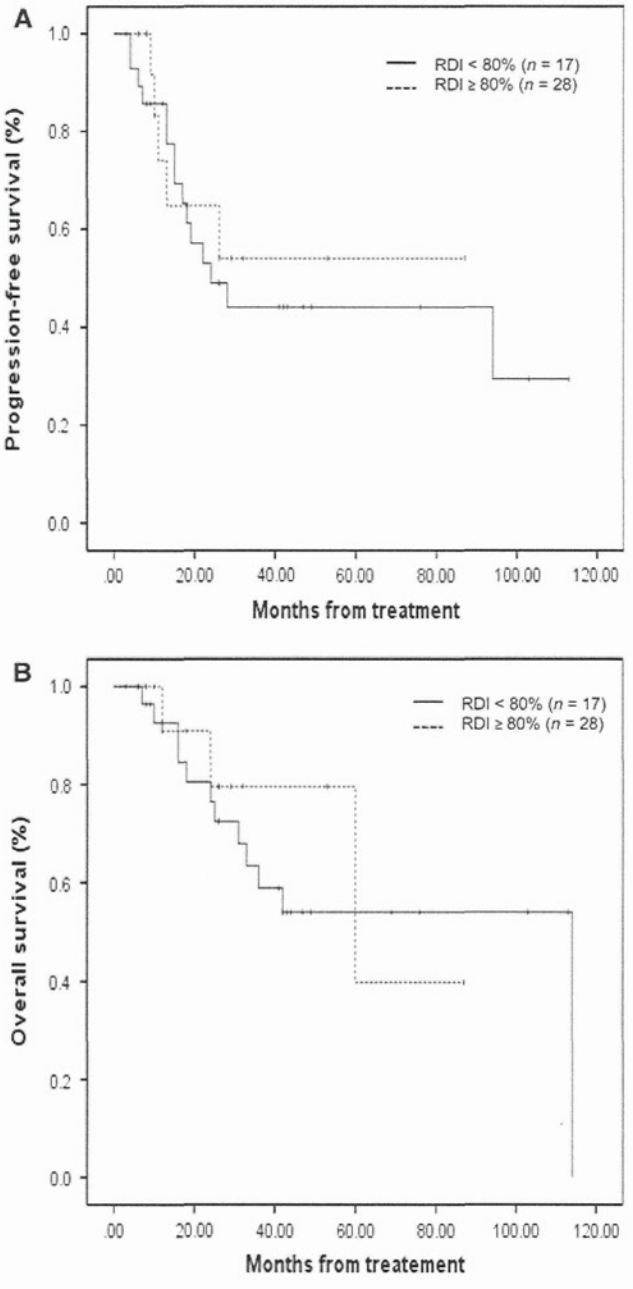

Fig. 3 **a** Kaplan–Meier curve of progression-free survival in patients with high relative dose intensity of cyclophosphamide (*dash line*) and low relative dose intensity of cyclophosphamide (*black line*). **b** Kaplan–Meier curve of overall survival in patients with high relative dose intensity of cyclophosphamide (*dash line*) and low relative dose intensity of cyclophosphamide (*black line*)

VAC chemotherapy, especially in maintenance phase. The reason for the low RDI was not apparent, but we demonstrated that VAC chemotherapy for adult rhabdomyosarcoma patient may not be feasible as VAC chemotherapy was developed mainly targeting pediatric patients. We also suggested that none of the differences regarding RDIs of both vincristine and cyclophosphamide on PFS and OS were detected. However, in our previous data focusing on childhood RMS and adult RMS survival suggested significant differences in survival in localized tumor [17]. Although we could not observe significant differences in survival in metastatic tumors for both childhood RMS and adult RMS, controversy remains as to the standard treatment for patients with adult rhabdomyosarcoma. Recently, several types of trials for these patients have demonstrated to show additional benefit of adding active new agents to standard VAC chemotherapy, which failed to show survival benefit [18–20].

In IRS-V study, the dosage of cyclophosphamide was designed 1.2 g/m^2/cycle. High-dose therapy with stem cell transplantation for high-risk metastatic RMS did not

Table 3 Adverse event in patients who received VAC regimen

	Adults			Children		
	Induction phase ($n = 27$)	Maintenance phase ($n = 25$)	Total phase	Induction phase ($n = 18$)	Maintenance phase ($n = 17$)	Total phase
Neutropenia Gr. 4	27 (100 %)	23 (92.0 %)	27 (100 %)	18 (100 %)	17 (100 %)	18 (100 %)
Anemia Gr. 3/4	24 (88.9 %)	21 (84.0 %)	27 (100 %)	16 (88.9 %)	14 (82.6 %)	16 (88.9 %)
Thrombocytopenia Gr. 4	12 (44.4 %)	14 (56.0 %)	19 (70.3 %)	13 (72.2 %)	10 (58.8 %)	13 (72.2 %)
FN Gr. 3/4	23 (85.2 %)	19 (76.0 %)	26 (96.3 %)	17 (94.4 %)	14 (82.6 %)	18 (100 %)
Peripheral neuropathy ≥Gr. 2	11 (40.7 %)	12 (48.0 %)	15 (55.6 %)	6 (33.3 %)	5 (29.4 %)	6 (33.3 %)

VAC vincristine, *d*-actinomycin, cyclophosphamide, *FN* febrile neutropenia, *Gr* grade

improve outcome significantly [21]. Accordingly, reduced dose of VAC chemotherapy for adults might not be inferior to standard VAC dose regarding survival.

This study has several limitations as of the nature of retrospective design and small sample size. More patients may be needed to detect the small differences regarding survival in low RDI patients and high RDI patients. Decision of administration of vincristine on day 8 and 15 may vary by physicians as evaluation of peripheral neuropathy by vincristine is not integrated. However, considering poor prognosis of adult RMS with highly toxic regimen of VAC, new strategy to treat this rare cohort must be developed urgently.

In summary, adult rhabdomyosarcoma is a rare malignancy with poor prognosis. The treatment strategy has been performed along with child rhabdomyosarcoma; however, the RDIs of vincristine and cyclophosphamide in the maintenance phase were significantly lower than that in children. Causes of low RDIs were generally myelosuppression, infection, and peripheral neurotoxicity in both groups. VAC chemotherapy for adults may not be feasible; thus, the prospective trial for adult rhabdomyosarcoma should be designed.

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Conflict of interest None declared.

References

1. Pappo AS, Shapiro DN, Crist WM (1997) Rhabdomyosarcoma. Biology and treatment. Pediatr Clin North Am 44(4): 953–972
2. Raney RB, Maurer HM, Anderson JR, Andrassy RJ, Donaldson SS, Qualman SJ, Wharam MD, Wiener ES, Crist WM (2001) The Intergroup Rhabdomyosarcoma Study Group (IRSG): major lessons from the IRS-I through IRS-IV studies as background for the current IRS-V treatment protocols. Sarcoma 5(1):9–15. doi: 10.1080/13577140120048890
3. Breitfeld PP, Meyer WH (2005) Rhabdomyosarcoma: new windows of opportunity. Oncologist 10(7):518–527. doi:10.1634/theoncologist.10-7-518
4. Maurer HM, Beltangady M, Gehan EA, Crist W, Hammond D, Hays DM, Heyn R, Lawrence W, Newton W, Ortega J et al (1988) The Intergroup Rhabdomyosarcoma Study-I. A final report. Cancer 61(2):209–220
5. Maurer HM, Gehan EA, Beltangady M, Crist W, Dickman PS, Donaldson SS, Fryer C, Hammond D, Hays DM, Herrmann J et al (1993) The Intergroup Rhabdomyosarcoma Study-II. Cancer 71(5):1904–1922
6. Crist W, Gehan EA, Ragab AH, Dickman PS, Donaldson SS, Fryer C, Hammond D, Hays DM, Herrmann J, Heyn R et al (1995) The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 13(3):610–630
7. Crist WM, Anderson JR, Meza JL, Fryer C, Raney RB, Ruymann FB, Breneman J, Qualman SJ, Wiener E, Wharam M, Lobe T, Webber B, Maurer HM, Donaldson SS (2001) Intergroup Rhabdomyosarcoma Study-IV: results for patients with nonmetastatic disease. J Clin Oncol 19(12):3091–3102
8. Arndt CA, Stoner JA, Hawkins DS, Rodeberg DA, Hayes-Jordan AA, Paidas CN, Parham DM, Teot LA, Wharam MD, Breneman JC, Donaldson SS, Anderson JR, Meyer WH (2009) Vincristine, actinomycin, and cyclophosphamide 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 27(31):5182–5188. doi:10.1200/JCO.2009.22.3768
9. Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A (2009) Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2,600 patients. J Clin Oncol 27(20):3391–3397. doi: 10.1200/JCO.2008.19.7483
10. Ferrari A, Dileo P, Casanova M, Bertulli R, Meazza C, Gandola L, Navarria P, Collini P, Gronchi A, Olmi P, Fossati-Bellani F, Casali PG (2003) Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. Cancer 98(3):571–580. doi:10.1002/cncr.11550
11. Little DJ, Ballo MT, Zagars GK, Pisters PW, Patel SR, El-Naggar AK, Garden AS, Benjamin RS (2002) Adult rhabdomyosarcoma: outcome following multimodality treatment. Cancer 95(2): 377–388. doi:10.1002/cncr.10669
12. Esnaola NF, Rubin BP, Baldini EH, Vasudevan N, Demetri GD, Fletcher CD, Singer S (2001) Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. Ann Surg 234(2):215–223
13. Hawkins WG, Hoos A, Antonescu CR, Urist MJ, Leung DH, Gold JS, Woodruff JM, Lewis JJ, Brennan MF (2001) Clinicopathologic analysis of patients with adult rhabdomyosarcoma.

Cancer 91(4):794–803. doi:10.1002/1097-0142(20010215)91:4<794:AID-CNCR1066>3.0.CO;2-Q
14. La Quaglia MP, Heller G, Ghavimi F, Casper ES, Vlamis V, Hajdu S, Brennan MF (1994) The effect of age at diagnosis on outcome in rhabdomyosarcoma. Cancer 73(1):109–117
15. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS (2002) 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34(6):730–751. doi:10.1086/339215
16. Lloyd RV, Hajdu SI, Knapper WH (1983) Embryonal rhabdomyosarcoma in adults. Cancer 51(3):557–565
17. Kojima Y, Hashimoto K, Ando M, Yonemori K, Hirakawa A, Kodaira M, Yunokawa M, Shimizu C, Tamura K, Katsumata N, Hosono A, Makimoto A, Fujiwara Y (2012) Clinical outcomes of adult and childhood rhabdomyosarcoma treated with vincristine, *d*-actinomycin, and cyclophosphamide chemotherapy. J Cancer Res Clin Oncol. doi:10.1007/s00432-012-1199-x
18. Klingebiel T, Boos J, Beske F, Hallmen E, Int-Veen C, Dantonello T, Treuner J, Gadner H, Marky I, Kazanowska B, Koscielniak E (2008) Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. Pediatr Blood Cancer 50(4):739–745. doi:10.1002/pbc.21494
19. Pappo AS, Lyden E, Breitfeld P, Donaldson SS, Wiener E, Parham D, Crews KR, Houghton P, Meyer WH (2007) Two consecutive phase II window trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: the Children's Oncology Group. J Clin Oncol 25(4):362–369. doi:10.1200/JCO.2006.07.1720
20. Lager JJ, Lyden ER, Anderson JR, Pappo AS, Meyer WH, Breitfeld PP (2006) Pooled analysis of phase II window studies in children with contemporary high-risk metastatic rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol 24(21):3415–3422. doi:10.1200/JCO.2005.01.9497
21. Bisogno G, Ferrari A, Prete A, Messina C, Basso E, Cecchetto G, Indolfi P, Scarzello G, D'Angelo P, De Sio L, Di Cataldo A, Carli M (2009) Sequential high-dose chemotherapy for children with metastatic rhabdomyosarcoma. Eur J Cancer 45(17):3035–3041. doi:10.1016/j.ejca.2009.08.019

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Jpn J Clin Oncol 2012;42(4)359

Image of the Month

A Case of Stage IV Neuroblastoma Treated with Aggressive Surgery Following Intensive Neoadjuvant Chemotherapy with Autologous Stem Cell Transplantation

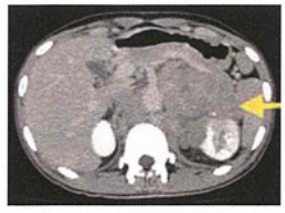

Figure 1.

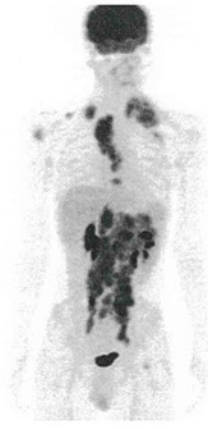

Figure 2.

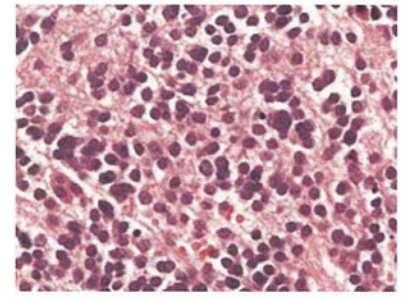

Figure 3.

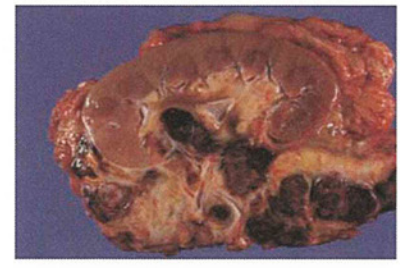

Figure 4.

A 16-year-old male complaining of recent body weight loss of 10 kg and supraclavicular lymph node swelling was referred to our hospital. Computed tomographic scan demonstrated a left retroperitoneal tumor (Fig. 1, arrow) and multiple enlarged lymph nodes along the aorta, mediastinum as well as in the supraclavicular area. The systemic spread of the disease was apparent on F^{18}-fluorodeoxyglucose-positron emission tomography including multiple bone metastases (Fig. 2). The urine level of vanillylmandelic acid and homovanillic acid and the serum level of neurospecific enolase were elevated to 107.8, 118.1 mg/g creatinine (Cr) and 140.9 ng/ml, respectively (reference range: 2.1–5.0, 2.2–5.8 mg/g Cr and $<$15 ng/ml, respectively). Histological analysis of the biopsied cervical lymph nodes confirmed the diagnosis of neuroblastoma, showing unfavorable histology (poorly differentiated) and no MYCN amplification (Fig. 3). According to the International Neuroblastoma Risk Group classification, the patient was categorized into the high-risk group due to the presence of metastatic disease and age $>$18 months. Because neoadjuvant chemotherapy with standard cisplatin-containing regimen was not effective, the patient underwent second-line ifosfamide-based chemotherapy followed by melphalan-containing high-dose chemotherapy with concomitant autologous peripheral blood stem cell transplantation. Then, he underwent surgical resection of abdominal tumor and lymph nodes (Fig. 4), followed by resection of mediastinal tumor and supraclavicular lymph nodes 50 days after the initial operation. Tumor beds and bone lesions were treated with post-operative radiation therapy. The patient is doing well without any signs of recurrence or treatment-related sequelae 8 months after completion of therapy.

Yuki Yamamoto and Atsushi Makimoto
Pediatric Oncology Division
National Cancer Center Hospital
Tokyo, Japan
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ORIGINAL PAPER

Clinical outcomes of adult and childhood rhabdomyosarcoma treated with vincristine, *d*-actinomycin, and cyclophosphamide chemotherapy

Yuki Kojima · Kenji Hashimoto · Masashi Ando · Kan Yonemori · Akihiro Hirakawa · Makoto Kodaira · Mayu Yunokawa · Chikako Shimizu · Kenji Tamura · Noriyuki Katsumata · Ako Hosono · Atsushi Makimoto · Yasuhiro Fujiwara

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Abstract
Background Outcomes in adult patients with rhabdomyosarcoma are poor, with a 5-year survival rate of approximately 30 %. The current study aimed to compare the clinical outcomes of adult and childhood rhabdomyosarcoma patients with local and metastatic disease and to examine the impact and timing of local therapy on metastasis.
Methods Clinicopathological features and patient outcomes were reviewed retrospectively for rhabdomyosarcoma patients receiving chemotherapy between 1981 and 2010 at our institution. Adults were defined as those aged 21 years or older.
Results Of the 98 patients identified, 36 were adults (median age, 29; range, 21–72) and 62 were children (median age, 11; range, 0.6–20). Median progression-free survival of localized and metastatic disease for children and adults was as follows: localized disease, 166.9 versus 22.4 months ($p = 0.005$), and metastatic disease, 13.3 versus 13.3 months ($p = 0.949$), respectively. Multivariate regression analysis revealed that older age (≥21 vs. <21) was a significant poor prognostic factor in localized disease. Conversely, age was not related to survival in metastatic disease. Receiving radiotherapy to the primary site was an independent factor indicating a better prognosis. An analysis of the optimal timing of local therapy was performed for 53 patients; however, its significance on survival could not be determined.
Conclusions Age was a negative prognostic factor in rhabdomyosarcoma patients with localized disease, but it did not affect the survival in metastatic disease. For metastatic disease, although local therapies may be effective for survival, the timing of such therapies should be determined individually.

Keywords Adult · Child · Rhabdomyosarcoma · Clinical outcome

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Y. Kojima · K. Hashimoto (✉) · M. Ando · K. Yonemori · M. Kodaira · M. Yunokawa · C. Shimizu · K. Tamura · N. Katsumata · Y. Fujiwara
Department of Medical Oncology and Breast Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: gonmusao@k6.dion.ne.jp

Y. Kojima
Department of Hematology and Medical Oncology, Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 460-0001, Japan

A. Hirakawa
Department of Management Science, Graduate School of Engineering, Tokyo University of Science, 3-3-2 Kasumigaseki Chiyoda-ku, Tokyo 100-0013, Japan

A. Hosono · A. Makimoto
Department of Pediatric Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, but it is far less common in adults (Ferrari et al. 2003). Improvements in multimodal treatment of RMS have improved survival in children from 25 to approximately 70 % over the past 40 years (Pappo et al. 1997; Raney et al. 2001; Breitfeld and Meyer 2005; Leaphart and Rodeberg 2007). In contrast, the prognosis for adult RMS remains poor, with a 5-year survival rate of approximately 30 % (Sultan et al. 2009; Ferrari et al. 2003;

La Quaglia et al. 1994; Little et al. 2002; Esnaola et al. 2001; Hawkins et al. 2001).

Metastatic RMS affects approximately 15 % of all children with RMS (Breneman et al. 2003). According to the risk categories identified by the Intergroup Rhabdomyosarcoma Study (IRS), low- and intermediate-risk patients have improved outcomes, with 96–97 % of low-risk patients achieving 5-year survival (Meza et al. 2006) and 79 % of intermediate-risk patients attaining 4-year survival (Arndt et al. 2009). However, survival for high-risk patients remains poor, with 34 % achieving 3-year survival (Oberlin et al. 2008) and 24 % achieving 5-year survival (Carli et al. 2004). Consequently, standard treatment for high-risk patients remains controversial (Klingebiel et al. 2008; Pappo et al. 2007; Lager et al. 2006).

The treatment strategy for RMS requires multidisciplinary therapy, including chemotherapy, surgery, and radiation therapy. Vincristine and *d*-actinomycin, with or without cyclophosphamide (VAC) regimens, are considered the standard option for RMS (Maurer et al. 1988, 1993; Crist et al. 1995, 2001; Meza et al. 2006; Arndt et al. 2009), with wide surgical resection of tumor and postoperative radiation therapy required for local control of localized RMS (La et al. 2011; Rodeberg et al. 2011; Schuck et al. 2004). The timing of radiation therapy is critical: for localized RMS, radiation is appropriate to start during weeks 9–12, and for parameningeal RMS with intracranial extension, local radiation treatment should begin during the first 1–2 weeks of chemotherapy (Michalski et al. 2004; Raney et al. 2002). However, the impact and optimal timing of local therapy for metastatic disease is unknown. Therefore, the purpose of the current study was to compare the clinical outcomes of local or metastatic adult and childhood RMS and to examine the impact and timing of local therapies on metastatic disease.

Patients and methods

Patients

All patients included in this analysis met the following criteria: histologically diagnosed with RMS, treated at the National Cancer Center Hospital in Tokyo between 1981 and 2010, and received VAC or VAC-like chemotherapy. Medical records were then retrospectively reviewed to obtain the following information: date of birth, gender, date of diagnosis, primary tumor site, histopathology, initial tumor size, presence of central nervous system (CNS) invasion, clinical stage, group category as defined by the IRS (Breitfeld and Meyer 2005), date of treatment initiation, chemotherapy regimen, best response, chemotherapy administration schedule, date of radiotherapy, date of surgery, date of progression, date of last follow-up, and survival status.

Treatment

The VAC regimen after the year of 2000 consisted of vincristine at a dose of 1.5 mg/m^2 (up to 2 mg/body), given intravenously on days 1, 8, and 15; cyclophosphamide at a dose of 2.2 g/m^2, given intravenously on day 1; and *d*-actinomycin at a dose of 1.5 mg/m^2 (up to 2.5 mg/body), given intravenously on day 1. The treatment course was repeated according to IRS-IV or Children's Oncology Group (COG) Study (D9803) protocols (Arndt et al. 2009). Before the year of 2000, the VAC-like regimen includes the following regimens: vincristine, *d*-actinomycin, and either ifosfamide, etoposide, or doxorubicin. The treatment course was administered according to IRS-II or III protocols.

Local therapy includes surgery, radiation therapy, or both. Surgical resection defined in this manuscript includes only total gross resection. Microscopic complete resection (Group I) was confirmed microscopically later on. Radiation therapy was delivered to each primary tumor site and regional lymph nodes where applicable. The total dose ranged from 30 to 56.3 Gy, with a median dose of 45 Gy.

Definitions of terms

We defined adults as patients aged 21 years or more, and considered the remaining patients to be children. The induction phase was defined as the first six cycles of the VAC/VAC-like regimen, and the maintenance phase was defined as the later cycles following the induction phase. Response to chemotherapy was compared with baseline status. A complete response (CR) was defined as the disappearance of tumors with no evidence of disease. A partial response (PR) was a 50 % or greater decrease in the sum of tumor diameters. Stable disease (SD) was a less than 50 % decrease in the sum of tumor diameters. Progressive disease (PD) was defined as a 25 % or greater increase in the sum of tumor diameters and/or the appearance of new lesions.

Surgery or radiation therapy in this study means resection or radiation therapy to the primary site during primary treatment, respectively. Resection or radiation therapy to a relapsed site or metastatic site is not included in this category; likewise, biopsy only is not included in this definition.

Statistical analyses

Progression-free survival (PFS) was defined as the time from the date of initial chemotherapy to the date when

local recurrences or distant metastases were recognized. Overall survival (OS) was defined as the time from the date of initial chemotherapy to the date of death due to any cause. Patients who survived were treated as censored observations on the last day of follow-up. PFS and OS were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Multivariate Cox regression analysis was used to estimate the hazard ratios and 95 % confidence intervals (CI). A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS (version 9.1.3; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

We identified 98 patients who met the eligibility criteria. The distributions of clinical and pathologic characteristics of patients are listed in Tables 1 and 2. There were 36 adults (age: median, 29; range 21–72) and 62 children (age: median, 11; range, 0.6–20). Seventy-three patients had localized disease (22 adults and 51 children) , while 25 patients had metastatic disease (14 adults and 11 children). The most common histology was embryonal in localized disease (56.2 %) and alveolar in metastatic disease (68.0 %). Botryoid was found in only one patient. Common primary sites in localized disease were parameningeal (38.4 %), head and neck (21.9 %), and extremity (15.1 %), while common primary sites in metastatic disease sites were parameningeal (32.0 %), extremity (28.0 %), and other (24.0 %) (Table 3). The most common metastatic

Table 1 Characteristics of patients with localized rhabdomyosarcoma ($n = 73$)

	Adults ($n = 22$)		Children ($n = 51$)	
	No.	%	No.	%
Gender				
Female	5	22.7	24	47.1
Male	17	77.3	27	52.9
Tumor size				
<5 cm	9	40.9	23	45.1
≥5 cm	13	59.1	28	51.9
Site				
Favorable	5	22.7	22	43.1
Unfavorable	17	77.3	29	56.9
Histology				
Alveolar	9	40.9	18	35.3
Embryonal	12	54.5	29	56.9
Other	1	4.5	4	7.8
Group				
1	3	13.6	9	17.6
2	3	13.6	5	9.8
3	16	72.7	37	72.5
Stage				
1	4	18.2	21	41.2
2	5	22.7	8	15.7
3	13	59.1	22	43.1
CNS invasion				
No	20	90.9	46	90.2
Yes	2	9.1	5	9.8

CNS central nervous system

Table 2 Characteristics of patients with metastatic rhabdomyosarcoma ($n = 25$)

	Adults ($n = 14$)		Children ($n = 11$)	
	No.	%	No.	%
Gender				
Female	6	42.9	6	54.5
Male	8	57.1	5	45.5
Tumor size				
<5 cm	2	14.3	4	36.4
≥5 cm	12	85.7	7	63.6
Site				
Favorable	1	7.1	1	9.1
Unfavorable	13	92.9	10	90.9
Histology				
Alveolar	11	78.6	6	54.5
Embryonal	2	14.3	5	45.5
Other	1	7.1	0	0
CNS invasion				
No	14	100	10	90.9
Yes	0	0	1	9.1

CNS central nervous system

Table 3 Primary site of rhabdomyosarcoma in localized and metastatic disease

	Localized disease No. (%)	Metastatic disease No. (%)
Extremity	11 (15.1)	7 (28.0)
Parameningeal site	28 (38.4)	8 (32.0)
Head and neck	16 (21.9)	1 (4.0)
Genitourinary primary site (non-bladder/prostate)	6 (8.2)	0 (0.0)
Orbit	5 (6.9)	1 (4.0)
Genitourinary primary site (bladder/prostate)	2 (2.7)	2 (8.0)
Unfavorable other	5 (6.9)	6 (24.0)

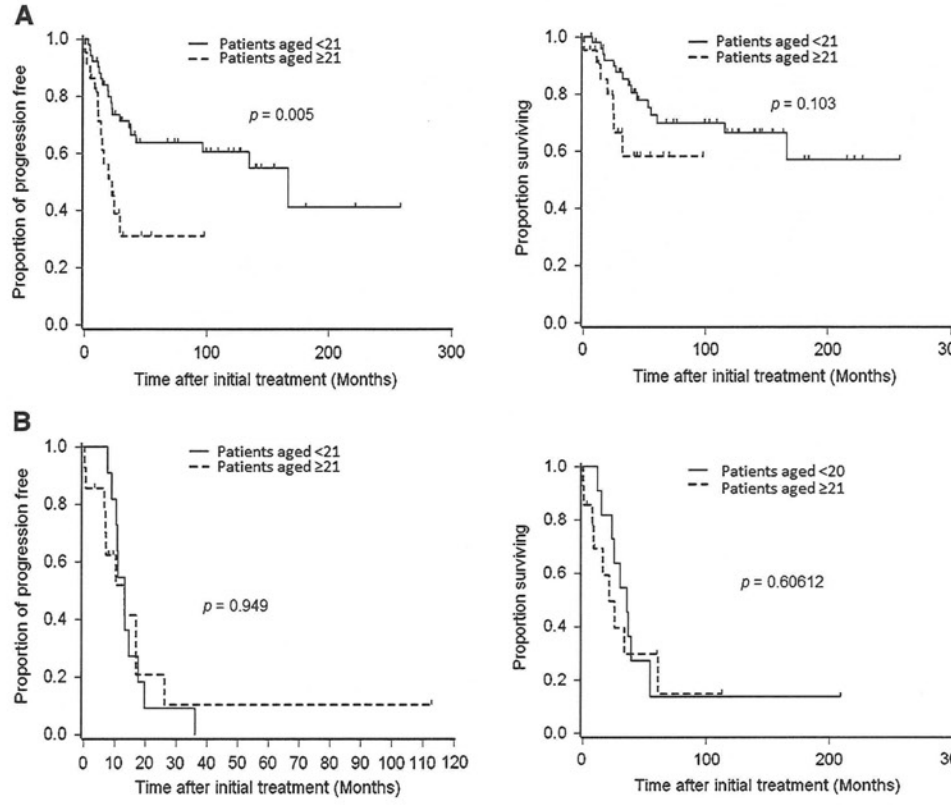

Fig. 1 **a** Kaplan–Meier curve of progression-free survival and overall survival in patients with localized disease of adults (*dashed line*) and children (*solid line*). **b** Kaplan–Meier curve of progression-free survival and overall survival in patients with metastatic disease of adults (*dashed line*) and children (*solid line*)

sites were bone ($n = 17$), bone marrow ($n = 7$), and lung ($n = 6$). Eleven patients had metastases to multiple sites.

Thirty-one patients (31.6 %) underwent surgical resection at RMS diagnosis. Ten patients were classified as IRSG Group I, 7 as Group II, and 14 as Groups III/IV. Surgery (primary tumor resection at diagnosis or second-look surgery) was performed in 43 patients (58.9 %) with localized disease and in 5 patients (20.0 %) with metastatic disease. We identified 59 patients (60.2 %) who had received VAC regimens and 39 patients (39.8 %) who had received VAC-like regimens. Radiation therapy was performed in 52 patients (71.2 %) with localized disease and in 18 patients (72.0 %) with metastatic disease during the course of treatment.

Patient outcomes in adults and children

The best responses to chemotherapy were as follows: among those with localized disease, 65 patients (89.0 %) achieved CR/PR, 5 patients (6.9 %) achieved SD/PD, and the data are not available for 3 patients (4.1 %); among patients with metastatic disease, 22 patients (88.0 %) achieved CR/PR and 3 patients (12.0 %) achieved SD/PD ($p = 1.000$). The overall median follow-up period was 37 months (range, 0–263 months); 37 months in metastatic disease (range, 0–213 months); and 43 months in localized disease (range, 0–263 months). At the time of analysis, 50 patients (51.0 %) experienced recurrence, and 41 of these patients (41.8 %) later died. Sites of first recurrence/progression were locoregional in 26 patients and distant metastases in 24 patients. Seven patients in whom the sites of first recurrence/progression were locoregional achieved CR and were still alive following second-line treatment.

Adult patients with localized disease had a significantly greater probability of poor outcome compared with children. The median PFS times for localized and metastatic disease for children and adults were as follows: localized disease, 166.9 versus 22.4 months ($p = 0.005$) (Fig. 1a), and metastatic disease, 13.3 versus 13.3 months ($p = 0.949$) (Fig. 1b), respectively. Median OS times were not statistically different in patients with metastatic disease for both adults and children.

Analyses of prognostic factors in localized and metastatic disease

To determine the independent predictors of survival, we used a multivariate Cox regression model. The results of multivariate analysis for PFS and OS in localized and metastatic disease are shown in Tables 4 and 5. According to Table 4, age (<21 vs. ≥21) was the only statistically significant negative predictor of PFS for patients with localized disease ($p = 0.018$). In contrast, for metastatic disease, age was not significantly different with respect to

Table 4 Multivariate analyses of PFS and OS in localized rhabdomyosarcoma ($n = 73$)

	No. of patients	PFS			OS		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value
Age							
<21	51						
≥21	22	2.60	1.18–5.70	0.018	1.67	0.62–4.52	0.311
Stage							
1	25						
2	13	2.73	0.90–8.29	0.076	7.36	1.38–39.2	0.019
3	35	2.42	0.94–6.24	0.069	5.66	1.19–26.9	0.029
Radiotherapy							
No	21						
Yes	52	0.69	0.29–1.63	0.394	0.95	0.32–2.85	0.924
Surgery							
No	30						
Yes	43	0.60	0.29–1.24	0.167	0.63	0.26–1.54	0.312
Presence of CNS invasion							
No	66						
Yes	7	1.68	0.52–5.36	0.384	1.75	0.52–5.84	0.363

CNS central nervous system, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

Table 5 Multivariate analyses of PFS and OS in metastatic rhabdomyosarcoma ($n = 25$)

	No. of patients	PFS			OS		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value
Age							
<21	11	1.00			1.00		
≥21	14	0.97	0.37–2.55	0.947	1.03	0.35–3.06	0.960
Radiotherapy							
No	7						
Yes	18	0.14	0.04–0.51	<0.001	0.24	0.07–0.82	0.023
Surgery							
No	20						
Yes	5	1.15	1.15–3.95	0.394	0.30	0.06–1.47	0.137
Presence of CNS invasion							
No	24						
Yes	1	1.85	0.20–16.8	0.585	0.99	0.12–8.45	0.995

CNS central nervous system, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

PFS and OS. Radiotherapy was the only significant factor in improved PFS or OS in metastatic disease.

Local therapy for metastatic disease

Of 25 patients with metastatic disease, 21 patients (84.0 %) received local therapy as part of their primary treatment that included radiotherapy ($n = 16$), surgery and radiotherapy ($n = 3$), and surgery ($n = 2$). Sixteen of these 21 patients (76.2 %) experienced relapse at the following sites: distant metastatic site ($n = 11$) and primary site progression ($n = 5$). Among four patients with metastatic disease who did not receive local therapy, three patients relapsed: two experienced local relapse and one relapsed at a distant metastatic site. In the 25 patients with metastatic disease, median PFS times in patients with or without local therapy (surgery and/or radiotherapy) were 13.4 versus 7.0 months ($p < 0.001$) (Fig. 2a), respectively, and median OS times were 36.1 versus 7.6 months ($p < 0.001$), respectively (Fig. 2b).

Timing of local therapy

We further sought information about the optimal timing of local therapy in 53 patients who received local therapy (both radiotherapy and surgery) during their course of treatment (localized disease, $n = 38$; metastatic disease, $n = 15$). PFS and OS were not significantly different

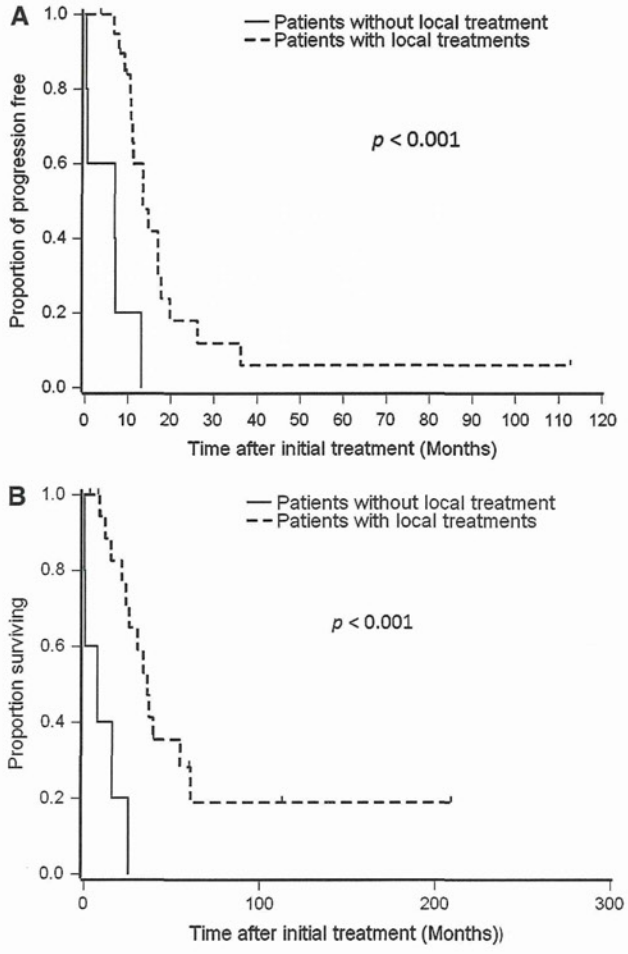

Fig. 2 Kaplan–Meier curve of progression-free survival (**a**) and overall survival (**b**) in patients with metastatic disease with local therapy (*dashed line*) and without local therapy (*solid line*)

between patients who received local therapy within or after 18 weeks of starting initial treatment (see Table 6 for our multivariance analysis of OS). In the 38 patients with localized disease, median PFS was 134.7 months in patients who received radiotherapy in the induction phase and 101.6 months in patients who received it during the maintenance phase ($p = 0.921$); median OS was similar for patients during both phases ($p = 0.277$). Median PFS and OS times were also similar in patients who received surgery either in the induction phase or in the maintenance phase ($p = 0.304$ for PFS and $p = 0.502$ for OS).

In the 15 patients with metastatic disease, the median PFS in patients who received radiotherapy was similar for both phases (induction, 18.4 months; maintenance, 13.3 months, $p = 0.177$); however, median OS was significantly longer for the patients receiving radiotherapy in the induction phase than for those receiving radiotherapy in the maintenance phase (60.7 and 25.7 months, respectively, $p = 0.048$). Median PFS and OS were similar in patients who received surgery in either the induction or maintenance phase ($p = 0.304$ for PFS and $p = 0.214$ for OS).

Discussion

In this study, we evaluated the clinical outcomes of adults and children with RMS who received VAC/VAC-like chemotherapy as their initial treatment. This study resulted in two main findings. First, we showed that age was an independent negative prognostic factor for PFS in RMS with localized disease, but it was not associated with survival in metastatic disease. Second, local therapy to the

Table 6 Multivariate analysis of OS to determine the significance of timing for local therapy in localized and metastatic rhabdomyosarcoma

	Localized disease ($n = 38$)			Metastatic disease ($n = 15$)		
	HR	95 % CI	p value	HR	95 % CI	p value
Age						
<21	1			1		
≥21	1.04	0.24–4.49	0.961	0.63	0.11–3.66	0.610
Stage						
1	1			–	–	–
2	30.74	0.68–1,390.3	0.078	–	–	–
3	12.98	0.50–339.5	0.124	–	–	–
Timing of radiotherapy						
≥18 weeks	1			1		
<18 weeks	0.89	0.23–3.36	0.857	0.30	0.04–2.31	0.246
Timing of surgery						
≥18 weeks	1			1		
<18 weeks	0.45	0.04–3.31	0.429	3.11	0.07–138.2	0.558
Presence of CNS invasion						
No	1			1		
Yes	1.45	0.38–5.56	0.587	2.81	0.18–45.0	0.465

CNS central nervous system, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

primary tumor site during the treatment course may be necessary for metastatic RMS, as the patients who received local therapies showed significantly longer survival than those who did not. Although our findings suggest that patients with metastatic RMS should be treated at an early stage with local radiotherapy to improve OS, this aspect of our results requires more research; thus, the timing of local therapy should be individually determined depending on patient conditions.

Several studies have reported that age is associated with poor survival in patients with RMS. Sultan et al. reported on the prognosis of pediatric (age $\leqq$ 19 years) and adult (age > 19 years) RMS patients, and their findings suggested that the 5-year survival rate was significantly poorer in adults compared to that in children (5-year OS, 27 and 61 %, respectively; $p < 0.0001$) (Sultan et al. 2009). Another study clarified that the outcomes of patients with intermediate-risk RMS varied depending on age (Meza et al. 2006). Oberlin et al. (2008) also reported on the prognosis of metastatic RMS, and their data suggested that the 3-year event-free survival rate was significantly poorer in RMS patients <1 year and >9 years of age compared to that in RMS patients aged 1–9 years ($p < 0.001$). In our study, age was a negative prognostic factor of PFS in RMS with localized disease, but outcomes for metastatic disease were not different between adults and children. Previous studies have mostly focused on age in children, but our study reported different prognoses for adults and children in both localized and metastatic disease. Therefore, our results would be expected to be different than those of Oberlin et al. (2008). The poor prognosis in adult metastatic RMS may depend on the tumor biology and drug delivery.

Histopathological classification of adult RMS is somewhat difficult to categorize conventional subtypes. Although our data include alveolar subtype most, pleomorphic and spindle subtypes in part may be included in the heterogeneous tumor and these subtypes are suggested poor prognosis (Mentzel, 2000 #3204). For the drug delivery, unpublished data in our institute suggest that the dose intensity of vincristine and cyclosporine is lower in adult when compared to children as hematological toxicities and neurotoxicity are severe. These data suggest that categorizing adult RMS and its treatment may be necessary to be developed independently to that of child RMS.

Radiation therapy and surgery are important for local tumor control and survival in the treatment of RMS. However, the optimal timing of radiation therapy is unclear. IRSG and COG protocols incorporate radiation therapy scheduled at weeks 9 or 12 after the induction of initial chemotherapy (Crist et al. 2001; Arndt et al. 2009). Minn et al. (2010) analyzed the risk of early treatment failure in intermediate-risk RMS, and the majority of patients with early progression experienced local failure. Earlier radiation therapy may improve outcomes by the prevention of early local progression, and the current COG study (ARST0531, http://www.clinicaltrials.gov) plans to perform radiation therapy at week 4 for intermediate-risk RMS. Although there has been no randomized trial to compare the timing of local therapy in RMS, early initiation of local treatment would seem to be preferable. In our study, local therapy was effective in improving survival even in metastatic disease. We could find the efficacy of radiotherapy in metastatic patients but not for surgery probably because of the shortage of patients number included. However, except for local radiotherapy in patients with metastatic disease, the timing of local therapy had no significantly different effect on outcomes in patients who received local therapy during the induction phase versus the maintenance phase. The threshold we used for dichotomization (within 18 weeks or later than 18 weeks after initial treatment onset) may have been a factor in our inability to detect a significant difference in outcomes. This result implies that the timing of local therapy for metastatic disease, whether radiotherapy or surgery, may be varied depending on the individual patient's characteristics, that is, the radiotherapeutic field or the operability of the patient's local site.

Several limitations to our study should be mentioned. Our analysis was limited by its retrospective design and small sample size. Patients receiving VAC-like chemotherapy had undergone chemotherapy during the period prior to 2000, and the dose intensity of chemotherapy varied by protocol. The dose of irradiation and radiation methods also varied. Further, the patients who received local therapy might have been in better general condition or had a smaller primary tumor, which could be included in one radiation field, compared with those who did not. To reduce these biases, we compared the baseline characteristics of each group and demonstrated their similarity. However, adult RMS is a rare cancer; thus, our results should contribute to further advances in this field of oncology.

In conclusion, we showed that age was a negative prognostic factor for PFS and OS in RMS patients with localized disease, but age was not associated with survival in metastatic disease. For metastatic disease, local therapy may have a beneficial effect on survival, but the optimal timing of local therapy is unclear and should be determined individually. Future clinical trials for metastatic RMS should focus on the timing of local therapy, and evaluation of treatment strategies limited to adult RMS patients is warranted.

Conflict of interest None.

References

Arndt CA, Stoner JA, Hawkins DS, Rodeberg DA, Hayes-Jordan AA, Paidas CN, Parham DM, Teot LA, Wharam MD, Breneman JC, Donaldson SS, Anderson JR, Meyer WH (2009) Vincristine, actinomycin, and cyclophosphamide 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 27(31):5182–5188. doi:10.1200/JCO.2009.22.3768

Breitfeld PP, Meyer WH (2005) Rhabdomyosarcoma: new windows of opportunity. Oncologist 10(7):518–527. doi:10.1634/theoncologist.10-7-518

Breneman JC, Lyden E, Pappo AS, Link MP, Anderson JR, Parham DM, Qualman SJ, Wharam MD, Donaldson SS, Maurer HM, Meyer WH, Baker KS, Paidas CN, Crist WM (2003) Prognostic factors and clinical outcomes in children and adolescents with metastatic rhabdomyosarcoma–a report from the intergroup rhabdomyosarcoma study IV. J Clin Oncol 21(1):78–84

Carli M, Colombatti R, Oberlin O, Bisogno G, Treuner J, Koscielniak E, Tridello G, Garaventa A, Pinkerton R, Stevens M (2004) European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors. J Clin Oncol 22(23):4787–4794. doi:10.1200/JCO.2004.04.083

Crist W, Gehan EA, Ragab AH, Dickman PS, Donaldson SS, Fryer C, Hammond D, Hays DM, Herrmann J, Heyn R et al (1995) The third intergroup rhabdomyosarcoma study. J Clin Oncol 13(3):610–630

Crist WM, Anderson JR, Meza JL, Fryer C, Raney RB, Ruymann FB, Breneman J, Qualman SJ, Wiener E, Wharam M, Lobe T, Webber B, Maurer HM, Donaldson SS (2001) Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 19(12):3091–3102

Esnaola NF, Rubin BP, Baldini EH, Vasudevan N, Demetri GD, Fletcher CD, Singer S (2001) Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. Ann Surg 234(2):215–223

Ferrari A, Dileo P, Casanova M, Bertulli R, Meazza C, Gandola L, Navarria P, Collini P, Gronchi A, Olmi P, Fossati-Bellani F, Casali PG (2003) Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. Cancer 98(3):571–580. doi:10.1002/cncr.11550

Hawkins WG, Hoos A, Antonescu CR, Urist MJ, Leung DH, Gold JS, Woodruff JM, Lewis JJ, Brennan MF (2001) Clinicopathologic analysis of patients with adult rhabdomyosarcoma. Cancer 91(4):794–803. doi:10.1002/1097-0142(20010215)91:4<794:AID-CNCR1066>3.0.CO;2-Q

Klingebiel T, Boos J, Beske F, Hallmen E, Int-Veen C, Dantonello T, Treuner J, Gadner H, Marky I, Kazanowska B, Koscielniak E (2008) Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. Pediatr Blood Cancer 50(4):739–745. doi:10.1002/pbc.21494

La Quaglia MP, Heller G, Ghavimi F, Casper ES, Vlamis V, Hajdu S, Brennan MF (1994) The effect of age at diagnosis on outcome in rhabdomyosarcoma. Cancer 73(1):109–117

La TH, Wolden SL, Su Z, Linardic C, Randall RL, Hawkins DS, Donaldson SS (2011) Local therapy for rhabdomyosarcoma of the hands and feet: is amputation necessary? A report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys 80(1):206–212. doi:10.1016/j.ijrobp.2010.01.053

Lager JJ, Lyden ER, Anderson JR, Pappo AS, Meyer WH, Breitfeld PP (2006) Pooled analysis of phase II window studies in children with contemporary high-risk metastatic rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol 24(21):3415–3422. doi:10.1200/JCO.2005.01.9497

Leaphart C, Rodeberg D (2007) Pediatric surgical oncology: management of rhabdomyosarcoma. Surg Oncol 16(3):173–185. doi:10.1016/j.suronc.2007.07.003

Little DJ, Ballo MT, Zagars GK, Pisters PW, Patel SR, El-Naggar AK, Garden AS, Benjamin RS (2002) Adult rhabdomyosarcoma: outcome following multimodality treatment. Cancer 95(2):377–388. doi:10.1002/cncr.10669

Maurer HM, Beltangady M, Gehan EA, Crist W, Hammond D, Hays DM, Heyn R, Lawrence W, Newton W, Ortega J et al (1988) The intergroup rhabdomyosarcoma study-I. A final report. Cancer 61(2):209–220

Maurer HM, Gehan EA, Beltangady M, Crist W, Dickman PS, Donaldson SS, Fryer C, Hammond D, Hays DM, Herrmann J et al (1993) The Intergroup Rhabdomyosarcoma Study-II. Cancer 71(5):1904–1922

Meza JL, Anderson J, Pappo AS, Meyer WH (2006) Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: the Children's Oncology Group. J Clin Oncol 24(24):3844–3851. doi:10.1200/JCO.2005.05.3801

Michalski JM, Meza J, Breneman JC, Wolden SL, Laurie F, Jodoin M, Raney B, Wharam MD, Donaldson SS (2004) Influence of radiation therapy parameters on outcome in children treated with radiation therapy for localized parameningeal rhabdomyosarcoma in Intergroup Rhabdomyosarcoma Study Group trials II through IV. Int J Radiat Oncol Biol Phys 59(4):1027–1038. doi:10.1016/j.ijrobp.2004.02.064

Minn AY, Lyden ER, Anderson JR, Million L, Arndt CA, Brown K, Hawkins DS, Donaldson SS (2010) Early treatment failure in intermediate-risk rhabdomyosarcoma: results from IRS-IV and D9803–a report from the Children's Oncology Group. J Clin Oncol 28(27):4228–4232. doi:10.1200/JCO.2010.29.0247

Oberlin O, Rey A, Lyden E, Bisogno G, Stevens MC, Meyer WH, Carli M, Anderson JR (2008) Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. J Clin Oncol 26(14):2384–2389. doi:10.1200/JCO.2007.14.7207

Pappo AS, Shapiro DN, Crist WM (1997) Rhabdomyosarcoma. Biology and treatment. Pediatr Clin North Am 44(4):953–972

Pappo AS, Lyden E, Breitfeld P, Donaldson SS, Wiener E, Parham D, Crews KR, Houghton P, Meyer WH (2007) Two consecutive phase II window trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: the Children's Oncology Group. J Clin Oncol 25(4):362–369. doi:10.1200/JCO.2006.07.1720

Raney RB, Maurer HM, Anderson JR, Andrassy RJ, Donaldson SS, Qualman SJ, Wharam MD, Wiener ES, Crist WM (2001) The Intergroup Rhabdomyosarcoma Study Group (IRSG): major lessons from the IRS-I through IRS-iv studies as background for the current IRS-V treatment protocols. Sarcoma 5(1):9–15. doi:10.1080/13577140120048890

Raney RB, Meza J, Anderson JR, Fryer CJ, Donaldson SS, Breneman JC, Fitzgerald TJ, Gehan EA, Michalski JM, Ortega JA, Qualman SJ, Sandler E, Wharam MD, Wiener ES, Maurer HM, Crist WM (2002) Treatment of children and adolescents with localized parameningeal sarcoma: experience of the Intergroup Rhabdomyosarcoma Study Group protocols IRS-II

through -IV, 1978–1997. Med Pediatr Oncol 38(1):22–32. doi: 10.1002/mpo.1259

Rodeberg DA, Anderson JR, Arndt CA, Ferrer FA, Raney RB, Jenney ME, Brecht IB, Koscielniak E, Carli M, Bisogno G, Oberlin O, Rey A, Ullrich F, Stevens MC, Meyer WH (2011) Comparison of outcomes based on treatment algorithms for rhabdomyosarcoma of the bladder/prostate: combined results from the Children's Oncology Group, German Cooperative Soft Tissue Sarcoma Study, Italian Cooperative Group, and International Society of Pediatric Oncology Malignant Mesenchymal Tumors Committee. Int J Cancer 128(5):1232–1239. doi:10.1002/ijc.25444

Schuck A, Mattke AC, Schmidt B, Kunz DS, Harms D, Knietig R, Treuner J, Koscielniak E (2004) Group II rhabdomyosarcoma and rhabdomyosarcoma like tumors: is radiotherapy necessary? J Clin Oncol 22(1):143–149. doi:10.1200/JCO.2004.04.180

Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A (2009) Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2,600 patients. J Clin Oncol 27(20): 3391–3397. doi:10.1200/JCO.2008.19.7483