RESEARCH ARTICLE

Replacing Actinomycin-D with Carboplatin for Newly Diagnosed Rhabdomyosarcoma

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Abstract

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in the pediatric age group. All patients with RMS regardless of their initial stage or group receive combination chemotherapy as 'standard therapy' consisting of vincristine, actinomycin-D and cyclophosphamide. Actinomycin-D was not readily available in Turkey at one time. Carboplatin was used instead in order to prevent delays in treatment. The aim of this report is to present the results of patients with rhabdomyosarcoma receiving carboplatin or actinomycin-D therapy. Materials and Methods: Twenty four patients with rhabdomyosarcoma treated between December 2000 and June 2011 were included in this retrospective study. The patients were treated according to International Rhabdomyosarcoma Study Group guidelines. Eleven patients were treated with actinomycin-D and 13 with carboplatin (250 mg/m²/dose for 2 days). The two groups were then compared in terms of 2- and 5-year overall survival (OS) and hematological and non-hematological toxicities. Results: Age, sex, stage and the mean duration of follow-up were similar in both groups (p>0.05). Two- and five-year OS levels were 68.2% in the carboplatin group and 78.0% and 40.0%, respectively, in the actinomycin-D group. There was no statistical difference in the number of febrile episodes (p=0.86) and no other hematological and non-hematological adverse effects were recorded in both groups. Conclusions: The findings show that carboplatin can be used as an alternative drug in the primary treatment of rhabdomyosarcoma in the event that actinomycin-D is unavailable or not tolerated.

Keywords: Carboplatin - actinomycin-D - rhabdomyosarcoma chemotherapy

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Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in pediatric age group. The incidence is 4-5 per million children and half of cases are seen in the first decade of life (Lanzkowsky et al., 2011; Wexler et al., 2011). Rhabdomyosarcoma is usually curable in most children with localized disease who receive combined modality therapy, with more than 70% survival 5 years after diagnosis. Relapses occur for patients who have gross residual disease in unfavorable sites following initial surgery and those who have metastatic disease at diagnosis. All patients with RMS regardless of their initial stage or group receive combination chemotherapy as 'standard therapy' consisting of Vincristine, Actinomycin-D, Cyclophosphamide (VAC) or Ifosfamide (VAI) (Maurer et al., 1993; Crist et al., 1995; Crist et al., 2001; Missaoui et al., 2010).

Carboplatin is a second generation analog of cisplatin that causes DNA cross-links and single-strand breaks. Although major toxicities include myelosuppression and renal impairment; it has improved toxicity profile as compared to cisplatin (Alberts et al., 1998). Carboplatin has established activity against neuroblastoma and pediatric brain tumors (Gaynon et al., 1990; Castleberry et al., 1994). Carboplatin has also been used in the treatment of intermediate-high risk rhabdomyosarcoma in clinical trials (Frascella et al., 1996; Stevens et al., 2005; Chisholm et al., 2007; Oberlin et al., 2012; Dharmarajan et al., 2013). Because of the unavailability of Actinomycin-D in Turkey, carboplatin was used instead in the treatment of rhabdomyosarcoma patients. This study is a retrospective analysis of patients who were treated with or without carboplatin. Since the results with the carboplatin group were good, scientific presentation of this research in the form of a paper would be of use to other physicians.

Materials and Methods

We reviewed the medical records of 24 consecutive patients with the diagnosis of RMS seen at the Division of Pediatric Oncology/Stem Cell Transplantation Unit, Cukurova University, Balcali Research Hospital between December 2000 and June 2011. Demographic

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data collected for these 24 patients included sex, age at diagnosis and duration of follow-up. Tumor characteristics identified included site of primary tumor (head and neck, genitourinary tract, extremities, trunk and other), histologic pattern (embryonal, alveolar, undifferentiated), size (≤5 cm or >5 cm), presence or absence of local invasion, and presence or absence of nodal and distant metastatic spread. Local invasion was defined as tumor extension to an adjacent structure or organ different from the primary site of tumor. Treatment administered, tumor progression, recurrence and outcomes were documented. Disease was classified according to the Soft-Tissue Sarcoma pretreatment TNM staging system developed by Children's Oncology Group (STS-COG).

Overall survival (OS) was defined as the interval from the date of diagnosis to date of death from any cause or to last follow-up for patients still alive. Hematological and non-hematological toxicities were graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Vincristine, actinomycin-D and cyclophosphamide combination have long been used in newly diagnosed RMS patients in Turkey. Actinomycin-D and cyclophosphamide dosages were age adjusted and radiotherapy was administered according to the IRSG protocol guidelines. Carboplatin was given 250 mg/ m^2 on days 1 and 2 as used in ICE protocol replacing Actinomycin-D (Figure 1) (Van Wilke et al., 2005).

The data were analyzed on SPSS software, version 11. Descriptive statistics and frequency distributions were reported for patient characteristics. Values are presented as mean±SD. Univariate analyses of patient characteristics and tumor responses were performed using Pearson's chi-square test, Fisher's exact test or the Mann-Whitney U-test as appropriate. OS were calculated according to the Kaplan-Meier method. The log-rank test was used to compare survival curves. P values less than 0.05 were regarded as significant.

Results

The twenty four patients included seven (29.2%) girls and seventeen boys (70.8%). The median age at diagnosis was 48 months (range 10 to 199 months). In terms of clinical stage by STS-COG, 18 (75%) were stage I-II, 6 (25%) were stage III-IV. Twenty patients (83.3%) had embryonal, three patients (12.6%) had unclassified and one patient (4.1%) had alveolar histology. In ten patients tumor was resected completely except one with positive margins. Nine patients received radiotherapy. Patients were treated according to IRS group guidelines. In eight (33.4%) cases site of origin was genitourinary tract, in five (20.8%) patients head and neck, in five (20.8%) of the cases thorax and abdomen was involved and six (25.1%) patients had the tumor in the extremities. Thirteen patients (54.2%) received carboplatin and eleven (45.8%) did not. Mean duration of follow-up in the carboplatin group was 23.1±20 months and 43.6±34 months in the non-carboplatin group. Age, sex, stage and the mean duration of follow-up were similar to those in the non-carboplatin group (p>0.05) as outlined in Table 1. Seven patients had recurrence of their disease in the primary tumor site; one patient had recurrence at a different site. Five of the patients with recurrent disease died. One patient died in the VCC group and four in the VAC group. One patient with recurrent disease in the VAC group left for another medical center. Seven patients died; five in the VAC group and two in the VCC group (Table 2). One patient

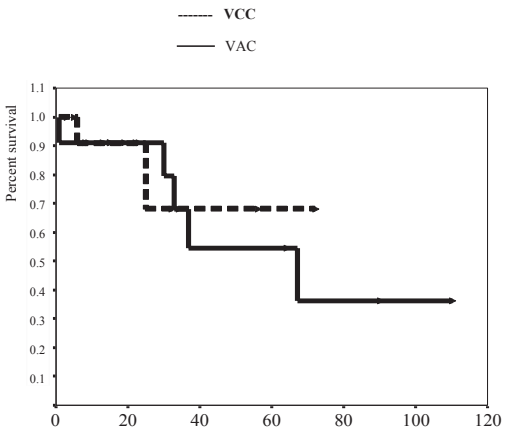

Figure 2. Kaplan-Meier Estimation of Overall Survivals for Patients with rhabdomyosarcoma Receiving both Treatment Regimens. Log-rank Test p>0.05 Dashed Line, VCC (n=13); Soild Line, VAC (n=11)

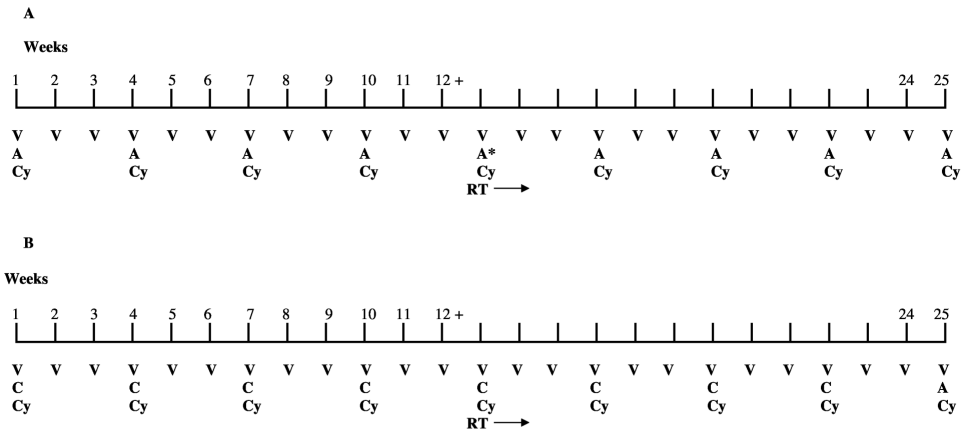

Figure 1. Treameant Protocols Administered in Patiends with RMS. A) Standard Treatment with Actinomycin-D. **B)** Treatment with Carboplatin. V Vincristine; A, Actinomycin-D; Cy ,Cyclophosphamide; RT, Radiotherapy applied to tumor bed; * Actinomycin D should be omitted when receiving RT

Table 1. Characteristics of the Patients

Variable	VAC (n=11)	VCC (n=13)	Total (n=24)	p value
Age (months, mean±SD)				
	69.4±64.7	69.0±54.3	69.2±57.9	0.52
Sex				
Female	2 (18.1%)	5 (38.4%)	7 (29.2%)	0.27
Male	9 (81.9%)	8 (61.6%)	17 (70.8%)	
Stage (STS-COG)				
I- II	8 (72.7%)	10 (76.9%)	18 (75%)	0.81
III-IV	3 (27.3%)	3 (23.1%)	6 (25%)	
Pathology				
Embryonal	9 (81.8%)	11(84.6%)	20 (83.3%)	
Alveolar	0	1 (7.7%)	1 (4.1%)	
Not otherwise specified	2 (18.2%)	1 (7.7%)	3 (12.6%)	
Duration of follow up (months, mean±SD)				
	43.6±34.0	23.1±20.0	32.8±29.1	0.08
Location				
Head, neck	2 (18.1%)	3 (23.3%)	5 (20.8%)	
Thorax, abdomen	4 (36.3%)	1 (7.6%)	5 (20.8%)	
GUS, bladder	3 (27.5%)	5 (38.4%)	8 (33.3%)	
Extremities	2 (18.1%)	4 (30.7%)	6 (25.1%)	
Surgery				
(-) margins	4 (44.4%)	5 (55.6%)	9	
(+) margins	-	1	1	
No resection	7 (50.0%)	7 (50.0%)	14	
Relapse	5 (45.4%)	3 (23.0%)	8 (33.3%)	
Death	5 (45.4%)	2 (15.3%)	7 (29.1%)	

VAC, Vincristine, Actinomycin-D, Cyclophosphamide; VCC, Vincristine, Carboplatin, Cyclophosphamide; SD, standard deviation; STS-COG, Soft Tissue Sarcoma Children's Oncology Group; GUS, genitourinary system

Table 2. Outcome of Patients Treated with Both Chemotherapy Regimens

Variable		VAC (n=11)	VCC (n=13)
Relapse	Absent	6 (1 died)	10 (1 died)
	Present	5 (4 died)	3(1 died)
Outcome	Dead	5	2
	Alive	5	11
	No follow-up	1	-

died from sepsis, the others were due to primary disease itself. There was no statistical difference in the number of febrile episodes (p=0.86) and no other hematological and non-hematological adverse effects were recorded in both groups. Two- and five-year OS levels were 68.2% in the carboplatin group and 78.0% and 40.0%, respectively, in the non-carboplatin group (Figure 2). The differences were not statistically significant (p>0.05). Event free survival was not calculated due to low number of events in the patients.

Discussion

All patients with rhabdomyosarcoma require chemotherapy for both local and systemic control of the disease. Standard chemotherapy for rhabdomyosarcoma in North America consists of 25 weeks of VAC based on trials of IRSG/STS COG. European trials have generally used ifosfamide as the alkylator in combination with vincristine and actinomycin-D. Recently, both North American and European groups have conducted trials with the goal of maintaining superior outcome besides reducing treatment and thereby reducing acute and long-term toxicity for low-risk patients. For intermediate, high, or very high risk patients the goal is to improve outcome (Lanzkowsky et al., 2011; Weler et al., 2011; Gosiengfiao et al., 2012). New therapeutic modalities are under investigation. These include new chemotherapeutic agents; use of radiosensitizing chemotherapy; administration of maintenance chemotherapy; administration of chemotherapeutic agents in a novel schedule; or introduction of molecularly targeted agents in combination with chemotherapy (Kang et al., 2011; Gosiengfia et al., 2012; Oberlin et al., 2012; Ge et al., 2013; Dharmarajan et al., 2013).

Platinum compounds, carboplatin and cisplatin has been used in high risk sarcoma treatment. Cisplatin first generation compound, either with etoposide or doxorubicin have been shown to be effective in phase II studies of advanced sarcomas (Carli et al., 1987). However,the addition of cisplatin and etoposide to front-line therapy with VAC did not appear to improve the complete response rate or failure-free survival in selected patients in IRSG III study (Crist et al., 1995). Second generation compounds, carboplatin and epirubicin, have been utilised as front-line therapy in newly diagnosed children with metastatic soft tissue sarcomas in the European trial with a 53% response rate (Frascella et al., 1996). In the third study of the International Society of Pediatric Oncology, carboplatin was used together with epirubicin / epidophyllotoxin and vincristine in selected cases of non-metastatic rhabdomyosarcoma (Stevens et al., 2005). Carboplatin was shown to be effective in treatment of refractory / recurrent rhabdomyosarcomas in combination with ifosfamide and etoposide with an overall response rate of 51% (Van Wilke et al., 2005). Moderate response rates were obtained in a window therapy with single-agent carboplatin given in chemotherapy- naive patients with high-risk metastatic RMS and other metastatic soft tissue sarcomas. Carboplatin had some activity in these tumours and was tolerable at this dose (Chisholm et al., 2007). Recently, preliminary results of irinotecan and carboplatin administered with concurrent RT in intermediate- and high-risk RMS showed favorable tolerability, efficacy, and local control (Dharmarajan et al., 2013).

Our patients have been treated using the IRSG/STS COG system. Actinomycin-D is not produced in Turkey and because of the low profit margins pharmaceutical companies are unwilling to import it. To avoid treatment delays we have used carboplatin which is readily available. There was no difference between the two regimens in terms of toxicity or results. Although OS was longer in the carboplatin group no statistical difference was found. We also found no significant difference between the two groups in terms of serious hematological and non-hematological toxicities. Actinomycin-D, a radiosensitizing agent, should be discontinued in patients receiving radiotherapy due to its hepatotoxicity, particularly in terms of veno-occlusive disease (Estlin et al., 2003). Carboplatin, also a radiosensitizer, could be used if actinomycin-D is too toxic in patients with rhabdomyosarcoma.

In conclusion, our data demonstrate the carboplatin can be used as an alternative to actinomycin-D chemotherapy in the treatment of rhabdomyosarcoma in countries where there is shortage of the drug or in patients with excess toxicity on actinomycin-D. Further studies are needed to confirm these results.

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