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Impact of treatment protocol on outcome of localized Ewing's sarcoma

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Abstract

Background: The outcome of localized Ewing's sarcoma has improved with multi-disciplinary approach. Survivals of Ewing's sarcoma from the Asian countries differed between centers. **Methods:** We retrospectively analyzed the records of newly diagnosed localized Ewing's sarcoma patients from 2002 to 2012. The patients were analyzed in three groups; Group 1 (2002-2004) who received non-ifosfomide based regimens, Group 2 (2005-2008) who received VDC/IE for 12 cycles, and Group 3 (2009-2012), who received VDC/IE for 17 cycles. The groups were compared for their baseline characteristics, treatment protocol and outcome. **Results:** Seventy three patients were included in the study. The median age of presentation was 15 years, with slight male predominance. Axial primary was seen in 62%. The median RFS of the three groups was 26.4, 31.4 and 36.8 months respectively (P = 0.0018). The median OS was 27.9, 35 and 43 months respectively (P = 0.0007). At a median follow-up of 35 months, the 3 year RFS and OS for the three treatment groups were 17%, 31%, 60% and 35%, 45% and 70% respectively. Larger tumor size, axial primary, high LDH were associated with poorer survival. Radiotherapy was associated with inferior local control and survival. **Conclusions:** We found that the survival of our ESFT patients improved over time with intensified multiagent chemotherapy and with lesser time to local therapy. But the results were still inferior to those reported in literature. We had majority of patients presenting in axial site and radiotherapy as the predominant mode of local control. The outcome may further improve with surgery as local control procedure.

Key words: Localized Ewing's sarcoma, locoregional therapy, multiagent chemotherapy

Introduction

Ewing's sarcoma family of tumors (ESFT) is highly malignant, small, round cell neoplasm arising from bone and soft tissue. The treatment outcomes of localized ESFT have improved over the past decades with the multimodality approach.[1-3] The objectives of the current study are (1) to assess the outcome of localized ESFT at our center with different treatment protocols and (2) to correlate the significance of prognostic factors to the outcome.

Methods

Hospital records of newly diagnosed localized Ewing's sarcoma patients from January 2002 to December 2012 were analyzed. The clinical records were analyzed for their clinical features, chemotherapy protocol received, number of cycles of chemotherapy received, mode of locoregional therapy, and outcome. Standard protocols were used for diagnosis and staging.

The patients were analyzed in three groups: (1) those treated from 2002 to 2004 (Group 1) who received nonifosfomide-based regimens (vincristine, doxorubicin, cyclophosphamide [VDC]/vincristine, actinomycin-D, cyclophosphamide/vincristine, actinomycin-D, cyclophosphamide, and doxorubicin), (2) those treated from 2005 to 2008 (Group 2) who received VDC/ifosfamide, etoposide (VDC/IE) for 12 cycles, and (3) those treated from 2009 to 2012 (Group 3) who received VDC/IE for 17 cycles. Locoregional therapy was either surgery or radiation therapy after few cycles of neoadjuvant chemotherapy.

Statistical analysis

Relapse-free survival (RFS) was calculated from the date of diagnosis to the onset of progression or recurrence. Overall survival (OS) was calculated from the date of diagnosis to date of death or loss to follow-up. RFS and OS rates were estimated using the Kaplan–Meier method. The log-rank test was used for analyzing the prognostic significance of variables.

Results

Seventy-three patients were included in the study. The median age of presentation was 15 years (range: 3–45 years), with slight male predominance (male:female = 1.28:1). Primary in axial site was seen in 62% of the patients and 19% had an extraosseous primary. The baseline characteristics and outcomes of the three groups are enumerated in Table 1.

The median RFS of the three groups was 26.4, 31.4, and 36.8 months, respectively (P = 0.0018). The median OS was 27.9, 35, and 43 months, respectively (P = 0.0007). At a median follow-up of 35 months, the 3-year RFS and OS for the three treatment groups were 17%, 31%, 60% and 35%, 45%, 70%, respectively.

Among the patients with primary in extremity (28), radiotherapy and surgery were given to 17 (60.7%) and 11 (39.3%) patients, respectively. Among the patients with axial primary (45), 35 (77.8%) received radiotherapy and 10 (22.2%) underwent surgery. Eleven (out of 52) patients who took radiotherapy and three (out of 21) patients in the surgery group had local recurrence. Three-year local recurrence-free survival of radiotherapy and surgery groups was 42% and 75%, respectively (P = 0.01).

Univariate analysis showed that a larger tumor size, axial primary, high LDH was associated with poorer RFS and OS. Time to local therapy <4 months was associated with better outcome. Radiotherapy as the mode of local control procedure was associated with inferior outcome. The results of univariate analysis of the prognostic variables are listed in Table 2.

Discussion

The patients in Group 2 had improved outcome over the Group 1 patients, with the addition of IE to the VDC regimen.[4-6] Group 3 had even better outcome with extended chemotherapy for 17 cycles and decreasing the time to local

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Table 1: Baseline characteristics and outcome of the three groups

	Group 1, *n*=17 (23.3%)	Group 2, *n*=29 (39.7%)	Group 3, *n*=27 (37.0%)	*P* (Fisher test)
Median age	14	15	14	
Male:female	1.43:1	0.93:1	1.7:1	
Axial primary (%)	10 (58.8)	18 (58.6)	17 (62.9)	0.96
Extraosseous primary (%)	4 (23.5)	4 (13.8)	6 (22.2)	0.63
Tumor size>8 cm (%)	8 (47)	13 (44.8)	11 (40.7)	0.91
High TLC (%)	6 (35.3)	8 (27.6)	6 (22.2)	0.64
High LDH (%)	6 (35.3)	11 (37.9)	12 (44.4)	0.81
Median number of chemotherapy cycles	9	12	17	
Time to locoregional therapy (months)	4.7	5.2	3.6	
Mode of local therapy				
Radiotherapy (%)	13 (76.5)	20 (69.0)	19 (70.4)	0.86
Surgery (%)	4 (23.5)	9 (31.0)	8 (19.6)	
Median RFS (months)	26.4	31.4	36.8	0.0018*
Median OS (months)	27.9	35	43	0.0007*
3-year RFS (%)	17.0	31.0	60.0	0.01
3-year OS (%)	35.3	44.8	70.3	0.02
3-year LRFS (%)	23.5	50	63.9	0.04

**P* value by log-rank test. LDH=Lactate dehydrogenase, TLC=Total leukocyte count, RFS=Relapse-free survival, OS=Overall survival, LRFS=Local recurrence-free survival

Table 2: Univariate analysis of prognostic variables

	n	Median RFS (months)	*P*	Median OS (months)	*P* (log-rank test)
Age (years)					
≤15	38	32.9	0.29	36.0	0.37
>15	35	32.3		37.0	
Sex					
Male	41	31.3	0.13	33.8	0.19
Female	32	32.7		37.7	
Systemic symptoms					
Yes	18	31.5	0.57	36	0.51
No	55	33.9		37.1	
Site of primary					
Axial	45	31.2	0.005	33.8	0.006
Appendicular	28	37.1		40.8	
Osseous	59	31.5	0.66	35	0.56
Extraosseous	14	36.8		40.8	
Tumor size (cm)					
<8	41	34.3	0.03	37.8	0.01
≥8	32	30.8		32.8	
TLC					
<11,000	55	33.8	0.30	37.7	0.19
≥11,000	18	26.3		29.8	
LDH					
Normal	43	36.4	0.0006	38	0.0025
High	30	27.9		28.5	
Time to local therapy (months)					
≤4	36.8	0.004		42.5	0.004
>4	27.9			32.6	
Mode of local therapy					
Radiotherapy	52	31.2	0.03	33.0	0.02
Surgery	21	40.5		45.5	

RFS=Relapse-free survival, OS=Overall survival, LDH=Lactate dehydrogenase, TLC=Total leukocyte count

therapy to 3–4 months. However, radiotherapy had been the predominant method of local therapy in all the three groups.

Although the outcome improved over the period with intensified multiagent chemotherapy and with decrease in time to local therapy, the survival was inferior to that of EuroAmerican data. This could be due to poor local control and relapses with radiotherapy as local control procedure[7] as the majority of our patients had axial presentation.

Conclusion

We found that the survival of our ESFT patients improved over time with intensified multiagent chemotherapy and with lesser time to local therapy. However, the results were still inferior to those reported in literature. We had majority of patients presenting in axial site and radiotherapy as the predominant mode of local control. The outcome may improve with prospective multicenter trials and uniform standard protocols.

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Conflicts of interest

There are no conflicts of interest.

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