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Results of Rhabdomyosarcoma Treatment in a Developing Country

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Fifty-one children (median age: 4.5 years; 4 months-16 years) diagnosed with rhabdomyosarcoma were treated in our center between 1980-1999. The primary sites were head and neck in 31.4%, the genito-urinary system in 21.6%, and extremities in 9.8% of the patients. The histopathologic subtypes were embryonal in 80.4%, alveolar in 9.8%, and undifferentiated in 9.8%. The majority of the patients were considered group III (47%) and group IV (25.5%) according the criteria of the Intergroup Rhabdomyosarcoma Study (IRS). Primary total tumour resection was performed in only 27.5% of the patients. The patients were treated with assigned regimens of IRS II and IRS III protocols. Radiotherapy was applied to 92.1% of the patients. Thirty-four patients (66.7%) were lost to follow up, and of the remaining 17 patients, 7 patients (41.2%) died, relapse occurred in 9 patients (52.9%) and 10 patients (58.8%) are alive. The percentage of cases lost to follow up during the first 10 years and the following 9 years of the study were 77.4% and 50%, respectively. Incompliance with cancer treatment remains a major problem in developing countries.

Key words: rhabdomyosarcoma, pediatric oncology, chemotherapy

Rhabdomyosarcoma (RMS) which originates from the primitive mesenchimal cells and forms complex and heterogenous solid tumors is the most frequent soft tissue sarcoma seen in childhood. It comprises 4-8 % of all pediatric cancers (1). Most series have shown a slight male predominance with 2 age peaks (2-6 years and 15-19 years) (1, 2). RMS arises in any part of the body where striated muscle is found, and its clinical picture differs according to the primary site. Head and neck, the genito-urinary system and the extremities are the most frequently affected sites (3-5). Since the introduction of multimodality therapy in the 1960's, there has been a significant increase in the survival rates of children with RMS. Current multimodality treatments including surgery, irradiation, and chemotherapy have increased the overall 5-year-survival rate of clinically treated patients to 55-75% (3-8). In the present study, the clinical and histopathologic features of RMS, the problems relating to patient incompliance with chemotherapy, and the outcomes of 51 pediatric RMS patients in a developing country are presented.

Patients and Methods

Between 1980 and 1999, 51 children with a median age of 4.5 years (4 months-16 years) were treated for RMS in Istanbul University School of Medicine, Department of Pediatric Hematology/Oncology and Our Children Leukemia Foundation Medical Center. The medical records of the patients were retrospectively reviewed for specific diagnostic and therapeutic information including primary tumor site, histologic subtype, clinical groups, extent of surgery, radiotherapy, and follow up. A biopsy/excision or debulking surgery was performed in all patients. For tumor staging, Intergroup Rhabdomyosarcoma Study (IRS) Clinical Grouping Classification was used. The patients were treated according to IRS II and III protocols without randomization (3, 8). Four different chemotherapeutic regimens were used, which consisted of vincristine and actinomycin-D (VA), with the addition of cyclophosphamide (pulse VAC); sequential vincristine, adriamycin, actinomycin D and cyclophosphamide (pulse

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VAC/VADRAC); etoposide, vincristine, doxorubicin, ifosphamide, actinomycin-D (EVAIA). The protocols used were dependent upon the period (IRS II (1980-1984) and IRS III (1985-1999), primary site, and clinical group. Radiotherapy was used according to IRS recommendations, with a mean dose of 48.8 Gy applied to 92.1 % (n = 47) of the patients.

Results

Over a 19-year period, 51 patients with the initial diagnosis of RMS were followed up in our center. There were 33 boys and 18 girls with a M/F: 1.8. The age, sex, primary site at presentation, histology, and clinical group distribution of patients are summarized in Table 1. Of 51 patients 47% and 86.2% were younger than 5 and 10 years, respectively. The most frequent primary tumor localizations were head and neck (31.4%), followed by the genito-urinary system (21.6%), and extremities (9.8%). The histological subtypes were embryonal in 80.4% (n = 41), alveolar in 9.8% (n = 5), and undifferentiated in 9.8 % (n = 5). The percentages of patients in clinical groups I through IV were 3.9%, 23.6%, 47% and 25.5%, respectively, indicating that the majority had advanced disease. The treatment schedules applied to patients according to IRS II and III are shown in Table 2. Total resection of the tumor was performed in 14 cases (27.5 %), all of these patients were in groups I and II. Partial resection was possible in 26 patients (50.9%), 20 of these 26 patients belonged to group III. An excisional biopsy was done in 11 cases (21.6%), 7 of these 11 cases were in group IV. Therapeutic regimen VA ± RT was applied to 14 patients (27.5%), 12 of them were in group II and 2 cases were in group I. Pulse VAC + RT was the protocol used in 29 patients (56.9%), 19 of these 29 patients were in group III and 10 of them belonged to group IV. A total of 4 patients (7.8%) received pulse VAC/VADRC + RT, 2 of them were in group III and the other 2 were in group IV. Four patients (7.8%) were treated with EVAIA protocol, 3 of them were in group III and 1 patient was in group IV.

Remarkably, of 51 RMS patients, 34 patients (66.7 %) were lost to follow up. When dropouts were investigated with respect to clinical groups it was found that

Table I Patients' characteristics by clinical group, histology and primary site

	Group I	Group II	Group III	Group IV	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
No. of patients	2 (3.9)	12 (23.6)	24 (47)	13 (25.5)	51 (100)
Sex					
Male	1 (1.9)	7 (13.7)	18 (35.4)	7 (13.7)	33 (64.7)
Female	1 (1.9)	5 (9.8)	6 (11.8)	6 (11.8)	18 (35.3)
Age					
< 5 years	1 (1.9)	6 (11.8)	13 (25.5)	4 (7.8)	24 (47)
5-10 years	1 (1.9)	6 (11.8)	10 (19.7)	3 (5.9)	20 (39.3)
10-15 years	- -	- -	1 (1.9)	5 (9.8)	6 (11.7)
> 15 years	- -	- -	- -	1 (1.9)	1 (1.9)
Histologic subtype					
Embryonal	2 (3.9)	9 (17.7)	21 (41.1)	9 (17.7)	41 (80.4)
Alveolar	- -	2 (3.9)	1 (1.9)	2 (3.9)	5 (9.8)
Undifferentiated	- -	1 (1.9)	2 (3.9)	2 (3.9)	5 (9.8)
Primary Site					
Head and neck	1 (1.9)	- -	12 (23.6)	3 (5.9)	16 (31.4)
Orbita	- -	- -	1 (1.9)	- -	1 (1.9)
Parameningeal(PM)	1 (1.9)	- -	9 (17.6)	3 (5.9)	13 (25.5)
NonPM	- -	- -	2 (3.9)	- -	2 (3.9)
Genito-urinary	- -	4 (7.9)	6 (11.8)	1 (1.9)	11 (21.6)
Extremity	- -	2 (3.9)	- -	3 (5.9)	5 (9.8)
Trunk	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)	4 (7.8)
Other	- -	5 (9.8)	5 (9.8)	5 (9.8)	15 (29.4)

there were 7/14 (50%) dropouts, in groups I and II, 17/24 (70.8%) in group III, and 10/13 (76.9%) in group IV. When dropout cases were further analyzed, it was recognized that a total of 31 children were diagnosed in the former 10 year period of the study. The number of lost follow up patients in this period was 24/31 (77.4%). Twenty patients were diagnosed and treated during the latter 9 year period of the study. The ratio of the dropout patients during this period was 10/20 (50%). Dropouts occured in 24/34 patients (73.5%) during chemotherapy, compared with 9/34 (26.5%) dropouts during relapse. Relapse occured in 9 lost follow up patients. More strikingly, dropouts occured during relapse especially in the latter 9 year period, 2/24 (8.3%) versus 7/10 (70%).

The treatment results of 17 followed-up patients with respect to clinical groups are summarized in Table 3. Within a median of 5 months, 9 out of 17 patients (52.9 %) relapsed. Local relapse occured in 7 patients and distant relapse was found in 2 patients. Sites of distant relapse were the lung in 1 patient and the central nervous system in the other. Seven of the relapsed patients died and 2 of them are still alive with a median follow up 11 months. Seven out of 17 patients died (41.2%), all having been relapsed patients, and 10 patients are alive. None of the patients in group IV survived.

Discussion

The present study represents a heterogenous group of patients with RMS treated over a 19-year-period. In IRS III, 66% of the eligible patients were younger than 10 years at diagnosis (3). The majority of our patients (86.2 %) were younger than 10 years at diagnosis. In Turkey, teenagers over 15 years of age are usually admitted to adult clinics. Therefore, the second age peak was not available in the present study. In our patient group, the male to female ratio was 1.8:1. This slight male predominance was found to be similar to previous reports (3, 5, 7). In our series, the distribution of predominant primary sites at presentation being head and neck and the genitourinary system was similar to other series published in recent years (7, 9, 10). It is known that 60% of RMS

Table 2 Treatment schedules in patient with Rhabdomyosarcoma

	Group I	Group II	Group III	Group IV	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Primary surgery					
Total resection	2 (3.9)	12 (23.5)	- -	- -	14 (27.5)
Partial resection	- -	- -	20 (39.2)	6 (46.1)	26 (50.9)
Biopsy	- -	-	4 (7.8)	7 (13.7)	11 (21.6)
Therapeutic protocol					
VA ± RT	2 (3.9)	12 (23.5)	-	- -	14 (27.5)
Pulse VAC + RT	- -	- -	19 (37.3)	10 (19.6)	29 (56.9)
VAC/VADRC + RT	- -	- -	2 (3.9)	2 (3.9)	4 (7.8)
EVAIA	- -	- -	3 (5.8)	1 (1.9)	4 (7.8)
Irradiation					
Yes	- -	10 (19.6)	24 (47.1)	13 (25.5)	47 (92.1)
Total	2 (3.9)	12 (23.5)	24 (47.1)	13 (25.5)	51 (100)

Table 3 Outcome of 17 patients according to the clinical groups

	Group I	Group II	Group III	Group IV	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Alive	1 (5.9)	4 (23.5)	5 (29.4)	- -	10 (58.8)
Exitus	- -	2 (11.8)	2 (11.8)	3 (17.6)	7 (41.2)
Total	1 (5.9)	6 (35.3)	7 (41.2)	3 (17.6)	17 (100)

patients have the embryonal subtype, which includes the botryoid type, followed by the alveolar type (20%) (9-13). The histologic subtype of the present series of 51 patients revealed a marked predominance of the embryonal subtype (80.4%). The present clinical study also pointed out that the total number of patients in groups III and IV exceeded the total number of patients in groups I and II (37 versus 14). This may be a characteristic of pediatric oncology in a developing country. Late admission and late diagnosis of advanced stages of cancer is an important factor relating to the disappointing results of childhood tumors in developing countries. The other important cause for the dismal prognosis of patients with malignancy in these countries is the phenomenon wherein the patient is lost to follow up. This problem is frequently encountered in developing countries. Luna-Fineman *et al.* (14) reported that 41% of all pediatric cancer patients in Guatemala between 1993 to 1997 were lost to follow up (13% abandoned treatment against medical advise and 28 % did not return to their appointments). A report from India revealed that 31% of Non-Hodgkin's Lymphoma cases between 1986 to 1996 were lost either before or after the start of treatment (15). In the present study 66.7 % of the patients were lost to follow up. The percentage of dropping out cases during the first 10 years and the following 9 years of the study were 77.4% and 50%, respectively. The decline in the rate of cases lost to follow up is a hopeful result, but 50% is still an unacceptably high rate. The dropouts were mostly in the late clinical groups (70.8% of group III and 76.9% of group IV, versus 50% of groups I and II). The percentage of dropouts during relapse in the first 10 years and the following 9 years of the study are 8.3% and 70%, respectively. This points out that in the early years of the study, the major reason for patient not to return for treatment was socioeconomical, but later the hopelessness of the parents seemed to be an important factor in patients neglecting to be followed up. Psychological support is important for the parents of cancer patients in order to make them committed to treatment and to decrease the rate of patients who do not return for treatment (16). Psychologists have participated in our treatment team for 9 years. This might have also influenced the decline in the rate of patients who drop out of treatment programs.

Incompliance with cancer treatment is a major problem in developing countries. Socio-economic status, the high number of children in families, lack of social security, and delay of diagnosis play important roles in this problem. The high rate of dropout cases is also a handicap for statistical analysis.

In order to save children with cancer, our responsibility is to call the population's attention to this problem. We hope that in the near future, the number of cases lost to follow up will decrease in parallel with advances in socio-economic conditions and with the appreciation of the importance of psychological support. This would provide for better treatment results and more realistic statistical analyses of oncologic patients.

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