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MALIGNANT GERM CELL SACROCOCCYGEAL TUMORS IN CHILDREN

Improved prognosis after introduction of cisplatin-containing multiple drug treatment

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Abstract

The survival of children with malignant germ cell sacrococcygeal tumors has improved during the last few years after introduction of a multidrug protocol including cisplatinum. Treatment for 10 patients registered in 1965–1978 was not uniform and consisted of surgical resection or biopsy and radiotherapy with or without multiple drug chemotherapy (methotrexate + actinomycin D + cyclophosphamide). Only one of these patients is alive. Fifteen patients registered between 1978 and 1986 were treated with actinomycin D + cyclophosphamide + vincristine + doxorubicin + bleomycin + cisplatinum. Four patients also received radiotherapy. Seven out of these 15 children are alive without evidence of disease.

Key words: Germ cell tumors, sacrococcygeal, children, multiple drug chemotherapy, prognosis.

Non-seminomatous malignant germ cell tumors are uncommon malignancies in children and occur most often in the gonads and the sacrococcygeal region.

Some recent studies suggest an improved prognosis for gonadal tumors since the introduction of polychemotherapy (1–4).

In the present report we are comparing treatment results in children with malignant germ cell sacrococcygeal tumors from an earlier period with results obtained by a cisplatinum containing multidrug protocol advocated by Flamant et al. (4).

Material and Methods

Between 1965 and 1986 25 children with malignant germ cell sacrococcygeal tumors were treated in the Oncology Unit of the Children's Hospital Ricardo Gutierrez and the Oncology Section of the Pediatric Department of the Italian Hospital, Buenos Aires, Argentina.

The median age at diagnosis was 18 months with a range from 5 months to 6 years. Nineteen were female. The histologic diagnoses were pure yolk sac carcinoma in 22, and yolk sac carcinoma plus immature teratoma in 3 patients. Five children presented with sacrococcygeal tumors at birth. Three of these had total removal of the tumor without any other treatment and relapsed after 11, 13 and 24 months. All patients were staged according to criteria proposed by Brodeur et al. (3) (Table 1).

The treatment for the 10 patients registered between 1965 and 1978 (group A, Table 2) was not uniform and consisted of surgical resection or biopsy and radiotherapy with or without MAC chemotherapy (methotrexate 7 mg/m^2 days 1 to 5, actinomycin D 0.3 mg/m^2 days 1 to 5, and cyclophosphamide 300 mg/m^2 days 1 to 5).

Fifteen patients registered between 1978 and 1986

Table 1

Staging system for malignant germ cell tumors

Stage I	Localized disease, completely resected, without microscopic disease in the resected margins or in the regional lymph nodes
Stage II	Microscopic residual disease, capsular invasion, or microscopic lymph node involvement
Stage III	Gross residual disease, gross lymph node involvement or cytologic evidence of tumor cells in ascites or pleural fluid
Stage IV	Disseminated disease involving lungs, liver, brain, bone, distant nodes or other sites

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Table 2

Group A: 10 patients treated 1965–1978

Case	Age/sex/stage	Treatment	Course
1	13 m/F/I	Complete resection +MAC	NED 8 + years
2	13 m/F/I	Complete resection MAC+lumboaortic RT 30 Gy	Local relapse 5 m. Died 9 m. Progressive disease.
3	8 m/F/III	Biopsy + colostomy	Died 1 m.
4*	20 m/F/III	Biopsy + local RT 30 Gy	Lung metastases. Died 4 m.
5	36 m/F/III	Biopsy + MAC + local RT 30 Gy	Local + CNS relapse 4 m. Died 7 m.
6	7 m/F/III	Biopsy + MAC	Progressive disease. Died 9 m.
7	6 y/M/IV (supraclavicular node)	Biopsy + conventional RT 70 Gy	Progressive disease. Died 5 m.
8*	11 m/IV (inguinal node)	Partial resection + RT 30 Gy	Progressive disease. Died 3 m.
9	19 m/F/IV (lung)	Biopsy + MAC + local RT 30 Gy + lung + lung RT 12 Gy	Local relapse 7 m. Died 8 m.
10	24 m/F/IV (lung + liver)	Biopsy + MAC	Progressive disease. Died 2 m.

Group B: 15 patients treated 1978–1986

Case	Age/sex/stage	Treatment	Response	Course
1	11 m/F/III	CT	NR	PD. Died 1 m
2	32 m/M/III	CT	CR	NED + 84 m
3	27 m/F/III	CT + local RT 17 Gy	CR	Died NED 6 m due hematologic toxicity
4	12 m/M/III	CT	CR	Died NED 12 m due sepsis 1 month of therapy
5	5 m/F/III	CT	CR	NED + 27 m
6	19 m/M/III	CT	CR	NED + 24 m
7*	24 m/F/III	CT	CR	NED + 12 m
8	18 m/F/IV (lung)	CT + local RT 22 Gy + lung 16 RT 16 Gy	CR	NED + 98 m
9	18 m/F/V (inguinal) node)	CT + local RT 40 Gy	NR	PD. Died 9 m
10*	17 m/M/IV (lung)	CT + local RT 30 Gy	NR	PD. Died 11 m
11	28 m/F/IV (lung)	CT	CR	NED + 58 m
12	20 m/F/IV (lung) Down syndrom	CT	NR	PD. Died 4 m
13	24 m/F/IV (lung + liver)	CT	CR	Relapsed lung 10 m. Died 15 m. cardiotoxicity
14	6 y/F/IV (lung)	CT	CR	NED + 27 m
15	13 m/F/IV (lung)	CT	NR	PD. Died 4 m medular aplasia

* Tumor at birth.

(group B, Table 2) were treated with actinomycin D 0.3 mg/m^2 days 1 to 5, cyclophosphamide 300 mg/m^2 days 1 to 5, vincristine 1.5 mg/m^2 day 21, doxorubicin 60 mg/m^2 day 21, bleomycin 15 mg/m^2 days 21 and 23, and cisplatinum 100 mg/m^2 day 24. Each course was repeated every 21 days for a total of 6 courses. Four patients also received radiotherapy.

Results

Out of the 10 patients in group A (Table 2) one is alive NED after more than 8 years from diagnosis. The other 9 patients died from the disease within 1 to 9 months.

Ten of the 15 children in group B (Table 2) achieved complete remission (CR), and 7 of them are alive NED

after a median time of 27+ months (12+ to 98+ months). One patient relapsed after 10 months and died 15 months after diagnosis. Two died without evidence of tumor disease at 6 and 12 months due to toxic effects of chemotherapy. The other 5 children in group B died with progressive disease (PD) after a median time of 4 months (1 to 11 months).

Treatment in group B was quite toxic. Two children died due to hematologic toxicity (one of haemorrhage and one of sepsis) without evidence of tumor disease. One child had severe cardiotoxicity and also one child who died with progressive disease had bone marrow aplasia. None of the patients developed renal failure. Because of the low median age (18 months) of the patients serial pulmonary function tests could not be performed but none had clinical symptoms of pulmonary impairment.

Discussion

Our experience with a multidrug regimen containing bleomycin and cisplatinum has shown a dramatic improvement of the survival even in advanced stages of the disease.

Prior to the introduction of multiple drug therapy the prognosis of children with malignant germ cell sacrococcygeal tumors was very poor. In 1974 Altman et al. (2) reported 398 cases of sacrococcygeal germ cell tumors; 60% of the patients with malignant tumors died within 10 months after the operation, 20% were alive with residual disease, 11% were alive without apparent disease and 9% were lost to follow-up.

Raney et al. (5) reported that combination chemotherapy (vincristine, actinomycin D, and cyclophosphamide with or without doxorubicin) combined with radiation therapy could be effective. The treatment was, however, highly toxic in young infants with a high risk of fatal hematologic, pulmonary and cardiac complications.

In a review 1986 by the Pediatric Oncology Group of the USA (6) 13 of 21 children with malignant germ cell sacrococcygeal tumors were reported as disease-free at a median time of 45.5 months after diagnosis. Only 2 of these children had been treated with complete resection alone while all the others had received multidrug chemotherapy (usually vincristine, actimomycin D, and cyclophosphamide with or without additional drugs).

Side effects of our 6-drug chemotherapy protocol can be severe and the protocol might be considered as too toxic. Nevertheless it has been accepted by other authors (4, 7, 8). Given the toxicity of this regimen and the fact that 9 of 10 children achieved complete remission already after 2 courses if seems reasonable to shorten the length of chemotherapy. Furthermore, Einhorn et al. (9) showed that in adult patients with metastatic testicular non-seminomatous tumors the addition of doxorubicin to PVB (cisplatinum, vinblastine, bleomycin) did not improve the results. For these reasons we started, in January 1988, a new protocol without doxorubicin and including only 3 courses of chemotherapy in those patients who achieve complete remission after 2 courses. We expect a decrease in toxic side effects and, hopefully, similar good results.

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