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Original Article

A Retrospective Analysis Of The Treatment Results Of 36 Cases Of Pediatric Germ Cell Tumors.

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ABSTRACT

The aim of this work is to evaluate the treatment results of pediatric germ cell tumor cases who attended the pediatric unit of Kasr-El-Aini center of radiation oncology and nuclear medicine (NEMROCK) from January 1991 until January 2000.

Thirty-six patients with pediatric germ cell tumors were analyzed. Low-risk patients included patients with ages less than 10 years, an alpha-feto-protein level (AFP) < 10.000, stages I and II, and gonadal sites. High-risk patients included patients with ages > 10 years, alpha-feto-protein levels > 10.000, stages III and IV, and non-gonadal sites. Orchiectomy was done for testicular tumors. Unilateral salpingo-opherectomy was done for ovarian tumors. Excision of sacro-coccygeal tumors with the coccyx as a safety margin was performed. Other sites underwent initial biopsy followed by surgery after cyto-reduction by chemotherapy. Chemotherapy was given for 4 cycles (PEB regimen), except for stage I testicular tumors with normal post-operative markers and stages I and II mixed germ cell tumors of other sites with normal markers.

Males constituted 44.5% of the cases and females 55.5%. The most common affected sites were the sacrococcyx (38.8%) followed by the testes (19.43%), then intra-abdomenal sites (13.88%). The most common pathological subtype was teratoma (44.32%) followed by yolk sac tumor (33.24%) then endodermal sinus tumor (16.62%). High-risk cases constituted 55.4% of the cases while low-risk cases constituted 44.32% of the cases. CR was achieved in 83.1% of the cases; PR in 5.54% and DP occurred in 11.08% of the cases.

After a median follow-up period of 6 years, thirty cases were alive and disease free (83.1%) and 6 cases had died (16.62%). The overall 5-year survival was 78%. The 5-year survival for stages I and II was 85%, the 5-year survival for stages III and IV was 10%. The 5-year survival for low-risk patients was 100%, whereas for high-risk patients it was 45% (P<0.00001). Grade I neutropenia was the most common acute toxicity.

Initial AFP level, disease stage, and primary site were the most important prognostic factors on analysis. Prognostic models should allow the stratification of patients for a risk adopted approach to treatment.

Key words: pediatric, germ cell tumors, PEB.

Introduction

Germ cell tumors are neoplasms that develop from primordial germ cells of the human embryo that are normally destined to produce sperms and ova [1].

Germ cell tumors account for approximately 2.3% of childhood malignancies. The incidence of germ cell tumors is 2.5 per million in white children and 10 per million in black children under 15 years of age with a male to female ratio of 10:11[2]. Cisplatinum based chemotherapy dramatically changed the prognosis of these tumors by improving long-term survival from 20 to 70% [3].

Several studies have addressed which factors determine patients of high risk for developing resistant disease. The most important features predictive of poor prognosis reported are, extra-gonadal location of the primary tumor, advanced

stage of the disease, patient's age less than 10 years, elevated levels of serum markers at diagnosis and incomplete removal of the tumor mass [4].

Patients and Methods

Children younger than 16 years with pathologically proven localized or metastatic malignant germ cell tumors (36 cases) who presented to the pediatric oncology unit of Kasr-El-Aini center of radiation oncology and nuclear medicine from January 1991 to January 2000 were eligible for the study.

The diagnostic work up included history taking and a thorough physical examination.

Laboratory investigations included; a complete blood count (CBC), liver and renal function tests and were performed before each course of chemotherapy.

Serum alfa-feto-protein (AFP) and serum beta-human-chorionic-gonadotrophine (BHCG) were measured by radioimmunoassay before surgery and 5 days postoperatively and then repeated weekly until normal values were reached; then monthly for 2 years and then every 3 months for a further year to facilitate early detection of treatment failure [5].

A chest x ray (CXR), CT scan at the site of initial tumor involvement, and abdominal CT scan for testicular tumor cases were requested at diagnosis and at the time of treatment response evaluation.

The patients were classified into low-risk and high-risk according to the level of AFP, BHCG, and TNM staging system, tumor site, and patient's age.

Low-risk patients included patients with AFP levels < 10.000, ages < 10 years, gonadal sites and stages I and II [6,7,8].

High-risk patients included patients with serum AFP levels > 10.000, ages > 10 years, extragonodal sites and stages III and IV [6,7,8].

The surgical approach to testicular tumors was orchiectomy and high ligation of the spermatic cord (8). For ovarian tumors, unilateral salpingo-opherctomy was done followed by a biopsy from the contra lateral ovary [9].

Sacro-coccygeal tumors were resected together with the Coccyx [10]. An initial biopsy was recommended for retroperitoneal and mediastinal tumors. A second surgery was done after neo-adjuvant chemotherapy to remove any residual tumor.

Chemotherapy was not recommended for stage I testicular tumors and stage I mixed germ cell tumors occurring at other sites with complete excision and normal post-operative consecutive markers. Chemotherapy regimens included cisplatinum 20 mg/m2 IV infusion Day 1 to Day 5, vepesid 100 mg/m2 IV infusion over 1 hour Day 1 to Day 3, and bleomycin 30 units/m2 IV D 2, 9 and 16, the regimen was given every 3 weeks for 4 cycles [11]. Assessment of toxicity was done using the WHO grading criteria.

The patients were followed up for a median interval of 6 years. The overall survival (OS) (time from diagnosis until lost follow up or death), disease free survival (DFS) (time from complete remission until radiologicaly and clinically documented disease progression or recurrence) were assessed. The response to treatment was assessed. Complete response (CR) is defined as normalization of tumor markers and absence of tumor residue. Partial response (PR) is defined as > 50% reduction of the volume of measurable disease along with normalization of the markers. Stable disease (SD) is defined as < 50% reduction of tumor size and or persistently elevated tumor markers. Disease progression (PD) is defined as increase of tumor mass and level of tumor markers.

Relapsed and progressed cases received palliative radiation therapy and salvage chemotherapy. Holoxan 1.2 gm/m2 IV infusion with mesna Day 1 to Day 3 and vepesid 100 mg/m2 IV infusion Day 1 to Day 3 [11].

Statistical methods

The Kaplan Meier method was used to estimate overall survival and disease free survival, the log rank test was applied to compare the different groups (P value is significant at 0.05 levels) [12].

The non-parametric T test was used to compare AFP and ßHCG before and after treatment.

Results

Thirty-six cases of germ cell tumors were included in the study. Males constituted 44.5% of the cases (16 cases) and females constituted 55.5% of the cases (20 cases). History of consanguinity was present in 12 cases (33.3%). The most common affected site was the sacrococcyx 38.8% (14 cases), followed by the testis 19.43% (7 cases), intra-abdominal sites 13.88% (5 cases), then the CNS and ovary, each had the same prevalence 11.1% (4 cases) followed by the extremities 5.55% (2 cases) (Fig. 1). Thirty percent of the cases had a genital

site of origin, whereas, 70% of them were in extra-genital sites.

The most common pathological subtype was teratoma 44.32% (16 cases), followed by yolk sac tumor 33.24% (12 cases), then endodermal sinus tumor 16.62% (6 cases) and finally mixed germ cell tumors 5.54% (2 cases). Stage I constituted 30.47% of the cases (11 cases), stage II 49.86% (18 cases), stage III 13.85% (5 cases) and stage IV 5.54% (2 cases).

Lymph node metastases prevailed in 13.85% of the cases (5 cases). Lung metastases were found in 5.54% of the cases (2 cases). High-risk cases constituted 55.4% of the cases (20 cases) and low-risk cases constituted 44.32% (16 cases).

As regards treatment modalities, surgical biopsy was performed in 19.39% of the cases (7 cases), incomplete surgery in 19.39% of the cases (7 cases), and complete surgery in 60.94% of the cases (22 cases).

Chemotherapy; PEB regimen was given to 30 cases (83.1%) and the remaining 6 cases who had no indication for chemotherapy were kept under regular follow-up.

CR was achieved in 83.1% of the cases (30 cases), PR in 5.54% of the cases (2 cases) and DP in 11.08% of the cases (4 cases).

Relapse occurred in 7 cases (23.33%): 4 cases relapsed locally (13.33%) and 3 cases relapsed distantly (10%). Progressed and relapsed cases received palliative radiation therapy and salvage chemotherapy.

Salvage chemotherapy was given to 11 cases (30.47%) and palliative radiation therapy was given to 2 cases (5.54%). Salvage surgery was done to 4 cases (11.08%).

Regarding responses to relapsed and progressed disease, CR was achieved in 2 cases (5.54%), PR in 2 cases (5.54%) and DP occurred in 7 cases (19.39%).

After a median follow up period of 6 years (range 2-10 years); 30 cases were alive disease free (83.19%) and 6 cases had died (16.62%).

As regards overall survival the 5-year, overall survival was 78%. (Fig. 2).

The 5-year survival for non-gonadal sites was 94% and for gonadal sites, it was 45%. The difference was statistically significant (P<0.00001). (Fig. 3).

The 3-year survival for stages I and II was 85%, whereas, the 3-year survival for stages III and IV was 66.7%. The difference was statistically significant (P<0.00001). (Fig. 4).

The 5-year survival for low-risk and high-risk patients was 100% and 45% respectively. The difference was statistically significant (P<0.00001). (Fig 5).

The pretreatment median AFP was 130 (2-39350) and the post-treatment median AFP was 4 (0-932). The difference was statistically significant (p = 0.001).

The pretreatment median BHCG was 7 (0-3400) and the post-treatment median BHCG was 1 (0-4000). The difference was statistically significant (p=0.031).

CR occurred in 17 cases with gonadal site involvement (68%) and in 13 cases with non-gonadal site involvement (86.6%). CR in stages I and II was 85.2% and in stages III and IV it was 66.7% (p = 0.401). CR in low-risk patients and high-risk patients was 100% and 72.7% respectively (p = 0.212). CR for patients who underwent surgical biopsy, incomplete surgery and complete surgery was 75%, 75% and 91.7% respectively (p = 0.602). CR for patients who received chemotherapy to those who did not receive chemotherapy was 72.7% and 100% respectively (p = 0.221).

As regards toxicity grade I neutropenia developed in 80% of the cases, grade II and III neutropenia in 20% of the cases. Grade I anemia in 20% of the cases. Grade I nephropathy developed in 15% of the cases and grade II neuropathy in 10% of the cases. The doses of bleomycin were kept within the maximum allowed tolerance dose and no cases of bleomycin pneumotoxicity were met with throughout the study.

Discussion

Our current study is a retrospective analysis of the treatment results of 36 cases of pediatric germ cell tumors who had attended to the pediatric unit of (NEMROCK) from January 1991 till January 2000.

In the present study, males constituted 44.5% of the cases (16 cases) and females 55.59% of the cases (20 cases) this coincides with the work of Calamenus [11] where males constituted 45% of the cases and females 55%.

We found that the most common pathological subtype was teratoma 44.32% (16 cases), then yolk sac tumor 33.24% (12 cases), followed by endodermal sinus tumor 16.62% (6 cases) and finally mixed germ cell tumors 5.54% (2 cases), this coincides with the work of Billmire [13] in a study carried on 40 patients where yolk sac tumor was found in 7 cases, choriocarcinoma in 2 cases,

endodermal sinus tumor in 5, mixed malignant teratoma in 10, and teratoma in 17 cases.

In our present study extragonadal sites constituted 69.5% of the cases (15 cases) and gonadal sites 30.5% of the cases (11 cases). This contrasts with the work of Neyssa [14] where gonadal sites constituted 69.8% and extragonadal sites constituted 30.2%. This finding is also different from the work of Popaduk where gonadal sites constituted 54% of the cases [15].

In our present study stage, I constituted about 30.47% of the cases, stage II 49.86%, stage III 13.85%, and stage IV 5.54% of the cases. This resembles the work of Lo-curto [16] where stage I cases constituted 41% of the cases, stage II 5.2%, stage III 37.8%, and stage IV 15%.

In our current study adjuvant chemotherapy (PEB) was given to 30 cases (83.1%) for 4 cycles, as in the work of Dimopoulos [9] where PEB was given as standard adjuvant chemotherapy for 4 cycles. Rescorla [17] also administered adjuvant chemotherapy (PEB) for 4 cycles.

CR occurred in 83.1% of the cases, PR in 5.54% and DP in 11.08%. CR was achieved in 100% of low-risk patients and 72.7% of the high-risk patients. This coincides with the work of Bhutani [7] where CR occurred in 71% of the cases, PR in 15% of the cases and DP in 5% of the cases. CR occurred in 95% of the low-risk patients and in 47% of the high-risk patients.

In this study, the overall 5-year survival was 78%. This agrees with the work of Schlatter [8] where the overall 5-year survival was 100%. Kosler [18] also stated in his series that the overall 5-year survival was 86%.

In our present study the 3-year survival for stages I and II was 85% and the 3-year survival for stages III and IV was 66.7%. This goes with the work of Lo-curto [16] where the 3-year survival for stages I and II was 100%, and for stages III and IV it was 53%. The work also goes with the work of Billmire [13] where the 3-year survival for stage I was 95.1%, stage II 93.8%, stage III 65.5% and stage IV 33.5%. Suita [19] also came up with similar figures; where the 3-year survival for stage I was 100%, stage II 63%, stage III 43.1% and stage IV 25%. In our present study, the 5-year survival for non-gonadal sites was 94% and for gonadal sites, it was 45%. This is different from the work of Locurto (16) where the 5-year survival for ovarian and testicular germ cell tumors was 88.2% and 100% respectively. Whereas the 5-year survival for sacrococcygeal germ cell tumors was 69.6% and for other nongonadal sites it was 33%. The low 5-year survival for gonadal sites in our series is due to a small number of patients and an excess of lost follow up of patients.

In our present study grade I neutropenia developed in 80% of the cases, grade II and grade III neutropenia occurred in 20% of the cases. Grade I anemia developed in 20% of the cases. Grade I nephropathy and neuropathy happened in 15% and 10% of the cases respectively. These findings resemble the work of Lim [20] where 20% of the cases developed grade II and III neutropenia, 15% of the cases developed grade I nephropathy. Our findings were also supported by the work of Mann [21] where 30% of cases developed grade I anemia requiring packed RBC'S transfusions. Moreover, portacath sepsis and febrile neutropenia was reported in 1 case and grade I nephropathy in 10% of the cases.

Conclusion

In general, the outcome of treatment of pediatric germ cell tumors is favorable in comparison to other pediatric solid tumors. However, there exists an entity of patients with resistant or relapsing disease which initial adjuvant therapy fails to eradicate. Initial AFP levels, disease stage and primary site involvement and the patient's age are the most important prognostic factors in the analysis of the outcome of treatment and lay the basis of the treatment strategy. Further research is needed to identify those patients early on at the time of diagnosis and to tailor optimum treatment for them as conventional PEB regimen is not enough for these patients and more intensified protocols are required. To finalize issues: prognostic models should allow the stratification of patients for a risk adopted approach to treatment in order to improve the outcome and survival of these high-risk patients.

Careful baseline assessment of the patients for organ reserve for example: the kidney, lungs, and the bone marrow is recommended to avoid any serious acute toxic events which might be fatal. Luckily enough no serious long-term or late effects were reported during the follow-up period after ending treatment.

Fig(1):Frequency of Cases by Site in 36 pediatric germ cell tumors

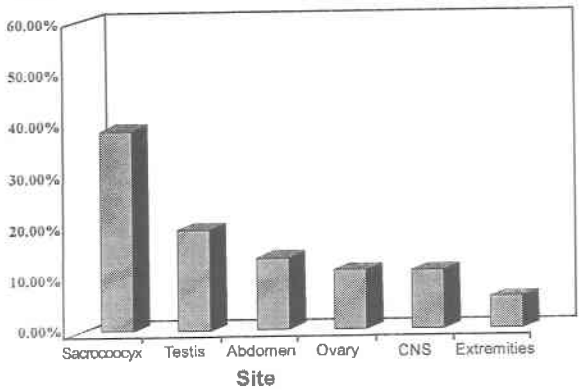


Fig.(2):Total Actuarial Survival of 36 cases of pediatric germ cell tumors.

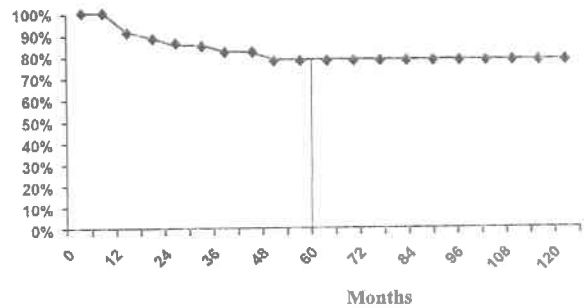


Fig.(3):Total Actuarial Survival of gonadal and non-gonadal sites in 36 cases of pediatric germ cell tumours.

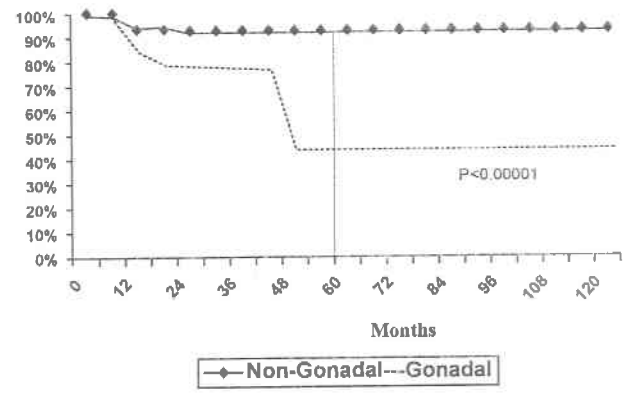


Fig.(4): Total Actuarial Survival by early and late stages in 36 cases of pediatric germ cell tumors

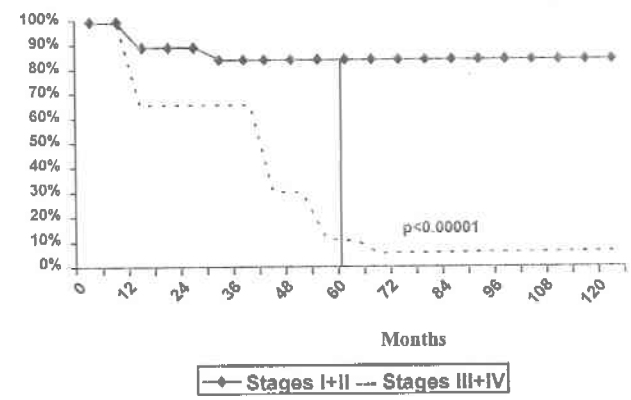
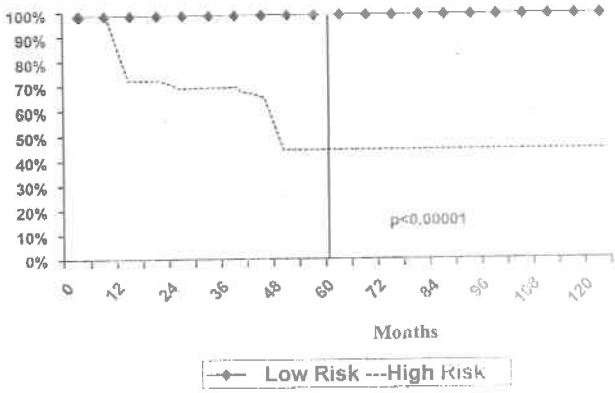


Fig.(5): Total Actuarial Survival of low and high-risk in 36 cases of pediatric germ cell tumors.



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