Original Article

Gynecological malignancies in pediatric and adolescent group: a ten year experience in a national cancer center of Nepal.

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ABSTRACT

Introduction: Gynecological malignancies in pediatric and adolescent group are common. Germ cell tumors and gestational trophoblastic neoplasia are the most frequently found malignancies which are highly chemosensitive. With prompt and appropriate treatment higher cure rate is attainable in such malignancies even in resource constraints country like Nepal.

Objective: To study the clinicopathological profile and treatment outcome of gynecological malignancies among pediatric and adolescent group seeking treatment at B.P. Koirala Memorial Cancer Hospital (BPKMCH), Nepal.

Methodology: Descriptive study was done at BPKMCH Nepal. All available case records of pediatric and adolescent girls diagnosed to have gynecological malignancies from 2002 to 2011 were collected and analyzed in terms of age, clinical features, malignancy types, treatment modalities and outcome.

Results: Total 60 girls were eligible for the study. There were five patients (8.3%) below five years, 14 (23.3%) between 6-12 years and 41 (68.4%) patients between 13-19 years. Gynecological malignancies observed among the study group were: ovarian cancer in 46 (76.66%), gestational trophoblastic disease in 11 (18.33%), uterine cancer in two (3.33%) and vaginal cancer in one (1.66%). Among the ovarian cancers, 42 had malignant germ cell cancer (91.3%), three had epithelial ovarian cancer (6.5%) and one had juvenile granulose cell tumor. The commonest presentation was abdominal distension and pain in 70%. Onset of symptoms ranged from three days to 730 days (mean 95 days). Early stage disease was noted in 18 (30%) and advanced disease in 42 (70%). Eight (13.33%) underwent fertility sparing surgery only, 21(35%) underwent chemotherapy only and 31(51.66%) underwent multimodality treatment. Twenty (33.33%) defaulted and 40 (66.66%) completed treatment among which progressive disease and mortality was recorded in seven (17.5%) patients and 33(82.5%) attended cure.

Conclusion: Malignant germ cell cancer is the commonest gynecologic malignancy among pediatric and adolescent girls. In country where childhood marriage is still prevalent, GTT is also more common among adolescent girls. Early presentation and prompt appropriate treatment would offer chances of cure even with preservation of fertility.

Keywords: Germ cell tumor, Gestational Trophoblastic disease, Gynecological malignancy.

Introduction:

Gynecological malignancies in pediatric and adolescent group are common among which germ cell tumors (GCTs) are the most frequently found malignancies which are highly chemo-sensitive. GCTs are heterogeneous group of tumors that account for 3% of pediatric cancers. Generally, in children age under 15 years GCTs predominantly in female child (M: F: = 0.8:1)[1]. The age distribution of GCTs is bimodal, in which the first peak is seen before the age of one year and the second peak starts along with puberty in adolescence.[2, 3] The incidence of GCTs Have increased in children in western world like United states, Europe and Australia.[4, 5, 6] The reason is not well known. GCTs are assumed to originate from the primordial germ cells in growing embryo in embryogenesis, which migrate along the midline of the body to the gonadal ridge[7-9]. The GCTs in extra gonadal site are believed to form due to failure of proper migration to gonad.[10]

In the pre-chemotherapy era, even localized malignant

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non-germinomatous ovarian GCTs were associated with survival of only 20%. [11] with the advent of platinum based regime for testicular cancer in 1977, there has been dramatically improve on survival [12] and subsequently apply for all extra cranial GCTs in children[13]. Although survival for those with treated with platinum based chemotherapy in early stage GCTs is more than 90%. [14] with the application of similar regime even in resource poor setting survival improved dramatically with higher cure rate. Life threatening late side effects of chemotherapy is the major challenge. Renal impairment, neurotoxocity and hearing loss are well recognized tocities.[15] Recent long term follow up studies of man testicular cancer have shown two fold increase in cardiovascular disease and second malignancy in adult mainly Hodgkin's lymphoma. [16] Theses side effect are not know in pediatric though the therapy are nearly identical.

Aim & Objective:

The aim and objective of this study is to find out the clinic-pathological profile of pediatric gynecological malignancies and their treatment outcome among pediatric and adolescent group (<19 years) seeking treatment at B.P. Koirala Memorial Cancer Hospital (BPKMCH), Nepal from 2002 to 2011.

Method:

This is the descriptive study was carried out at B P Koirala Memorial Cancer Hospital, Bharatpur, Chitwan (BPKMCH) Nepal. All available case records of pediatric and adolescent girls age less than 19 years with diagnosed to have gynecological malignancies from 2002 to 2011 were collected from hospital as well as departmental records. Girls with malignancies from female genital system were included. The diagnosis of inclusion was germ cell tumors like teratomas, embryonal carcinoma, choriocarcinoma, gestational trophoblastic diseases, ovarian epithelial malignancies and other malignancies noted. These children with malignancies were analyzed for their initial symptoms, diagnostic criteria's and categorize and stage according to COG guideline (Table 1). We tried to extract much information as far as possible and revised staging was done on the basis of COG guideline. These malignancies were analyzed in term of age, clinical features, malignancy types, treatment modalities and outcome of these children and adolescence.

Table 1: Pediatric and adolescent GCTs, staging and risk stratification

Testis, ovaries and extra gonadal COG staging			
Staging criteria			
Stage	**Testis**	**Extra-gonadal**	**Ovary**
I	Complete resection: high inguinal or high ligation scrotal orchiectomy and negative nodes	Complete resection at any site with negative margin or coccygectomy for sacrococcygeal teratoma	Limited to ovary (peritoneal evaluation should be negative), no clinical, histological or radiographic evidence of disease outside ovary
II	Trans-scrotal biopsy, microscopic disease in scrotum or cord, or failure of serum tumor markers to normalize	Microscopic residual, with lymph nodes negative	Microscopic residual, peritoneal evaluation negative, failure of serum tumor marker to normalize
III	Retroperitoneal lymph node involvement, but no visceral or extra-abdominal involvement	Lymph node involvement, gross residual disease or biopsy only	Lymph node involvement, metastatic nodule, gross residual disease or biopsy only contiguous visceral involvement (omentum, intestine, and bladder) peritoneal evaluation positive for malignancy
IV	Distant metastases, including liver	Distant metastasis, including liver	Distant metastases, including Liver
COG, Children Oncology Group			

We have categorizes all malignancies in low risk (early stage), intermediate risk (advanced disease) and high risk (distant metastatic disease). Early stage disease underwent surgery and close follow up. Advanced stage disease were manage with neoadjuvent chemotherapy to down stage disease and interval debulking surgery with fertility preservation where as high risk malignancies were treatment with neo-adjuvant chemotherapy, debulking surgery if possible and supportive care along with palliative chemotherapy.

All the patients were getting BEP Regime, Bleomycin 15mg/m2 weekly, Etoposide 100mg/m2 day 1-5, three weekly and Cisplatin 20mg/m2 day 1-5 three weekly. Early staged patients with adequate surgery received four cycles of chemotherapy. If there were any suspicious, further two cycles of chemotherapy was added. In advanced stage group received total six or more cycles of BEP was given evaluating the treatment response. The patients were followed up and findings recorded during the study.

Results:

There were total 1630 children and adolescent diagnosed with cancer during study period. Total of 70 children and adolescent girls were diagnosed with gynecological malignancies which is 4.3%. There were 60 girls eligible for the study. There were five patients (8.3%) below five years, 14 (23.3%) between 6-12 years and 41 (68.4%) patients between 13-19 years. Gynecological malignancies observed among the study group were: ovarian cancer in 46 (76.66%), gestational trophoblastic disease in 11 (18.33%), uterine cancer in two (3.33%) and vaginal cancer in one (1.66%). Among the ovarian cancers, 42 had malignant germ cell cancer (91.3%), three had epithelial ovarian cancer (6.5%) and one had juvenile granulose cell tumor. Among Malignant germ cell tumors immature teratoma (28%), yolk sac tumor (24%), mixed GCT (24%) remained top three ovarian malignancies. Rests were dysgerminoma (15%), epithelial carcinoma ovary 6.5% and granulossa cell tumor 2%. Commonest presentation was abdominal pain and distension in 70% children and adolescent. Only abdominal mass and per vaginal bleeding being next common symptom with 13.33% each. Few presented with only abdominal pain and vomiting only. Most of the patients (55%) reached hospital within two months, 33% between two to six months and 8.3% after six months of initial symptoms. Time of presentation to hospital from onset of symptoms ranged from 3 days to 730 days (mean 95 days). Disease stage at presentation was early stage 18 (30%) and advanced disseminated disease 42 (70%). In treatment modality, eight (13.33%) underwent fertility sparing surgery only, 21(35%) underwent chemotherapy only and 31(51.66%) underwent multimodality treatment. Most of the patients received BEP regime. Patient unable to afford Bleomycin and come weekly received EP Regime. Over all Cure rate among BEP Vs EP was 66% VS 47%. There were 20 (33.33%) dropped out and 40 (66.66%) received recommended treatment among which progressive disease and mortality was recorded in seven (17.5%) patients and 33(82.5%) attended cure.

Diagnosis of ovarian germ cell tumors		
Histology Type	**frequency**	**Percentage**
Immature teratoma	13	28.26%
Yolk sac tumors	11	23.91%
Mixed germ cell tumors	11	23.91%
Dysgerminoma	7	15.21%

Commonest presentation was abdominal pain and distension in 70% children and adolescent. Only abdominal mass and per vaginal bleeding being next common symptom with 13.33% each. Few were present with only abdominal pain and vomiting only.

Table 2: Common Presenting symptoms		
Symptoms	**No. of patients**	**%**
Abdomen pain & distention	42	70%
Abdominal mass	8	13%
P/V Bleeding	8	13%
Abdominal pain	1	1.66%
Vomiting	1	1.66%
Total	60	100%

Most of the patients were (55%) reached to hospital within two months, 33% between two to six months and 8.3% more than six months. Time of presentation to hospital from onset of symptoms ranged from 3 days to 730 days (mean 95 days).

Table 3: Time of presentation after onset of symptoms		
Onset of symptoms	**No of patients**	**Average day of presentation**
Within 2 months	33	34
2 to 6 months	22	112
After 6 months	5	327

Disease stage at presentation was early stage 18 (30%) and advanced disseminated disease 42 (70%). In treatment modality, 8 (13.33%) underwent fertility sparing surgery only, 21(35%) underwent chemotherapy only and 31(51.66%) underwent multimodality treatment. Most of the patients received BEP regime. Patient not affordable for bleomycin and unable to follow up weekly received EP Regime. 33% patient did not complete the recommended course of chemotherapy. Over all Cure rate among BEP Vs EP was 66% VS 47%. There were 20 (33.33%) dropped out and 40 (66.66%) received recommended treatment among which progressive disease and mortality was recorded in seven (17.5%) patients and 33(82.5%) attended cure. But there were no definite schedule follow up for cured children.

Discussion:

The incidence rate for GCTs in childhood in developed countries and adolescence in developed contries was similarly reported from the European and American countries.[17] In contrast to the GCTs in adulthood, which are mostly gonadal and encountered in male subjects,[21] the tumors in childhood were mostly extragonadal and in girls. The ratio of extragonadal/gonadal tumors (58% extragonadal) was equal to the other published ratios.[18] Median age at diagnosis varied according to tumor location, type, and gender, indicating the heterogeneity of the GCTs. The large difference seen in the median age at diagnosis between boys and girls for the gonadal GCTs most likely reflects biological differences. In boys, the germ cells undergo mitotic proliferation before and after birth, where as in unborn girls, the cells are subjected to meiotic arrest and are reactivated only in puberty. Accordingly, the incidence rate of testicular tumors peaked in boys before the age of 2 years and experienced a new rise at the onset of puberty, whereas in girls, the incidence rate of ovarian GCTs started to increase after the age of five years and continued toward puberty and was the highest for 10 to 14 year olds.[18,19,20] For GCTs, the diagnostics have been improved by the introduction of certain biochemical methods and computer tomography in the mid 1980s, which may have led to increased incidence rates in the 1980s.[21]

During the past 35 years, survival rates for children gyenecological malignancies especially with extracranial malignant germ cell tumors (GCTs) have increased significantly. Success has been achieved primarily through the application of platinum-based chemotherapy regimens; however, clinical challenges in GCTs remain[22]. Excellent outcomes are not distributed uniformly across the heterogeneous distribution of age, histologic features and primary tumor site. Despite overall good outcomes, the likelihood of a cure for certain sites and histologic conditions is less than 50%. In addition, there are considerable long-term treatment-related effects for survivors. Even modest cisplatin dosing can cause significant long-term morbidities. A particular challenge in designing new therapies for GCT is that a variety of specialists use different risk stratifications, staging systems, and treatment approaches for three distinct age groups (childhood, adolescence, and young adulthood). Traditionally, pediatric cancer patients younger than 15 years have been treated by pediatric oncologists in collaboration with their surgical specialty colleagues.[22] Adolescents and young adults with GCTs often are treated accordingly. The therapeutic dilemma for all is how to best define disease risk so that therapy and toxicity can be appropriately reduced for some patients and intensified for others. Due to the lack of adequate diagnosis, individualize therapy and lack of other advanced treatment option we are not able to limit the chemotherapy dose[22]. Timely and adequately treated GCTs may increase the cure rate even is developing countries. Regular long term follow up for side effects and long term survivorship follow up programme should be started for it monitoring. Furthermore, multicentric study based on common protocol is necessary to enrich our knowledge in our setting for cutting edges in the management of GCTs. There are other GCTs beyond reproductive organ line in central nerves system, spine and thorax. These tumors are also need especial management protocol for better outcome.

Conclusion:

Malignant germ cell cancer is the commonest gynecologic malignancy among pediatric and adolescent girls. We achieved 82.5% cure rate among those who completed the recommended course of treatment. In our children adolescent peak is higher with almost uniform in other age group. In country where childhood marriage is still prevalent, GTT is also more common among adolescent girls. Early presentation and prompt execution of appropriate treatment would offer chances of cure even with preservation of fertility. Still significant number of patients present at advanced stage (66%) and almost one third of them abandon treatment. Is shows the

serious concern about lack of awareness and discontinue treatment where cure was possible. BEP is the mainstay of treatment and different measure has to taken to minimized chemotherapy dose to avoid toxicity and long term side effects. Only 24% of patient after cure were on follow up. Long term follow up is required to monitor post treatment status and various issues like second malignancies, hormonal disorders, fertility, physical as well as psychological issues.

Acknowledgments:
We would like to acknowledge to all the doctors, nurses, administrative staff who are directly and indirectly involved in this study. I also like to acknowledge the all the children and adolescent who underwent treatment in our centre.

References:

1. Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev. 2010;36 (4): 277–285
2. Schneider DT, Calaminus G, Koch S, et al. Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer. 2004;42 (2): 169–175
3. Poynter JN, Amatruda JF, Ross JA. Trends in incidence and survival of pediatric and adolescent patients with germ cell tumors in the United States, 1975 to 2006. Cancer. 2010;116 (20): 4882–4891
4. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975–2011, Bethesda, MD: NationalCancer Institute. Available at: http://seer.cancer.gov/csr/1975_2011/. Accessed April 15, 2014
5. Kaatsch P, Steliarova-Foucher E, Crocetti E, Magnani C, Spix C, Zambon P. Time trends of cancer incidence in European children (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006;42 (13):1961–1971
6. Baade PD, Youlden DR, Valery PC, et al. Trends in incidence of childhood cancer in Australia, 1983-2006. Br J Cancer.2010; 102 (3):620–626
7. Teilum G. Classification of endodermal sinus tumour (mesoblatoma vitellinum) and so-called "embryonal carcinoma" of the ovary. Acta Pathol Microbiol Scand. 1965; 64(4):407–429
8. Rescorla FJ. Pediatric germ cell tumors. Semin Surg Oncol. 1999; 16(2):144–158
9. Schneider DT, Schuster AE, Fritsch MK, et al. Multipoint imprinting analysis indicates a common precursor cell for gonadal and nongonadal pediatric germ cell tumors. Cancer Res. 2001; 61(19): 7268–7276
10. Oosterhuis JW, Stoop H, Honecker F, Looijenga LH. Why human extragonadal germ cell tumours occur in the midlineof the body: old concepts, new perspectives. Int J Androl. 2007; 30 (4): 256–263; discussion 263–264
11. Kurman RJ, Norris HJ: Endodermal sinus tumor of the ovary: A clinical and pathologic analysis of 71 cases. Cancer 38:2404-2419, 1976
12. Einhorn LH, Donohue JP: Improved chemotherapy in disseminated testicular cancer. J Urol 117:65-69, 1977
13 Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide, bleomycin and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: A pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22:2691-2700, 2004
14. Rogers PC, Olson TA, Cullen JW, et al: Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: A Pediatric Intergroup Study—Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 22:3563-3569, 2004
15. Hale GA, Marina NM, Jones-Wallace D, et al: Late effects of treatment for germ cell tumors during childhood and adolescence. J Pediatr Hematol Oncol 21:115-122, 1999
16. Travis LB, Beard C, Allan JM, et al: Testicular cancer survivorship: Research strategies and recommendations. J Natl Cancer Inst 102:1114-1130, 2010
17. Li J, Thompson TD, Miller JW, Pollack LA, Stewart SL. Cancer incidence among children and adolescents in the United States, 2001-2003. Pediatrics,2008; 121 (6). Available at: www.pediatrics.org/ cgi/content/full/121/6/e1470
18. Ries LAG, Smith MA, Gurney JG, et al, eds. Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995. Bethesda, MD:National Cancer Institute, SEER
19. Castleberry R, Cushing B, Perlman E, et al. Germ cell tumors. In: Principles and Practice of Pediatric Oncology. Philadelphia, PA: Lippincott-Raven; 1997:921–945
20. Pinkerton CR. Malignant germ cell tumours in childhood. Eur J Cancer. 1997; 33 (6):895–901, discussion 901–902
21. Kroll ME, Carpenter LM, Murphy MF, Stiller CA. Effects of changes in diagnosis and registration on time trends in recorded childhood cancer incidence in Great Britain. Br J Cancer. 2012; 107(7):1159–1162
22. Thomas A. Olson, Matthew J. Murray, Carlos Rodriguez-Galindo, James C. Nicholson, Deborah F. Billmire, at al .Pediatric and Adolescent Extracranial Germ Cell Tumors: The Road to Collaboration. J Clin Oncol *J Clin Oncol 33:3018-3028, 2015*