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Malignant Germ Cell Tumours of Ovary

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Germ cell tumours of ovary (MOGCT) are rapidly growing tumours and occur commonly in girls and young women. Prognosis of patients with GCT of ovary has improved significantly over past two decades as a result of the introduction of cisplatin based chemotherapy after initial surgery. Following conservative surgery most patients can anticipate normal menstruation and a reasonable probability of having normal offsprings.

Incidence

Malignant GCT of ovary accounts for 1% of all the malignant tumours in young females and 3 to 6% of all ovarian tumours . The incidence is higher, almost 9% to 15% in developing countries and in Japan[1]. At our institute, MOGCT constitutes 9% of all ovarian tumours. The median age of onset is 20 to 22 years. Approximately, one fifth of these cases occur before menarche. At AIIMS, we have seen 125 patients of MOGCT over 16 years period (1988-2003); 5.6% of patients were below 10 years of age, 48.8% were between 11-20 years, 28% were between 21 and 30 years and 14% were between 31 and 40 years . Clinical Presentation of these patients is shown in table- 1.

Table-1 Clinical Presentation : Experience at AIIMS (n=125)

Duration of symptoms			
Median	:	3 months	
Range	:	6 days to 36 months	
Symptoms	:	**n**	**(%)**
Abdominal pain (n=122)			99(81%)
Abdominal +/-Pelvic lump (n=122)			99(81%)
Acute abdomen (n=121)			13(10.7)
Menstrual abnormalities(n=26)			17(20.0)
Ascitis (n=121)			24(19.8%)
Fever (n=119)			23(19.3%)
Dyspnoea (n=122)			6(5%)

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Diagnostic Work Up and Staging

Although ovarian GCTs are rare, it is important to consider this diagnosis in all young patients suspected of having an ovarian tumour/pelvic mass. Initial evaluation includes - detailed physical examination, haemogram, liver and renal function tests, chest x-ray, ultrasound or CT scan of abdomen & pelvis to determine the disease extent. Serum markers namely serum AFP, serum b-HCG, and serum LDH (Table-2) are important in the diagnosis and subsequent management and should be done in all patients suspected of having MOGCT . Dysgerminoma is the most common subtype (50%), followed by immature teratoma, endodermal sinus tumour, and mixed GCT. Embryonla carcinoma (3.5%) and choriocarcinoma (1.2%) are uncommon subtypes. Serum LDH is not specific to MOGCT , but when raised it is useful in the monitoring treatment of MOGCT patients negative for serum AFP and b-HCG e.g. Patients with metastatic dysgerminoma have elevated serum LDH but negative serum AFP & b-HCG. b-HCG may be elevated in less than 10% of patients with dysgerminoma and is usually less than 100 mIU/ml. If b-HCG is significantly elevated , diagnosis of mixed GCT should be considered. Fine needle aspiration cytology/ biopsy is not useful for the initial diagnosis of these tumours. However, it may be useful in confirming the suspected relapse, in a known case of MOGCT. Radiological studies of the upper and lower intestinal tract are not routinely recommended unless the patient is having symptoms related to the intestinal tract.

FIGO staging similar to epithelial ovarian cancer is followed for MOGCT. In a study at AIIMS , 60(48.8%) had stage I -II, 43(35%) stage III & 20 (16.3%) patients had stage IV disease at diagnosis.

Table-2 Tumour Markers

Histology subtype	B-HCG	AFP	Other
Dysgerminoma	*	-	LDH, CA-125
Endodermal sinus Tum,our	-	+	
Choriocarcinoma	+	-	
Immature teratoma	+/-	+/-	LDH, CA-125
Embryonal carcinoma	+/-	+	
	Normal levels		Half life
B-HCG	0-10 miu/ml		18-24 hrs
AFP	0-5 ng/ml		5-7 days

——AFP - alfa feto protein, B-HCG beta human chrionic gonadotropin
*-10% of patients with dysgerminoma may have elevated serum B-HCG which is usually less than 100 miu/ml. Higher values precludes pure dysgerminoma.

Surgery :

Initial treatment approach for such young patients is surgery which establishes the diagnosis and initiates therapy. The type of primary surgery depends upon the extent of disease. Bilateral ovarian involvement in absence of advanced disease is rare except in dysgerminoma. Therefore, unilateral salpingo-oophorectomy with preservation of contralateral normal ovary and uterus can be performed in most patients, thus preserving fertility. If contralateral ovary appears grossly normal, it should be left undisturbed. If the coontralateral ovary appears abnormal, biopsy or cystectomy should be performed [1]. At our institute, many of such patients are referred after surgery done outside without having adequate staging biopsies. For such patients, unless bulky residual disease is present, based on physical examination and imaging studies, it is our policy to proceed with chemotherapy as soon as possible rather than to resort to re-exploration for the purpose of gaining more precise staging information. If gonadal dysgenesis is confirmed, the risk of tumour (usually gonadoblastoma or dysgerminoma) in the contralateral ovary is high enough to warrant bilateral oophorectomy. In such cases, the uterus should be left 'in situ' for future embryo transfer

Chemotherapy

Because of the rarity of MOGCT, randomized studies have not been performed. Most of the lessons learnt from chemotherapy trials in testicular GCT have been applied to the MOGCT and these have now been validated in smaller studies in MOGCT. A combination of bleomycin, etoposide and cisplatin (BEP) is used widely[2-4] (table-3). Hitchins et al at Charring Cross Hospital-London, have developed - POMB-ACE, an alternative regimen [5]. In this regimen, relatively non myelosuppressive POMB (cisplatinum, vincristine, methotrexate and bleomycin) is alternated with more myelosuppressive , ACE(actinomycin-D, cyclophosphamide and etoposide) keeping the treatment interval between the treatments as short as possible to minimise the risk of drug resistance . They reported an overall survival of 83% at 12 years follow up among 58 patients of stage II-IV , non-dysgerminomatous OGCT. There were no deaths beyond 3rd year of entry into the study.

Table- 3 : Chemotherapeutic Regimens

BEP	Inj. Cisplatin 20 mg/m2 IV day 1-5
	Inj. Bleomycin 10 mg/m2 IV day 1-3
	Inj. VP-16 (etoposide) 100 mg/m2 IV day 1-5
	Q 3 weeks, 3-4 cycles
POMB-ACE	
POMB	
Day1	Vincristine 1 mg/m2 (Max 2 mg) IV bolus
	Methotrexate 300 mg/m2 IV infusion
Day 2	Bleomycin 15 mg IV infusion over 24 hours
	Folinic acid 15 mg at 24, 36, 48, 60 hours after methotrexate
Day 3	Cisplatin 120 mg/m2 IV infusion over 12 hours
ACE	
Day1	Etoposide 100 mg/m2IV infusion
	Actinomycin –D 0.5 mg IV bolus
Day 2	Etoposide 100 mg/m2IV infusion
	Actinomycin –D 0.5 mg IV bolus
Day 3	Etoposide 100 mg/m2IV infusion
	Actinomycin –D 0.5 mg IV bolus
	Cyclophosphamide 500 mg/m2 in 250 ml NS over 30 minutes.

William et al for the GOG have reported the results of adjuvant chemotherapy with BEP regimen; 93 patients with nondysgerminomatous MOGCTs with nil residual disease (stage I-III) received 3 cycles of BEP. At a median follow up of 38.6 months, 91 patients were alive and disease-free[4].

Chemotherapy for Germ Cell Tumours other than Dysgerminoma

Our policy is to give 3 cycles of adjuvant BEP chemotherapy to all patients with stage

I,II and completely resected stage III disease. The only exception is stage I, grade-I immature teratoma (table-4) patients who are followed up after surgery without adjuvant chemotherapy. Patients on adjuvant chemotherapy are followed up for any recurrence with periodical check up, ultrasound scan of abdomen and pelvis and serum marker studies.

Table-4 : Histologic Grading of Ovarian Immature Teratomas

Grade	Microscopic Appearance
0	Mature tissues only
1	Mainly mature tissue, but some immature tissue present. Neuroepithelium limited to 1 low power field per slide.
2	Moderate amount of immature tissue present. Neuroepithelium occupies 1 to 3 low power fields per slide.
3	Abundant immature tissue. Neuroepithelium occupies 4 or more low poer fields per slide.

Patients with advanced disease i.e. incompletely resected stage III and IV disease receive 4 cycles of BEP followed by assessment. Patients found to have complete response (CR) (no clinical, biochemical or radiological evidence of disease) are advised regular follow up. Patients with normal marker studies (who had elevated serum AFP +/- HCG at diagnosis) but with evidence of residual lesion of <3 cm size on imaging are advised 2 more cycles of chemotherapy and then follow up. Patients with elevated markers with gross residual tumour on clinical and radiological studies are advised laparotomy for debulking surgery. Those found to have evidence of disease on histopathology are advised salvage chemotherapy. Patients with evidence of mature teratoma or fibrosis are advised follow up after excision of the mass.

Dysgerminoma

The initial management of these patients is resection of the tumour and biopsy of any suspicious lesion in the contralateral ovary to rule out involvement. Similar to seminoma in males , dysgerminoma is radiosensitive and have higher propensity for retroperitoneal lymph node involvement. Till recently , most patients with early stage dysgerminoma have been treated with postoperative radiotherapy. However, since pelvic radiotherapy is likely to be associated with ovarian failure and sterility , the concept of observation after complete resection of stage IA disease has been developed[6]. Such patients will require careful follow up as in 15% to 25% of patients tumour will recur after unilateral oophorectomy. If regular follow up can not be ensured, it is better to treat them with 3 cycles of adjuvant BEP chemotherapy, if fertility is to be preserved or with adjuvant radiotherapy for those who have completed their family. Treatment guidelines are given below.

Table-5 : Malignant Germ cell tumours of ovary : Treatment Guidelines

Stage	Histology	Residual Disease	Treatment
I to III	Non dysgerminoma (Endodermal sinus Tumour MIxed GCT, Embryonal, Choriocarcinoma)	Nil or ≤ 1Cm	BEP: 3 cycles
III to IV	Any of above	≥ 1 Cm	BEP: 4 cycles
IA, grade I	Immature teratoma	Nil	Observation
IA, grade II-III, & IB-III	Immature teratoma	Nil or ≤ 1 Cm	BEP: 3 cycles
III-IV	Immature teratoma	≥ 1Cm	BEP: 4 cycles
IA	Dysgerminoma	Nil	Observation
IB to III	Dysgerminoma*	Nil or ≤ 1 Cm	BEP: 3 cycles
Any stage	Dysgerminoma	≥ 1 Cm	BEP: 4 cycles

Patients who have completed family and not willing for chemotherapy can be considered for radiotherapy.

Treatment of Relapse

About 10-20% of patients with advanced GCT of ovary relapse after achieving CR. Most relapses occur within two years of treatment and late relapses are rare . Patients who have relapsed after prior treatment with radiotherapy or VAC (vincristine, actinomycin-D and cyclophosphamide) regimen may respond to cisplatin based combination. Patients relapsing after PVB or BEP may respond to ifosphamide based chemotherapy with CR rate of 25-30%[7] . Some patients with platinum resistant/ refractory disease may even respond to high dose chemotherapy supported with autologous bone mar-

row/ peripheral blood stem cell transplantation. Occasional patient with immature teratoma who relapse after PVB or BEP have responded to VAC chemotherapy .

Follow Up

Similar to patients with epithelial ovarian cancer, we follow these patients in outpatients clinic once in 4-6 weeks during the first year, 2 -3 monthly during the second year and every 6 months during the 3rd year and then once in a year indefinitely. On each visit a detailed physical examination is done. Serum markers are repeated once in 2 -3 months during first 2 years then once in 6 months till 5 years. US scan of abdomen and pelvis is repeated once in 6 months till 3 years then once a year till 5 years. The risk of relapse after 3 years is rare.

Reproductive Functions

Preservation of fertility in these young patients is an important issue. A number of studies have reported successful outcome i.e. normal fertility following chemotherapy in these young patients in whom preservation of contralateral ovary and uterus was carried out. In our study , all 17 patients who had an intact contralateral ovary, tube and uterus have resumed menstruation. Thirteen patients who attempted pregnancy succeeded and have delivered 17 healthy babies, although one patient had a spontaneous abortion and another had vesicular mole. These and similar observations by other investigators [8-10] support the view that likelihood of retaining fertility after chemotherapy is reasonably good..

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