J Obstet Gynecol Ind Vol. 54, No. 2 : March/April 2004 Pg 162-166

Pure Dysgerminoma of Ovary : 11 Years Experience

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OBJECTIVE – To study the effect of conservative surgery and adjuvant combination chemotherapy in management of pure dysgerminoma of ovary. **METHODS** – This is a retrospective analysis of 22 patients having pure dysgerminoma of the ovary studied over a period of 11 years (January 1992 – December 2002). Nine patients were surgically staged and 16 had fertility preserving surgery. BEP (bleomycin, etoposide, cisplatinum) regimen was given postoperatively and response evaluated. **RESULTS** – Mean age of the patients under study was 20 years; six of them were premenarchal. According to the surgical staging, out of the nine two were in Stage-Ia, three in Stage-Ic, one in Stage-IIb, two in Stage-IIIb, one in Stage-IVb. Common toxic effects noted were nausea, vomiting and neuropathy. Followup ranged from 7 to105 months. 13.6% were lost to follow-up. 86.4% were disease free. Sixteen patients had fertility preserving surgery of which five were premenarchal (four of the five achieved menarche during follow up period) and one was lost to follow up. Of the remaining ten patients, nine resumed normal periods. **CONCLUSION** – Fertility preserving surgery followed by adjuvant combination chemotherapy with BEP is adequate in the management of pure dysgerminoma of the ovary.

Key words : dysgerminoma of ovary, fertility preserving surgery, combination chemotherapy

Introduction

Germ cell malignancies of the ovary are basically tumors seen in patients during the first and second decades of life, of which a large portion are seen in prepubertal girls. They constitute approximately 10% of all ovarian malignancies. Dysgerminoma, one of the subtypes of germ cell tumors of the ovary, represents only 3-5% of ovarian tumors. Dysgerminoma is the female equivalent of seminoma. It differs from its non-dysgerminomatous counterpart in several aspects. Firstly, it is more likely to be localized to the ovary at the time of diagnosis viz; in 75% of cases. They also have a propensity to occur in dygenetic gonads. Bilateral involvement of ovaries seen in 10-15% is more common compared to other germ cell tumors, which are mostly unilateral. The principal mode of transmission is nodal rather than transperitoneal and lastly it is extremely sensitive to radiotherapy[1,2]. Due to exquisite radiosensitivity of this tumor, the earlier recommendation for therapy after surgical removal of the tumor was postoperative radiotherapy for all patients with primary disease as well in patients with metastasis and recurrent disease. High cure rates were reported. However, abdominopelvic radiations, even with the rather low doses employed in such cases was associated with ovarian failure and sterility. Chemotherapy has been developed as an alternative treatment that could produce equivalent results in low stages and superior survival rates in metastatic disease while preserving the reproductive capacity[3].

The evolution of combination chemotherapy in treating germ cell malignancy resulted in overall disease free survival rates of greater than 90%[4]. In the present study we have described our experience of BEP (bleomycin etoposide and cisplatimum) regimen in 22 patients having pure dysgerminoma of ovary.

Material and Methods

This is a retrospective analytical study of 22 patients having pure dysgerminoma of ovary evaluated over a period of 11 years from January 1992 to December 2002. All cases had histologically proven pure dysgerminoma of ovary. Initial evaluation of each patient included the history, detailed physical examination, investigations such as hemogram, renal and liver function tests and tumor markers mainly-serum LDH, α-FP and β-HCG. Radiological investigations included x-ray chest and ultrasonography.

Proper treatment plan was decided upon. The type of surgery to be performed, whether conservative or radical, along with proper staging laparotomy was planned. If operated elsewhere and then referred to us, operative details and slides and blocks of the specimens removed were requested. Histology was again reviewed at our institute. Residual disease was documented according to the operative details and also from physical and ultrasound examinations. The following protocol was employed for chemotherapy with BEP regimen –

Paper received on 25/09/03 ; accepted on 26/11/03

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Injection bleomycin 15mg IV / IM weekly (total 12 doses)
Injection etoposide 100mg / m^2 IV day 1 to 5 every three weeks
Injection cisplatinum 20mg / m^2 IV day 1 to 5 every three weeks.

Prior to each cycle of chemotherapy, a complete blood count, blood urea, serum creatinine, serum bilirubin, SGPT level and tumor markers estimation were carried out. Therapy was delayed if neutrophils were lower than 3000 / mm^2 and platelets lower than 1,00,000 / mm^2. Patients having hemoglobin lower than 9gm were given transfusion along with chemotherapy. Toxicity of chemotherapy was evaluated and treated accordingly.

After completion of chemotherapy, all patients were evaluated at two monthly intervals for one year and at gradually increasing intervals thereafter. At each visit, they underwent physical examination and serum LDH estimation. Radiological assessment was done periodically and as and when required. Menstrual status was evaluated during and after completion of chemotherapy. Follow-up information was obtained up to December 2002.

Observations

Age - The age of the patients ranged from 9 to 37 years (median age 20 years). Seven patients (31.8%) were below 15 years of age.

Menstrual status and pregnancies – Six women were premenarchal and remaining 16 had normal periods. Among these 16, 11 were married, 9 of whom had two or more children.

Surgery – Thirteen patients were operated elsewhere and referred to us for further management. They were considered unstaged as no proper staging laparotomy was performed in them. Out of these 13 patients, 10 had tumor removal only (unilateral salpingo-oophorectomy) and 3 had total abdominal hysterectomy with bilateral salpingo-oophorectomy. In one of these patients, an ovarian mass was diagnosed during cesarean section whereupon, the tumor was removed (Table I).

Table I : Surgery

Type of Surgery	Operated elsewhere And Unstaged	Operated and Staged by us
No. of patients	13	9
Fertility preserving surgery	10	6
TAH and BSO[a]	3	3

[a]TAH and BSO – Total abdominal hysterectomy and bilateral salpingo-oophorectomy

Nine patients who were referred to us without any treatment underwent staging laparotomy. Staging laparotomy included meticulous exploration of the whole abdomen, four-quadrant cytology, tumor removal, infracolic omentectomy and retroperitoneal node dissection. Of these nine patients, six had fertility preserving surgery. Out of these six, two were in Stage Ia and one each in Stage Ic, stage IIb, stage IIIb and stage IVb. The patient in stage IVb had a supraclavicular node positive for metastasis. Yet she had fertility preserving surgery as her opposite ovary and uterus were normal. In the remaining three of the nine patients who were operated and staged, two had total abdominal hysterectomy and bilateral salpingo-oophorectomy as their childbearing was complete. They both were in stage Ic (Table II). One out of these three patients presented with a huge pelvic mass. On exploration, the huge mass was present in the pelvis and no pelvic structure were separately identifiable. Hence enbloc removal of the whole mass along with the uterus and ovaries was performed. She also had large paraaortic nodes engulfing the inferior vena cava, which were not resectable and not removed. She was in Stage IIIc. All nine patients had undergone lymphadenectomy. Three patients had residual disease (two had > 2cm disease).

Table II : Stage of the Disease

Stage N=9	No. of Patients
Stage Ia	2
Stage IIc	3
Stage IIb	1
Stage IIIc	2
Stage IVb	1

Thirteen patients were operated elsewhere and unstaged.

Chemotherapy – All the 22 patients were given BEP regimen postoperatively. They received three or six courses of chemotherapy depending upon the stage, response and toxicity. Thirteen patients who were operated elsewhere and were unstaged received chemotherapy. Of the nine patients in whom staging laparotomy was performed, seven had more than stage II disease and hence were given chemotherapy, while two had stage Ia disease, yet were given chemotherapy as they had very large size tumors (>10cm) and their serum LDH levels were very high.

Toxicity – All patients were evaluated for toxicity. The common side effects were nausea, vomiting and alopecia seen in all the patients. All patients experienced grade I and II type nausea and vomiting, which were managed by antiemetics and intravenous fluids. Neutropenic fever occurred in one patient for which higher antibiotics were given and chemotherapy was postponed for a week.

Cisplatinum induced peripheral neuropathy was seen in one patient after the 4th course and cisplatin induced autotoxicity was seen in another patient after the 3rd course of chemotherapy. In both these patients, cisplatinum was omitted thereafter. Abnormal skin pigmentation due to bleomycin toxicity was seen in one patient after the 4th course of chemotherapy; bleomycin was omitted thereafter in this patient. In all the above patients the toxicity regressed after omission of the drug and there was no permanent damage. One patient developed jaundice after the 1st course of chemotherapy (raised liver function tests). BEP was omitted for nearly one month. But thereafter she was given further course of chemotherapy in same doses without liver damage.

One patient had high-grade fever with swelling in right iliac region after the 2nd course of chemotherapy. As the swelling persisted after antibiotics, she was explored through a right extraperitoneal approach to rule out recurrence. The removed tissue revealed only old infected hemotoma. She was given two more courses of chemotherapy.

Amenorrhea and oligomenorrhea occurred during chemotherapy in menstruating patients. There was no life threatening infection or drug related death in our series.

Results

All the patients were analysed in December 2002. Of the nine patients, who were operated and staged, eight had complete response and are disease free. One patient had partial response (rise in serum LDH levels). She was the one having a paraaortic node engulfing the inferior vena cava. She was then radiated over both pelvic and paraaortic regions. Postradiation she achieved remission and the node disappeared. Thus, all the nine patients were disease free. Of the 13 unstaged patients, 10 achieved complete response and were disease free. Three patients had partial response, of whom two were lost to the follow up without further treatment and one was given radiation to the pelvic region. Postradiation, she had residual disease for which she was advised re-exploration but she refused it and was lost to follow up. Thus 10 out of the 13 patients were disease free (Table III).

Table III : Results

	No. of patients	Response to chemotherapy		Radiation to partial responders	Disease free
		Complete	Partial		
Operated and staged	9	8	1	1	9
Operated but unstaged	13	10	3[a] 2-LIF[c]	1 (Residual disease)	1

[a] Two of those three were lost to followup without further treatment while the third one had residual disease despite radiation, refused re-exploration and was lost to follow up.

[c] LIF = Lost to follow-up without further treatment

Follow-up: Follow-up ranged from 7 to 105 months with a median of 24 months. Two (9%) patients were lost to follow up with incomplete treatment. One patient had residual disease (4.5%) after both chemotherapy and radiotherapy. Nineteen of the 22 patients (86%) were disease free. Of these, 18 achieved complete response with chemotherapy alone and one required additional radiotherapy to achieve complete response. Five patients had less than one year follow up, 12 had 1 to 5 years follow up and two were followed for more than five years (Table IV).

Table IV : Number of disease free patients at last follow-up

Follow-up	No. of patients
< 1year	5
1-5 years	12
> 5 years	2

Two patients were lost to followup and have residual disease despite chemotherapy and radiotherapy.

Menstrual Status- Of the 16 patients who had fertility preserving surgery, one was lost to follow-up. Five were premenarchal of which four achieved menarche in the follow-up period. Of the remaining 10 patients, who were in childbearing age, 9 resumed normal periods.

Discussion

The evolution of treatment for malignant germ cell tumors has been one of the true success stories in oncology. Before combination chemotherapy was introduced in the mid – 1960s, the prognosis for patients with malignant germ cell tumors of the ovary was very disappointing. The successful introduction of cisplatinum into clinical trails for advanced stage testicular seminoma subsequently prompted investigators to use cisplatinum based regimen in patients with metastatic ovarian dysgerminoma[3].

In the early 1970s, the combination of vincristine, dactinomycin and cyclophosphamide (VAC) emerged as a standard therapy for the treatment of germ cell tumors of the ovary. In 1977, the combination of vinblastine, bleomycin and cisplatinum (VBP) for treating patients with testicular cancers was reported. Subsequently the efficacy of VBP in treating ovarian germ cell tumors was reported[4,5]. In 1977, etoposide (VP 16) was initially found to have single agent activity in patients with refractory testicular cancer. In a multi-institutional randomized trial, it was reported that compared with VBP regimen, the combination of bleomycin, etoposide and cisplatinum (BEP) showed equal efficacy but was less toxic in patients with testicular cancers[4]. Hence chemotherapeutic regimen has evolved to the current combination of BEP regimen with overall disease free survival rates greater than 90% and low toxicity. The late effects of the treatment revealed that reproduction potential can be preserved in most young patients[6].

Malignant ovarian germ cell tumors usually affect girls and young women. They are highly malignant and rapidly growing. They are commonly divided into two main groups – dysgerminomas and non-dysgerminomas. In contrast to epithelial ovarian cancers, they are rare, commonly present at an early stage and usually confined to one ovary. They respond well to initial chemotherapy. They frequently produce tumor markers that may be helpful in the initial management and follow up[1,6]. Dysgerminoma, a subtype, represents only 1-3% of all ovarian cancers and 5-10% of ovarian cancers in patients younger than 20 years of age. Seventy-five percent of dysgerminomas occur between the age of 10 and 30 years; 5% under the age of 10 years. They rarely occur over the age of 50 years[2]. In our series, the mean age was 20 years. These results are comparable with those of Culine et al[3] (median age 22 years) and Pao-Chen et al[7] (18.6 years).

Sesum LDH is a potentially useful tumor marker for dygerminoma of ovary. It was raised in all the patients in our series. It is also seen that 5% of dysgerminoma of the ovary may contain significant numbers of syncytiotrophoblastic cells which can be hormonally active causing elevated serum β-HCG levels. In our study, three of 22 patients had raised β-HCG levels. Culine et al[3] also reported elevation of β-HCG in three of 12 patients of dysgerminoma of ovary.

All young patients desirous of childbirth, regardless of stage of the disease are candidates for fertility preservation unless the contralateral ovary or uterus is invaded by the tumor. In patients with stage II or higher disease thorough cytoreductive surgery including omentectomy and retroperitoneal lymphadenectomy should be performed to minimize tumor burden and maximize the effectiveness of adjuvant chemotherapy, even though the opposite ovary and the uterus is preserved. In patients whose fertility need not be preserved, it is appropriate to perform a total abdominal hysterectomy and bilateral salpingo-oophorectomy. In our series, 16 of the 22 patients had fertility preserving surgery. This is comparable with the series of Culine et al[3], who had performed salpingo-oophorectomy in 10 out of 12 patients. All the nine patients operated and staged in our series, had undergone retroperitoneal lymphadenectomy as dysgerminoma of the ovary is known to spread via the lymphatics. Of the nine patients, three had nodal metastasis and hence were upstaged (two to stage IIIc and one to stage IVb). This indicates that retoperitoneal lymphadenectomy must be performed in dysgerminoma of the ovary.

All the 22 patients in our series were given BEP regimen postoperatively. Of these, two patients were in stage 1a, yet they received chemotherapy as they had large size tumors of more than 10 cm and high serum LDH levels. Thomas et al[2] (1987) stated that a tumor more than 10 cm in size needs initial aggressive therapy as expected rate of relapse in such patients is as high as 14%.

The commonest toxicity seen in our series was nausea, vomiting and alopecia. No death occurred. Culine et al[3] also reported minimal toxicity. The common side effect of chemotherapy as reported by Kumar et al[8] were nausea, vomiting, myelosuppression, fever, mucosities, diarrhea and alopecia. One patient died due to chemotherapy toxicity.

In our series, 19 of 22 patients were disease free with a median follow-up of 23 months. Eighteen patients were disease free with chemotherapy alone and one patient required additional radiotherapy to achieve cure. In Culine et al's[3] study of 12 patients, nine had complete response. In Pao-Chen et al's[7] series, of 28 patients of malignant germ cell, 22 achieved sustained remission. In the study of Kumar et al[8], 17 patients with germ cell tumors of ovary were treated with primary post-operative chemotherapy (PVB regimen). Eleven patients had complete response and were disease free. In a report of the Gynecologic Oncology Group (GOG), 19 of the 20 patients remained free of disease with a median follow up of 26 months[9]. A Hellenic Co-operative Oncology Group[10] studied 53 patients of germ cell tumors of ovary over a period of 14 years. Thirteen of their patients had dysgerminoma. They were given platinum based chemotherapy and five years survival was 100% in patients of pure dysgerminoma of ovary treated with chemotherapy and surgery.

Menstrual status was evaluable in 15 patients only (out of 19 patients who were disease free, four had hysterectomy). Of these 15 patients, five were premenarchal, four of whom achieved menarche. In the remaining 10 patients in childbearing age, nine resumed normal periods and one of these is currently 6 months pregnant. In Culine et al's[3] series four patients who had conservative surgery and adjuvant chemotherapy resumed normal menstrual function. In Pao-Chen et al's[7] study, menstrual function was normal in 19 of the 22 patients achieving persistent remission after treatment. In El-lamie et al's[6] study, 13 patients who had undergone conservative surgery resumed normal menstrual function after receiving BEP regimen and three became pregnant. Hence they stated that conservative fertility sparing surgery followed by cisplatinum based combination chemotherapy in the form of BEP regimen is an efficient treatment for young patients of malignant germ cell tumors of ovary without causing long term impairment of ovarian function or of subsequent pregnancy.

Thus, the literature and our data indicate that preservation of fertility with adjuvant chemotherapy does not jeopardize the outcome of the patients with dysgerminoma of the ovary. BEP in these patients remains the clear choice. Hence, chemotherapy should replace postoperative radiation in these patients for whom adjuvant therapy is considered. We would like to add that the current trend is not to offer chemotherapy without surgical staging and to treat patients with stage Ia disease without chemotherapy.

It is important that therapy of dysgerminoma of ovary be optimized because of the young age of the affected patients and the threat to fertility that therapy may pose. Although radiotherapy is an effective treatment for dysgerminoma of the ovary, BEP regimen has been found to be an effective alternative therapy, as the former treatment leads to ovarian failure and infertility due to radiation. BEP regimen not only has superior survival rates in low stages but also in advanced metastatic disease while preserving the reproductive capacities. With better understanding of dysgerminoma of ovary and availability of effective tumor markers, conservative surgery followed by combination chemotherapy offers a chance for preservation of fertility without compromising the chance of cure.

Reference

1. Williams SD, Gershenson DM, Horowtiz CJ et al. Ovarian germ-cell Tumors. In: Hoskins WJ, Pereza d CA, Young RC eds. Principle and Practice Of Gynecologic Oncology 2nd ed. New York. *Lipincott Raven Publishers. 1997:987-99.*
2. Thomas GM, Dembo AJ, Hacker NP et al. Current Therapy for dysgerminoma of the ovary. *Obstet Gynecol 1997;70:268-75.*
3. Culine S, Lhomme C, Kattan J et al. Cisplatin-based chemotherapy In Dysgerminoma of Ovary:Thirteen-year experience at The Institute Gustave Roussy. *Gynecol Oncol 1995;58:344-8.*
4. Gershenson DM. Update on malignant ovarian germ cell tumors. *Cancer supplement 1993;71:1581-90.*
5. Gershenson DM, morris M, Cangir A et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide and cisplatin. *J Clin Oncol 1990;8:715-20.*
6. El-lamie IK, Shehata NA, Abou-Loz SK et al. Conservative surgical management of malignant ovarian germ cell tumors: The experience of the gynecologic oncology unit at Ain Shams University. *Eur J Gynecol Oncol 2000;21:605-9.*
7. Pao-Chen W, Rong-Li H, Ljing-He L et al. Treatment of malignant ovarian germ cell tumors with preservation of fertility: A report Of 28 Cases. *Gynecol Oncol 1991;40:2-6.*
8. Kumar L, Bhargawa VL, Kumar S. Cisplatin, vinblastine and bleomycin in advanced and relapsed germ cell tumours of ovary. *Asia-Oceania J Obstet Gynecol 1993; 19:133-40.*
9. William SD, Blessing JA, Hatch KD et al. Chemotherapy of Advanced Dysgerminoma : Trial of the Gynecologic Oncology Group. *J Clin Oncol 1991; 9: 1950-5.*
10. Dimopouos MA, Papadopoulou M, Andreopoulou E et al. Favorable Outcome of Ovarian Germ Cell Malignancies Treated with Cisplatin or Carboplatin-Based Chemotherapy: A Hellenic Cooperative Oncology Group Study. *Gynecol Oncol 1998; 70:70-3.*