Review article
UDC:616-006:612.627:615.07

Omer M. DEVAJA
Andreas J. PAPADOPOULOS

Current management of immature teratoma of the ovary

ABSTRACT

Malignant germ cell tumors of the ovary are relatively rare and represent about 20% of all ovarian tumors, but represent also 60% of ovarian neoplasms in children and adolescents. Beeing highly curable by chemotherapy, these types of cancer had inspired enormous effort in designing best possible treatment protocols. This article aims to summarize the developments in this field and discusses the future prospects.

Key words: *Teratoma of the ovary; Malignant germ cell tumors; Chemotherapy regimens; Toxicity; Fertility*

Archive of Oncology 2000,8(3):127-30©2000, Institute of Oncology Sremska Kamenica, Yugoslavia

GUYS AND ST. THOMAS' HOSPITALS, LONDON, UK

Germ cell tumors (GCT) are composed of a number of histologically different tumor types derived from the primitive germ cells of the embryonic gonad. Teratomas are histological subgroup of germ cell tumors, originating from primordial germ cell. According to WHO Classification (1) they are further subdivided into several groups (Table 1).

Table 1. WHO histological classification of teratomas

Immature teratoma	
Mature teratoma	Solid, cystic, fetiform with secondary tumor formation
Monodermal	Struma ovarii, carcinoid, insular, trabecular strumal carcinoid, mucinous carcinoid, neuroectodermal tumors, sebaceous tumors

Benign mature teratoma (dermoid cyst) is the most common benign tumor in young age, but malignant version (immature teratoma) is uncommon tumor comprising less than 1% of teratomas of the ovary. Immature teratoma has specific age incidence, occurring most commonly in first two decades of life (2,3). Overall malignant germ cell tumors (MGCT) are relatively rare and represent about 20% of all ovarian tumors, but in children and adolescents more than 60% of ovarian neoplasms are of germ cell origin. MGCT are one of the highly curable types of cancer and this fact has inspired enormous effort in designing best possible treatment protocols. Whilst it is gratifying to see overall survival curves showing excellent results, there are still subgroups in which recurrences are still common, and some patients receive curative chemotherapy that is unnecessarily toxic compromising fertility and causing damage to the heart, lungs and second cancers. Unfortunately, rarity of these tumors makes almost impossible to adequately compare various chemotherapy regimens, and none of the currently used regimens have been tested in randomized controlled trial setting. This makes it difficult to decide the optimal treatment for this particular group of tumors. This paper aims to give an objective overview of possible treatments for immature teratoma.

Although this review will be concentrating on chemotherapy, it is important to stress that surgery is still an integral part of treatment of all MGCT. The role of surgery is in adequate staging and histologic diagnosis of the disease, which is the foundation of the adequate treatment. With high chemosensitivity of these tumors and the fact that they are almost exclusively unilateral (except Disgerminoma 10-20% bilateral) initial surgery should be conservative, preserving uterus and contralateral ovary in all patients in the reproductive age. It is not absolutely clear but it seems that patients with stage I grade 1 can be treated with surgery alone. In the study published by Norris et al. (4), they reported 14 patients with stage I grade 1 treated with surgery alone. In this group only one patient developed recurrence which was successfully treated subsequently with chemotherapy. Staging investigation in suspected MGCT should include CT/MRI scan of abdomen and chest and role of lymphadenectomy (pelvic and paraaortal) is still controversial. Probably CT scan could select patients with suspicious nodes which require sampling for staging purposes. Tumor markers (a-feto protein AFP, b-HCG, lactate dehidrogenase LDH, neuron specific enolase NSE) can be of great help in diagnosis and even more important in follow up and assessment of response to the treatment of MGCT. The initial level of tumor markers is probably of less importance than the rate of decline and eventual normalization. A slow decline may reflect relative chemoresistance, and persistent elevation is usually due to persistent active tumor, which requires surgical treatment, second line chemotherapy or irradiation. It is important to bear in mind that some MGCT are tumor marker negative. Only approximately one third of immature teratomas have raised AFP, and they are usually negative for other tumor markers (5-8). Nevertheless, the presence of a-fetoprotein raises the possibility of a mixed germ-cell tumor. In tumor marker negative group clinical examination and imaging techniques are required for follow up. Patients left with residual tumor after surgery are in higher risk of recurrence and have the worst prognosis. Dysgerminomas are highly radio sensitive tumors and rest of MGCT are less sensitive, because of diverse effect on fertility, radiotherapy (RT) is abandoned as a first line treatment in most cases. However, RT may be unavoidable where there is residual measurable tumor after second-line chemotherapy and surgery for relapsed disease.

Few papers addressed chemotherapy for immature teratoma separate from other MGCT, and chemotherapy for this particular tumor is usually the same as for the other MGCT. However there are some differences which will be discussed in this review. In the literature various chemotherapeutic protocols have been described in treatment of immature teratoma. In this article we will be summarizing only chemotherapy regimens tested in relatively large series of patients. Major improvements in results came in 1980´s when cis-platin was included in chemotherapy for MGCT, but before

Address correspondence to:
Dr Omer Devaja, Guys and St. Thomas' Hospitals, Lambeth Palace Road, London, SE1 7EH, UK

The manuscript was received: 12. 04. 2000.

Provisionally accepted: 14. 04. 2000.

Accepted for publication: 21. 04. 2000

cis-platin most commonly used drugs were Vincristine, Actinomicin-D and Cyclophosphamide (VAC regimen). Although there were some differences in VAC regimen in published data, it seems that high dose VAC regimen (Table 2) (9) had good results in the treatment of Stage I MGCT (5,10-12). Unfortunately, this regimen was not as efficient in higher stages and recurrences were common in this group of patients (13).

Table 3. Stage and survival of patients with Immature teratoma

Stage	No. of patients	Alive
I	4	4
II	4	4
III	5	3
IV	5	3

Table 2. VAC regimen

Vincristine	1.5 mg/m^2 iv weekly for 10-12 wk (max.dose 2.5mg)
Actinomicin-D	0.5 mg iv qd x 5 (repeat every 28 days)
Cyclophosphamide	6 mg/kg iv qd x 5 (repeat every 28 days)

iv = intravenous; qd = every day

Schwartz et al. (9) recommended 6 courses of VACchemotherapy followed by second-look operation in tumor marker negative group and the tumor marker positive group should be treated until the tumor markers were back to normal level. In their published results they had 6 immature teratomas (5 stage I and 1 stage III) and after the treatment with VAC all patients had no evidence of disease 34-82 months later, and all patients received more than 6 courses of chemotherapy (between 8 and 18 courses). The largest case series on immature teratoma only using VAC was published by Gershenson (5). They reported 41 patients out of which 16 were treated with surgery alone (11 stage I and 5 stage III). Fifteen of 16 patients treated with surgery alone developed recurrent disease and 11 survived after subsequent chemotherapy, only one patient was stage I grade 1 who also recurred after treatment with surgery alone. Twenty one patients received VAC protocol, 2 had RT and 2 patients received chemotherapy with Doxorubicin + Cyclophosphamide and Actinomycin-D, 5-flurouracil Cyclophosphamide (AcFuCy protocol). Twenty nine of the 41 patients (71%) were long term survivors. Ten patients died of tumor and two died of leukemia. In their series patients received between 12-18 cycles of VAC regimen. The published data it suggest that patients with stage I grade 2 & 3 and higher stages run a high risk of recurrence which justifies the use of adjuvant chemotherapy in this group of patients. However, it is unclear which therapy and how many cycles would give the best balance between efficacy and toxicity.

As it was already mentioned, the major improvement in terms of response and survival was inclusion of cis-platin in regimens for MGCT. One of the first regimens with cisplatin was reported by Newlands et al. (14) using sequential chemotherapy schedules in eighteen patients with immature teratomas. In this series the majority of treated patients had advanced disease (Table 3).

Protocol A:

day 1 - Vincristine 1mg/m^2 injestion folowed by Methotrexate 100 mg/m^2 and then Methotrexate 200 mg/m^2 in 12h infusion

day 2 - Bleomycin 15 mg/in 24h intravenous infusion; Folinic acid 24h after Methotrexate 15 mg/12h x 4

day 3 - Bleomycin 15 mg in 24h infusion

day 4 - Cis-platin 120 mg/m^2 with prehydratation

Protocol B:

day 1 - 5 Etoposide 100 mg/m2 iv
day 3,4,5 Actinomycin D 0.5 mg iv
day 5 Cyclophosphamide 500 mg/m^2 iv

Protocol C:

Hydroxyuirea, Vinblastine and Chlorambucil later omitted because of resistance

Protocol D:

Identical to Protocol A with omission of Cis-platin

Patients received two courses of regimen A, followed by regimen B. If there was no complete remission they alternated between treatment A and B until complete clinical and biochemical remission was achieved. After the remission, the treatment was continued alternating protocol B and D until remission had been maintained for approximately 12 weeks. Intervals between the courses of chemo therapy were adjusted to allow the recovery from myelosuppression and were normally between 9 and 14 days. This chemotherapy schedule showed good results in advanced stages but it was technically demanding and toxicity was not reported in this paper.

Schwartz treated one patient, with stage III immature teratoma, with new combination chemotherapy Cis-platin, Vinblastine and Bleomycin (PVB), and although this regimen showed good efficacy, the treatment was associated with high toxicity (9). Other reports confirm activity of this regimen in MGCT (15-18). Some authors added Methotrexate to this protocol but it seems with no great impact on efficacy.

PVB protocol:

days 1 - 5 Cisplatin 20 mg/m^2
days 1&2 Vinblastine 0.15 mg/kg
days 1, 8, 15 Bleomycin 30 mg
repeat every 21 days

Soon after, it was established that Etoposide is more effective than Vinblastine which resulted in the combination of Bleomycin, Etoposide, Cis-platin (BEP). This regimen was also associated with less toxicity and is given every 21 days.

BEP protocol:

day 1 - 5 Cisplatin 20 mg/m^2
day 1 - 5 Etoposide 100 mg/m^2
day 1 Bleomycin 30 mg
repeat weekly

Nowadays BEP protocol is most widely used as first line treatment with very good results (13,19,20). It is difficult to asses recurrence rate especially for immature teratomas because of small numbers and different stage distribution among the published series. Most of the authors suggest that 3 courses of BEP regimen should be given for all stage I grade 2&3 tumors to prevent recurrence. In higher stages number of courses required to achieve complete remission is more than 3 and total number depends on response and toxicity.

Recently, Bower et al. (21) published their series of 77 women with MGCT (19 with immature teratoma) treated in Charing Cross Hospital in London and majority of patients were in advanced stage disease (11 stage I, 15 stage II, 20 stage III, 13 stage IV). Using protocol POMB/ACE (Table 4) they achieved a 3-year survival of 80.7% for the whole population of 77 patients and the survival figure was 87.0% when 12 patients initially treated elsewhere were excluded from the analysis. This regimen had excellent efficacy with acceptable toxicity. There were no deaths related to the treatment although one patient died from acute myeloid leukemia 7 months after chemotherapy receiving a total of 1300 mg/m^2 of Etoposide.

POMB/ACE is administered every 14 days and alternates between POMB and ACE regiments after the first two cycles which are both POMBs.

Treatment of MGCT is a fine balance of optimal result with minimal toxicity. The high dose VAC regimen would be adequate for many tumors, but late sequelae of these agents (myelosuppresion, infertility, cardiac toxicity) are unacceptable when high cure rates can be achieved with platinum-based chemotherapy. Undoubtely, there are some late toxicities with platinum-based regimens, although, with limited total dose these sequelae should not be severe (22,23). Decline in glomerular filtration rate and high tone hearing loss on audiometry is almost inevitable where the cumulative dose of Cis-platin exceeds 3-400 mg/m^2.

Table 4. POMB/ACE regimen

POMB	day 1	Vincristine 1mg/m^2 (max 2 mg) iv bolus
		Methotrexate 300 mg/m^2 iv infusion
	day 2	Bleomycin 15 mg iv infusion over 24 h
		Folinic acid 15 mg at 24, 36, 48, 60 h after Metotrexate
	day 3	Cis-platin 120 mg/m^2 iv infusion over 12 h
ACE	day 1	Etoposide 100 mg/m^2 iv infusion
		Actinomycin D 0.5 mg iv bolus
	day 2	Etoposide 100 mg/m^2 iv infusion
		Actinomycin D 0.5 mg iv bolus
	day 3	Etoposide 100 mg/m^2 iv infusion
		Actinomycin D 0.5 mg iv bolus
		Cyclophosphamide 500 mg/m^2 in 250 ml NS over 30 min

Pulmonary toxicity is well recognized with the use of Bleomycin and toxicity is higher when weekly administration is used in the protocol. Adverse effect on fertility, persistent skin pigmentation and Raynaud's phenomenon are also attributed to Bleomycin. Vinblastine is less well tolerated than Etoposide and not more effective, which makes BEP regimen more acceptable than PVB. Etoposide has been associated with induction of second malignancy, although a theoretical problem, there is little evidence that second cancers occur due to three-weekly Etopside where cumulative dose is low (24-26). Studies looking at the value of replacing Cis-platin with Carboplatin in order to reduce the toxicity (27-30) indicate that Cis-platin is superior to Carboplatin, although, it has to be said that the dose of Carboplatin was suboptimal in majority of the cases as the dose was not calculated using Calvert/Newel formula (dose mg = desired AUC x uncorrected GFR + 20). Further studies are needed to answer this question. Another interesting question is: can Bleomycin be omitted to reduce long-term toxicity? In the study from Memorial Sloan-Kettering Cancer Center (31) comparing five drug regimen Cyclophosphamide, Vinblastine, Dactinomycin, Bleomycin and Cis-platin (VAB-6) with two drug regimen of Cis-platin and Etoposide, they concluded that there was no difference in a 2-year survival in good-risk group between the two regimens. Toxicity was substantially reduced in the group receiving the two drug regimen. In this study, they were using logistic model to determine the probability of complete response in order to define good-risk group. In other study (32), comparing PB versus PVB the CR rate was similar (89% versus 94%) but the eventual death rate from progressive malignancy was 15% in PB group versus 5% in PVB. The overall survival difference was not significant, due to higher proportion of toxic deaths in three drug regimen. Subsequent study compared BEP with EP in patients with favourable prognosis of disseminated MGCT (33). In this study, overall survival was better (95%) with BEP than (86%) with EP indicating a significant role of Bleomycin. There is clearly a need for large multicentric study to clarify this issue.

Not many reports addressed fertility rate in great detail which makes it difficult to compare different regimens in respect to their effect on fertility. However, many other factors not related to the treatment may influence final fertility rate. Fertility rate after conservative surgery and chemotherapy is between 70%-83.3 % according to published data which certainly justifies conservative approach in the treatment of MGCT (34,35). There have been no fetal abnormalities observed so far related to the treatment. Majority of conservatively treated patients retained their ovarian endocrine function.

It is still uncertain what the best salvage therapy for recurrent disease is. Several active chemotherapeutic agents can be used in the event of relapse following the first line treatments, and the decision depends on previously used drugs. Ifosfamide (36), Doxorubicin, Actinomycin and Methotrexate (37) and other regimens (38) showed effectivenes as salvage therapy in MGCT. Increase dose intensity with previously used drugs may produce responses (39). The role of very high dose combination chemotherapy, requiring autologous bone marrow or stem cell rescue is still uncertain (40-42). Radio therapy could be given in refractory tumors.

There are still several important questions waiting to be answered: the most effective the least toxic first line chemotherapy needs to be defined; clear identification of low-risk and high-risk groups to enable administration of most appropriate treatment; and the definition of the most active salvage therapy. Answering these questions would require large national or international collaborative randomized studies.

REFERENCES

1. Scully RE, Fox H, Russel P, Saksela E, Sasano N, Sobin LH. World Health Organisation and International Society of Gynecological Pathologist classification of the tumors of the ovary, fallopian tube and peritoneum. Heidelberg: Springer-Verlag, 1995 .

2. Breen JL, Neubecker RD. Malignant teratoma of the ovary. An analysis of 17 cases. Obstet Gynecol 1967;21:669.

3. Malkasian GD Jr, Symmonds RE, Dockerty MB. Malignant ovarian teratomas. Report of 31 cases. Obstet Gynecol 1965;25:810.

4. Norris HJ, Zirkin HJ, Benson WI. Immature (malignant) teratoma of the ovary. Cancer 1976;37:2359.

5. Gershenson DM, DelJunco G, Silva EG et al. Immature Teratoma of the Ovary. Obstet Gynecol 1986;68:624.

6. Bahari CM, Lurie M, Schoenfeld A. Ovarian teratoma with peritoneal gliomatosis and elevated serum alpha-fetoprotein. Am J Clin Pathol 1980;73:603.

7. Esterhay PJ, Shapiro HM, Sutherland JC et al. Serum alpha-fetoprotein concentration and tumor growth disassociation in a patient with ovarian teratocarcinoma. Cancer 1973;31:835.

8. Taleman A, Hagi WG. Alpha-fetoprotein and germ cell tumors: A possible role of yolk sac tumor in production of alpha-fetoprotein. Cancer 1974;34:1722.

9. Schwartz PE. Combination Chemotherapy in the management of ovarian germ cell malignancies. Obstet Gynecol 1984;64:564.

10. Piura B, Dgani R, Zalel Y et al. Malignant germ cell tumors of the ovary : A study of 20 cases. J Surg Oncol 1995;59:155.

11. Gershenson DM, Copeland LJ, Kavanagh JJ et al. Treatment of malignant nondysgerminatous germ cell tumors of the ovary with Vincristine, Actinomycin-D and Cyclophosphamide. Cancer 1985;56:2756.

12. Slayton RE Park RC, Silveberg SG. Vincristine, Dactinomycin and Cyclophosphamide in the treatment of malignant germ cell tumors of the ovary. A Gynaecologic Oncology Group Study. Cancer 1985;56:243.

13. Nair R, Pai SK, Saikia TK et al. Malignant germ cell tumors in childhood. J Surg Oncol 1994;56:186.

14. Newlands ES, Begent RHJ, Bagshawe KD. Potential for cure in metastatic ovarian teratomas and dysgerminomas. Br J Obst Gynaecol 1982;89:555.

15. Lokey JL, Baker JJ, Price NA et al. Cis-platin, Vinblastine and Bleomycin for endodermal sinus tumour of the ovary. Ann Intern Med 1981;94:56.

16. Julian CG, Barrett JM, Richardson et al. Bleomycin., Vinblastine and Cis-platin in the treatment of advanced endodermal sinus tumor. Obstet Gynecol 1980;56:396.

17. Williams S, Slayton R, Silveberg S et al. Response of malignant ovarian germ cell tumors to Cis-platin, Vinblastine and Bleomycin (PVB). Proc Am Assoc Cancer Res Am Soc Clin Oncol 1981;22:463.

18. Carlson RW, Sikic BI, Turbow MM et al. Combination Cis-platin Vinblastine and Bleomycin chemotherapy (PVB) for malignant germ-cell tumors of the ovary. J Clin Oncol 1983;1:645.

19. Williams SD, Blessing JA, Liao SY et al. Adjuvant therapy of ovarian germ cell tumors with Cis-platin Etoposide and Bleomycin: A trial of the Gynaecologic Oncology Group. J Clin Oncol 1994;12:701.

20. Williams SD, Birch R, Einhorn LH et al. Disseminated germ cell tumors: Chemotherapy with Cis-platin plus Bleomycin plus either Vinblastine or Etoposide. N Engl J Med 1987;316:1435.

21. Bower M, Fife K, Newlands ES et al. Chemotherapy for ovarian germ cell tumours. Eur J Cancer 1996;32A:593.

22. BoyerM, Raghavan D, Harris PJ et al. Lack of late toxicity in patients treated with cis-platin containing combination chemotherapy for metastatic testicular cancer. J Clin Oncol 1990;8:21.

23. Bokemeyer C, Berger CC, Kuczyk MA et al. Evaluation of long term toxicity after chemotherapy for testicular cancer. J Clin Ocol 1996;14:2923.

24. Bajorin DF, Motzer RJ, Rodriguez E et al. Acute nonlympholitic leukemia in germ cell tumor patients treated with Etoposide containing chemotherapy. J Natl Cancer Inst 1993;85:60.