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Original Paper

Chemotherapy for Ovarian Germ Cell Tumours

M. Bower,[1] K. Fife,[1] L. Holden,[1] F.J. Paradinas,[1] G.J.S. Rustin[2] and E.S. Newlands[1]

[1]Medical Oncology Unit, Charing Cross Hospital, Fulham Palace Road, London W6 8RF; and [2]Mount Vernon Centre for Cancer, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, U.K.

59 patients were treated for newly diagnosed metastatic ovarian germ cell tumours with POMB/ACE chemotherapy (which contains cisplatinum, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide). The median follow-up was 7.7 years. The 3 year survival is 87.8% (95% confidence interval 76.9–93.9%) and no relapses occurred more than 3 years after treatment. 4 (7%) patients had primary drug resistance to POMB/ACE and 4 (7%) have relapsed. One patient in complete remission developed secondary acute myeloid leukaemia after receiving a total of 1.3 g/m^2 etoposide. 6 of 12 (50%) patients referred at relapse were salvaged by POMB/ACE. 14 of 33 (42%) women (>18 years old) have had successful pregnancies after fertility conserving surgery and chemotherapy with no congenital abnormalities reported. The POMB/ACE regimen is as efficacious as other published regimens for ovarian germ cell tumours (OGCT) and balances a low incidence of life-threatening toxicity with a high success rate. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

MALIGNANT OVARIAN germ cell tumours (OGCT) are rare and account for 1% of all ovarian tumours. The average age at presentation is under 25 years. In women less than 20 years old, 58% of all ovarian tumours are OGCTs of which 65% are malignant [1]. Most patients even with extensive metastatic disease can be cured and in the majority of cases fertility can be preserved. The most widely used histopathological classification of OGCTs is the WHO classification [2].

The staging of germ cell tumours follows the standard FIGO classification of ovarian tumours [3] with a minor modification where stage IM indicates complete surgical resection but persisting or rising tumour markers. The staging investigations at Charing Cross Hospital (CXH) are undertaken approximately 1 month post-operatively and, if the tumour is shown to be stage I, chemotherapy is not administered but patients are enrolled into a close surveillance programme similar to the policy for stage I testicular germ cell tumours [4]. This approach is in contrast to a number of other centres who include stage I patients in their survival data for chemotherapy [5–9].

Correspondence to E.S. Newlands.
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PATIENTS AND METHODS

77 women with OGCT have been treated at CXH since 1977, including 12 who were initially treated elsewhere. These latter patients are excluded from the analysis of treatments. The median follow-up is 7.9 years (range 5 months–17 years). The mean age at diagnosis for all 77 patients was 22.8 years (range 3–47 years). The FIGO stage at presentation was stage IA (6), IM (10), II (21), III (22) and IV (18). The patients with stage IA disease at presentation were initially treated with surgery alone, but 3 relapsed on surveillance and the other 3 patients developed second primary dysgerminomas of the contralateral ovary 9–60 months after the diagnosis of the original tumour.

The histological diagnoses are shown in Table 1. The 12 patients initially treated elsewhere had received chemotherapy

Table 1. Histological diagnoses of patients described in this series

Endodermal sinus tumour	27 (35%)
Immature teratoma	19 (25%)
Dysgerminoma	15 (19%)
Mixed germ cell tumours	11 (14%)
Malignant transformation in teratoma	2 (3%)
Choriocarcinoma	2 (3%)
Embryonal carcinoma	1 (1%)

Table 2. Tumour markers at presentation for patients described in this series

	Raised hCG	Raised AFP	Both raised	Neither raised
Untreated ($n = 65$)	19 (29%)	31 (48%)	8 (12%)	7 (11%)
Prior treatment ($n = 11$)	2 (18%)	6 (55%)	2 (18%)	1 (9%)
Dysgerminoma ($n = 13$)	9 (69%)	0	0	4 (31%)
Other histologies ($n = 63$)	12 (19%)	37 (59%)	10 (16%)	4 (6%)

(7), irradiation (3) or both (2). The histologies of these patients were endodermal sinus tumour (5), dysgerminoma (2), immature teratoma (3), mixed teratoma (1) and malignant transformation in mature teratoma (1).

Both serum α-fetoprotein (AFP) and β-human chorionic gonadotrophin (β-hCG) were measured at presentation for all but one patient (who was treated initially elsewhere for dysgerminoma). The results are summarised in Table 2.

59 untreated patients received POMB/ACE chemotherapy, 5 received BEP (containing bleomycin, etoposide and cisplatinum) for early stage disease with low tumour burdens as assessed radiologically and serologically. One woman with relapsed stage 1 immature teratoma presenting with liver metastases during the third trimester of pregnancy, was treated with etoposide and platinum induction and died of a pulmonary embolism within a fortnight of commencing treatment. The POMB/ACE regimen consists of cisplatinum, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide (Table 3). The first two courses comprise POMB and thereafter POMB and ACE courses alternate at fortnightly intervals until tumour marker remission has been maintained for 4–8 weeks. Prior to 1988, 12 weeks of treatment were given after marker remission with cisplatinum omitted after five courses.

The mean age of the 59 patients treated with first line POMB/ACE was 22.1 years (range 4–47 years) and only 11 were under 15 years of age. The stages at presentation were I (11), II (15), III (20) and IV (13). The histological diagnoses were dysgerminoma (11), endodermal sinus tumour (21), immature teratoma (13), mixed tumours (10), embryonal carcinoma (1), choriocarcinoma (2) and transformed mature teratoma (1).

Statistical methods

Survival was calculated from the first day of treatment until death or the date of last follow-up. Overall survival duration curves were plotted according to the method of Kaplan and Meier [10]. The log rank method was used to test for the significance of differences in survival distributions [11].

RESULTS

The 3 year overall survival for the whole population of 77 patients is 80.7% (95% confidence interval (CI): 70.2–88.2%) and there were no deaths or relapses later than 3 years after the start of chemotherapy. The 12 patients initially treated elsewhere had a worse overall survival than patients referred after initial diagnostic surgery [$\chi^2 = 9.6$, $P = 0.002$, Hazards ratio (HR) = 10.9, 95% CI = 2.4–49.1], although all had received prior chemotherapy and/or radiotherapy. These 12 patients are not considered further in the analysis of outcome. The overall survival for the 65 patients referred after initial diagnostic surgery levelled at 87.0% (95% CI: 76.4–93.3%) at 3 years and no further events have occurred after this time. The age at diagnosis of the untreated patients influenced survival [age <30 years ($n = 50$) versus >30 years ($n = 15$), $\chi^2 = 4.8$, $P = 0.028$, HR = 7.2 (95% CI: 1.2–41.8%)]. Three year survival for patients under 30 years of age at presentation was 91.7% (80.5–96.7) compared to 69.3% (42.0–87.5) for those older than 30 years. Neither the stage at diagnosis nor the level of tumour markers (hCG > 50000 IU/l and/or

Table 3. POMB/ACE schedule

POMB		
Day 1	Vincristine	1 mg/m² (max 2 mg) i.v. bolus
	Methotrexate	300 mg/m² i.v. infusion
Day 2	Bleomycin	15 mg i.v. infusion over 24 h
	Folinic acid	15 mg at 24, 36, 48 and 60 h after start of methotrexate infusion
Day 3	Cisplatin	120 mg/m² i.v. infusion over 12 h
ACE		
Day 1	Etoposide	100 mg/m² i.v. infusion
	Actinomycin D	0.5 mg i.v. bolus
Day 2	Etoposide	100 mg/m² i.v. infusion
	Actinomycin D	0.5 mg i.v. bolus
Day 3	Etoposide	100 mg/m² i.v. infusion
	Actinomycin D	0.5 mg i.v. bolus
	Cyclophosphamide	500 mg/m² in 250 ml NS over 30 min

The POMB/ACE schedule is administered fortnightly and alternates between POMB and ACE regimens after the first two cycles which are both POMBs.

AFP > 500 kU/l) influenced survival in the previously untreated patients.

59 patients with newly diagnosed OGCT were treated with the POMB/ACE schedule. The median follow-up for this group was 7.7 years (range 10 months–17 years). 4 (7%) patients had drug-resistant disease and all 4 died of progressive disease. 55 patients achieved remission and 4 (7%) have relapsed. The median time to relapse was 4.0 months (range 2.9–33 months). The patients were all treated at relapse with chemotherapy. One patient is still alive after high dose chemotherapy and autologous bone marrow transplantation (ABMT) although she currently has active disease and is on palliative treatment. All relapses and deaths occurred within 3 years of diagnosis and the overall 3 year survival for these 59 patients is 87.8% (95% CI: 76.9–93.9%) (Figure 1).

Dosage reductions were instituted for 15/59 (25%) patients on POMB/ACE because of haematological toxicity or WHO grade 3/4 infection. Alopecia and nausea were universally experienced toxicities. In addition, 5 patients developed grade 3/4 mucositis, and 4 reported grade 1/2 peripheral neuropathy. 3 patients developed grade 1/2 nephrotoxicity and 2 had grade 1/2 pulmonary toxicity. There were no treatment related deaths among patients receiving POMB/ACE. However, one patient in remission following POMB/ACE treatment for stage III dysgerminoma died of acute myeloid leukaemia 7 months after completing chemotherapy. She had received a total of 1300 mg/m^2 of etoposide.

12 patients were referred at relapse after irradiation and/or chemotherapy. 6 of these patients were salvaged with POMB/ACE chemotherapy successfully and remain in remission after a median of 10.4 years (range 8.3–17.0 years). This included 1 patient initially treated elsewhere with VAC (containing vincristine, actinomycin D and cyclophosphamide) for stage IV endodermal sinus tumour who relapsed after 1 year and was re-treated with POMB/ACE followed by laparotomy to remove non-viable residual paraaortic disease. She relapsed 7 months later and was treated with surgical resection of a small pelvic recurrence of active tumour followed by EP/OMB chemotherapy, and she remains in remission 11 years after chemotherapy for her second relapse. The other 6 patients have all died, 5 of disease and 1 of a subarachnoid haemorrhage in serological remission 3 months after completing chemotherapy.

Second look laparotomy in the absence of radiological abnormalities was not routinely performed. This procedure has been abandoned at CXH for patients treated with chemotherapy as advocated by others [12, 13], but remains recommended for stage I patients undergoing surveillance. However, 20 patients had laparotomies for the removal of residual masses after completing chemotherapy (Figure 2). The histological findings were no viable tumour in 13, mature differentiated teratoma in 6 and active tumour in 1. Three women have had repeat laparotomies for the resection of further masses. In 1 case, the diagnosis was recurrent disease (vide supra), 1 was mature teratoma and 1 no viable tumour. Two women have undergone excision biopsies for nodular tumours in laparotomy scars and in both cases the histology was mature differentiated teratoma. One woman with stage IV mixed germ cell tumour underwent a thoracotomy for the removal of residual mass of necrotic tissue. Finally, one woman with recurrent drug resistant endodermal sinus tumour had two craniotomies for recurrent disease, but subsequently died of disease.

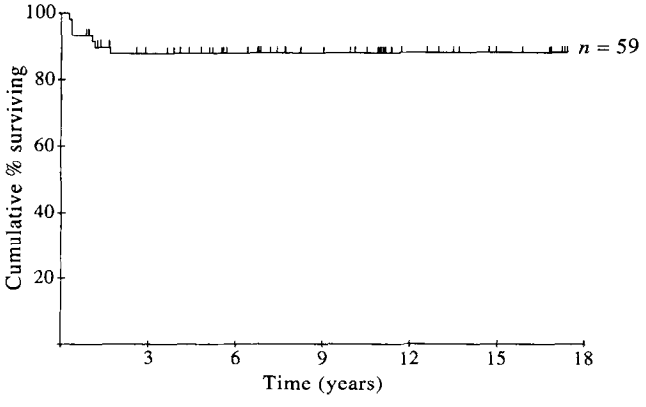

Figure 1. Overall survival of untreated patients treated with POMB/ACE.

One patient had Turner's syndrome and 1 patient had XY ovarian dysgenesis. The initial surgical approach was fertility conserving (unilateral salpingo-oophorectomy or ovarian cystectomy) in 43 patients. 5 of these patients have died of disease. 14 of the 38 women alive following fertility conserving surgery and chemotherapy have had successful pregnancies (this includes 5 patients who are still under 18 years old at the time of last follow-up).

DISCUSSION

Ovarian germ cell tumours are infrequent and extremely aggressive malignancies occurring in young women. Prior to the introduction of combination chemotherapy, the outcome was almost invariably fatal, but the majority of patients are now cured. Although a number of series of OGCT have been published, their rarity, histological heterogeneity and variable surgical approaches makes comparison of different chemotherapy regimens difficult. No randomised comparisons of chemotherapy regimens have been published.

Many institutions advocate postoperative chemotherapy for all OGCT, but our unit undertakes complete staging 3–4 weeks postoperatively, and patients with stage I disease at presentation with no evidence of residual tumour activity (including the normalisation of serum tumour markers) who are able to attend regularly for follow-up are enrolled in a surveillance programme [14], similar to that employed for testicular germ cell tumours [15].

The optimal chemotherapy for stage II–IV OGCT remains uncertain. The VAC regimen (containing vincristine, actinomycin D and cyclophosphamide) was used widely in the 1970s but is a long duration treatment with limited activity against advanced endodermal sinus and mixed tumours [16–19], although improved results were reported when the regimen was administered at higher doses [20]. The introduction of platinum led to higher sustained remission rates with PVB (containing ciplatinum, vinblastine and bleomycin) [17, 22–30]. Following the successful introduction of etoposide into the BEP regimen (combining bleomycin, etoposide and cisplatinum) in testicular GCTs, the combination has been used for OGCT [5, 24, 31, 32].

The POMB/ACE treatment was developed at Charing Cross Hospital for the management of testicular GCTs [33]. It allows early exposure of the tumour to seven cytotoxics in order to minimise the development of drug resistance. The regimen alternates the myelosuppressive ACE with the less

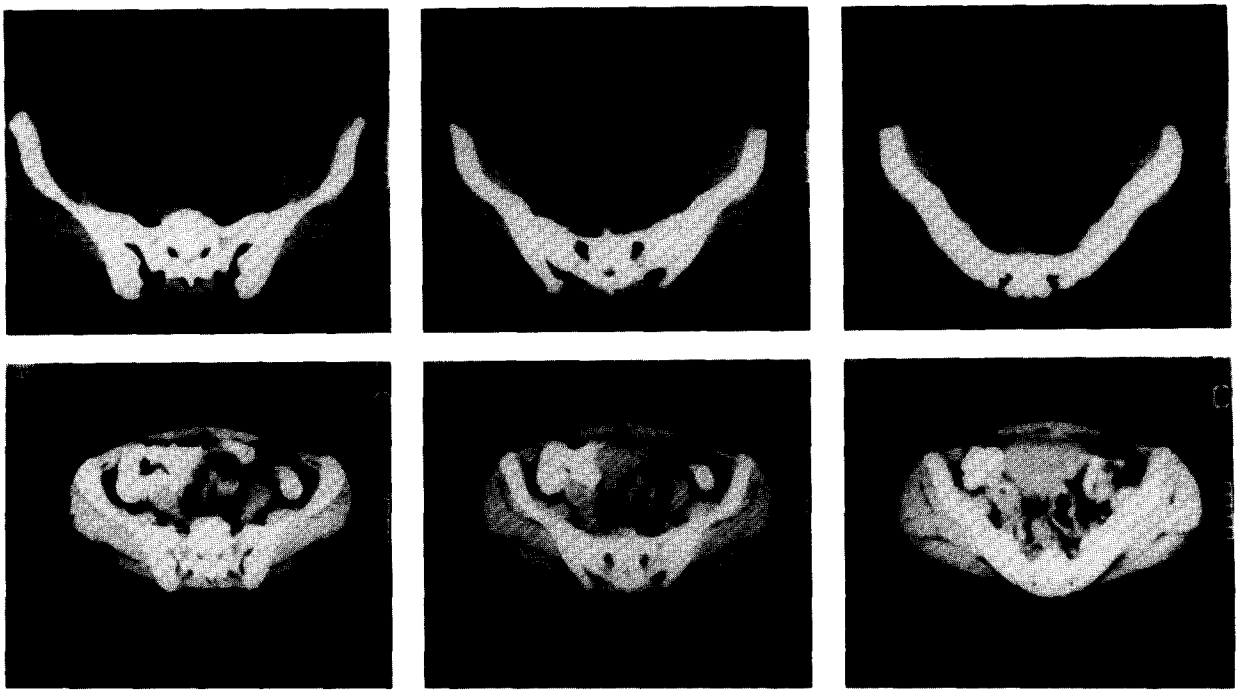

Figure 2. Pelvic CT scan images before and after treatment of a 19 year old patient presenting with massive primary mixed OGCT with para-aortic nodes and liver metastases. The patient was treated with POMB/ACE chemotherapy. At the end of chemotherapy cysts were removed at laparotomy from both ovaries but these contained no residual malignancy.

myelotoxic POMB combination and thus keeps the interval between courses to a minimum. The results presented here confirm initial reports of the activity and safety of the POMB/ACE schedule for OGCT [4, 34]. The 3 years survival rate is 88% for the 59 previously untreated patients given POMB/ACE. 4 patients (7%) had evidence of primary drug resistance to POMB/ACE and 4 (7%) of the patients achieving remission hvae relapsed, only 1 of whom was salvaged.

The management of OGCT at CXH includes surveillance for stage I disease. In contrast, many of the reported series from the other institutions include these patients and so their results appear better than they really are because the majority of stage I tumours do not require chemotherapy. Furthermore, POMB/ACE salvaged 5/11 patients previously treated with chemotherapy and/or radiotherapy. Similar results have been demonstrated using a modified version of the POMB/ACE regimen in Spain [14]. The POMB/ACE regimen compares favourably with the published results of PVB and BEP in OGCT, athough randomised comparisons have not been undertaken and are not envisaged in view of the low patient numbers.

An association between topoisomerase II inhibitors and the development of secondary acute myeloid leukaemia with the typical morphological and molecular characteristics has recently been described [35–38]. In our series, one woman in complete remission developed fatal secondary acute myelogenous leukaemia and this complication has also been described in a woman with OGCT treated with BEP chemotherapy [5]. By comparison, epipodophyllotoxin related secondary AML has been widely described following chemotherapy for testicular germ cell tumours. In the largest reported series of male patients with germ cell tumours treated with etoposide containing chemotherapy, the incidence of acute myeloid leukaemia was 6/679 (0.9%) [39]. At present, the benefits of etoposide containing regimens in the treatment of germ cell tumours in both sexes outweigh this small but significant risk of inducing secondary leukaemia.

Menstruation generally returns 2–6 months following the completion of POMB/ACE treatment and fertility is usually preserved if conservative surgery has been performed [40]. Children have been born to 14 of our patients who have received POMB/ACE and no congenital abnormalities have been reported. Similar results have been obtained for women having non-sterilising surgery and VAC chemotherapy for OGCT [41].

Salvage treatment for OGCT is disappointing with particularly poor results for patients who relapsed following POMB/ACE, although the results using this schedule for relapsed patients initially treated elsewhere with a variety of approaches has been more promising. The salvage rate for patients relapsing at Yale following BEP, VAC or PVB was 50% (4/8) [8] and 3/8 who failed VAC [42]. This compares to our results of 20% (15) salvage following initial treatment with POMB/ACE. These results suggest that inadequate initial therapy compromises overall outcome, but some of these patients may be salvageable. The low salvage rate following relapse after POMB/ACE contrasts with the situation for male GCT where a salvage rate of approximately 30% is seen after POMB/ACE relapses. This difference may reflect a more rapid development of drug resistance in the female version of the disease.

Although routine second look laparotomies were not performed, surgical resection of residual masses was undertaken in 20 patients. In 6 cases, mature teratoma was resected. The removal of residual differentiated mature teratoma is advocated in male germ cell tumours as these elements may undergo cystic enlargement or dedifferentiation [43, 44], and we advocate a similar policy in OGCTs.

In conclusion, the majority of patients with ovarian germ cell malignancies may be successfully treated by a combination

of conservative surgrey and multi-agent chemotherapy. This approach conserves fertility and gonadal function and, in conjunction with resection of residual abnormalities, has improved the prognosis and reduced the long-term morbidity of this disease.

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