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Chemotherapy of Germ-Cell Ovarian Tumours: First-Line Treatment with Etoposide, Bleomycin and Cisplatin or Carboplatin

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Abstract—*Of 9 patients with malignant ovarian germ-cell tumours (OGCT) treated with combination chemotherapy between 1980 and 1985, 8 are alive and disease-free at 6–62 months. All patients received etoposide and bleomycin and 8 out of 9 also received a platinum analogue; in one case carboplatin, in a second carboplatin plus cisplatin, and in the remainder, cisplatin. In one patient treated prior to the introduction of carboplatin, poor renal function precluded the use of cisplatin. Two patients with Stage III dysgerminomas are disease-free at 44 and 62 months after receiving chemotherapy followed by radiotherapy to the whole abdomen or pelvis. Of 7 patients with non-dysgerminomatous OGCT, including 2 dysgerminomas with raised serum alphafetoprotein, 6 are disease-free at 6–56 months.*

On the basis of these observations and experience reported elsewhere, surveillance after removal of the primary tumour is proposed for early-stage dysgerminoma, and chemotherapy is suggested for advanced presentations as an alternative to surgery and post-operative radiotherapy. Combination chemotherapy is indicated for all stages of non-dysgerminomatous OGCT.

INTRODUCTION

UNTIL relatively recently malignant ovarian germ-cell tumours (OGCT) other than dysgerminoma, hereafter called non-dysgerminomatous OGCT (NDOGCT), carried a poor prognosis. Thus, Kurman and Norris [1] reported only 9/65 surviving patients with endodermal sinus tumours (yolk sac carcinoma) even though 71% of patients had Stage I disease.

Although the overall results with surgery and radiotherapy for dysgerminoma have been good they have been achieved at the expense of loss of fertility in all but the earliest stage presentations, with some deaths in patients with advanced disease.

In recent years there have been dramatic advances in the treatment of male germ-cell malignancy and the chemotherapy devised for testicular cancer has been applied to the management of malignant OGCT. Cisplatin, vinblastine and bleomycin (PVB) developed by Einhorn and his colleagues [2] have been employed with encouraging results by several authors [3–10]. Similarly good results with other platinum-containing regimens have been reported [11, 12].

In this report we described the results of treatment in 9 patients with malignant OGCT using combination chemotherapy as employed in this unit to treat testicular tumours [13]. Initially, bleomycin, etoposide and cisplatin (BEP) was used but recently cisplatin has been replaced by carboplatin because of the absence of nephrotoxicity [14].

MATERIALS AND METHODS

Patients

Nine patients aged from 12 to 35 years with malignant OGCT seen between 1980 and 1985 are reported. A histological diagnosis of germ-cell malignancy was confirmed in all cases and classified according to the 1973 World Health Organization International histological classification of ovarian tumours, into one of the following categories: dysgerminoma, endodermal sinus tumour (EST), embryonal carcinoma (EC) or immature teratoma (IT). Two patients had pure dysgerminoma and 2 had apparently pure dysgerminoma but raised serum alphafetoprotein level and have been considered as NDOGCT. Two patients had EST, one an EC, one a mixed IT/EST and one IT. One

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Table 1. Malignant ovarian germ-cell tumours: clinical features and results of treatment
[The Royal Marsden Hospital (Sutton) (1980–1985)]

Patient	Age	Pre-chemotherapy stage	Histology*	Pre-treatment AFP (ng/ml)	Pre-treatment HCG (I.U./l)	Post CT RT Chemotherapy (number of cycles)	Post CT RT Current status time from start of chemotherapy (months)
1	26	III	DYS	< 5	< 2	EB‡ (4)	NED† 62m
2	12	III	DYS	< 5	< 1	BEP (4)	NED 44m
3	34	IC	EST	5100	2	BEP (4)	NED 56m
4	29	IIC	EST	3200	< 1	BEP (4)	Dead 24m
5	34	III	IT/EST	25,000	< 1	BEP (4) PVB (2)	NED 25m
6	14	III	EC	< 10	< 1	BEP (4)	NED 17m
7	35	Ia	IT	18	< 1	BEP (4)	NED 9m
8	16	IV	DYS	163	5	BEP (3) CEB (3)	NED 9m
9	30	III	DYS	28	3	CEB (4)	NED 6m

P = cisplatin e = etoposide V = vinblastine C = carboplatin B = bleomycin.
*For histology see text.
†NED—no evidence of disease.
‡Platinum omitted because poor renal function and congenital absence of one kidney.

woman with dysgerminoma had an abnormal karyotype (47xxx).

STAGING METHOD AND CLASSIFICATION

Pre-treatment investigations included measurement of serum alphafetoprotein (AFP) and human chorionic gonadotrophin (HCG) levels, lymphography, intravenous urography, computerized axial tomographic X-ray (CT) scans of thorax, abdomen and pelvis, renal clearance and liver function tests and full blood count. Patients were staged using the FIGO staging classification for ovarian tumours. Details of stage and extent of disease are summarized in Table 1.

MANAGEMENT POLICY

All patients were treated with combination chemotherapy and were assessed after 4 cycles with repeat AFP and HCG levels, CT scans of chest, abdomen and pelvis, intravenous urography and ultrasonic scanning. Laparotomy and laparoscopy were not performed as part of reassessment routinely, but more recently treated patients have had a second-look laparotomy, as with increasing experience, it was found that relapses could occur despite apparent complete clinical remission. Two patients received elective post-chemotherapy radiotherapy to the pelvis or whole abdomen.

Chemotherapy

BEP chemotherapy was employed as previously described [13]. Bleomycin, etoposide and cisplatin were administered intravenously as follows: bleomycin 30 mg, days 2, 9 and 16, etoposide 120 mg/m^2 day 1–3 of each cycle and cisplatin 20 mg/m^2 infused in 1 l. of normal saline over 6 hr on each of days 1–5. Hydration was started 12 hr prior to the first dose of cisplatin and maintained throughout each cycle with normal saline (1 l.) and KCl (2gl^{-1}) infused 6-hourly for 5 days and 200 ml of mannitol (10%) injected i.v. daily prior to the start of the cisplatin infusion. Bleomycin, etoposide and carboplatin (CEB) were given as described elsewhere [14]. The doses and scheduling of bleomycin and etoposide were as described above but cisplatin was replaced by carboplatin 300 mg/m^2 in 500 ml of 5% dextrose infused intravenously over 1 hr on day 1 of each cycle. For both BEP and CEB cycles were given at 3-weekly intervals and renal clearance measured prior to each course of chemotherapy. Full blood counts were carried out prior to each course of chemotherapy, twice weekly during the first week and on days 9 and 16. Blood urea and electrolytes were checked twice during the first week and plasma creatinine measured weekly. One patient with dysgerminoma had a congenital absence of one kidney and poor residual function of the remaining kidney with a renal clearance of 23 ml/min. In this patient who was treated before the introduction of carboplatin, cisplatin was omitted and a combination of etoposide and bleomycin (EB) employed.

RESULTS

Table 1 summarizes treatment and outcome for the 9 patients. Eight are alive without evidence of disease at 6–62 months from the date of starting chemotherapy. Both patients with pure dysgerminoma are disease-free at 44 and 62 months. Patient 1, who received EB only showed an objective partial

response but a residual pelvic mass remained. Because of the omission of cisplatin from first-line treatment abdominal irradiation (20 Gy in 15 fractions over 3 weeks with a pelvic boost to 35 Gy) was given. She subsequently came to laparotomy since a residual pelvic mass was present. This proved to be matted small bowel and there was no evidence of tumour. Patient 2 had very advanced disease with bilateral ovarian tumours, ascites, spread to the uterus, fallopian tubes, bladder, rectal wall, both pelvic side walls, para-aortic nodes, portahepatis nodes and involvement of omentum. She was given pelvic radiotherapy (30 Gy in 15 fractions over 3 weeks) after 4 courses of BEP because it was felt that with such extensive pelvic disease she was at high risk of relapse.

Of the 7 patients with NDOGCT 6 are alive and disease-free at 6, 9, 9, 17, 25 and 56 months. One patient (patient 4) who had an EST with bulky pelvic disease died of uncontrolled malignancy. This patient had a large ovarian tumour attached to the paracolic gutter and ascites, with a residual pelvic mass. She was treated with 4 courses of BEP and went into complete clinical remission. However, 2 months after completing treatment she relapsed with a pelvic mass and raised serum AFP. She subsequently received 4 courses of PVB and achieved complete remission, confirmed by laparoscopy. Two months later she again relapsed and in spite of further chemotherapy and surgery died.

Patient 5 had a mixed IT/EST with multiple peritoneal seedlings. After 4 courses of BEP she was clinically in complete remission. At second-look laparotomy there was no macroscopic evidence of disease, but there were microscopic foci of differentiated tumour on 2 biopsy specimens and she therefore received 2 further courses of chemotherapy with PVB. She remains disease-free at 25 months. Patient 8 recurred after conservative surgery and observation for an apparent Stage IA pure dysgerminoma. At the time of relapse she had nodes in the supraclavicular fossa, a para-aortic mass and an elevated AFP. She received 3 courses of BEP with good response and then 3 courses of CEB, carboplatin being substituted for cisplatin because of reduced renal clearance. On completion of chemotherapy she had a second-look laparotomy which was negative. Patient 9 had a bulky Stage III dysgerminoma with a raised AFP. After 4 courses of JEB she achieved complete clinical remission. The remaining 3 patients achieved complete remission after 4 courses of BEP; in 2 patients this was confirmed at laparotomy and the third has remained disease-free for 56 months.

Although all patients experienced considerable nausea and vomiting and alopecia and moderate bone marrow toxicity there were no cases of neutropaenic fever or proven septicaemia, no lung toxicity, and no significant renal toxicity.

DISCUSSION

Historically, the outlook for patients with NDOGCT was extremely poor. In the series of endodermal sinus tumours reported by Kurman and Norris [1] the actuarial survival rate was only 13% at 3 years, even though 71% of patients had Stage I disease. The few survivors received either surgery alone or surgery with vincristine, actinomycin-D and cyclophosphamide (VAC). There were no survivors among 12 Stage I patients treated with combined surgery and radiotherapy.

With the advent of combination chemotherapy results started to improve. Slayton *et al.* [15] reported that 16/27 (58%) of patients with NDOGCT who received vincristine, actinomycin-D and cyclophosphamide (VAC) post-operatively were alive and well. Of the 11 patients who failed on VAC, 6 patients had advanced disease. However, 5 patients who failed had Stage I EST.

As shown in Table 2 more recent experience with platinum-containing regimens has shown very promising results. Of a total of 61 previously untreated patients with NDOGCT reported in the literature (including the present series) 53 (87%) are alive and disease-free.

Although the prognosis for patients with NDOGCT has undoubtedly improved, the outcome of treatment with platinum-containing chemotherapy appears to be influenced by advanced stage and tumour bulk. Although data are scanty, several authors have reported deaths in Stage IV presentations [6, 9, 11, 12] and the 1 death in the present series occurred in a patient with a bulky pelvic mass.

The role of second-look laparotomy as part of routine reassessment following chemotherapy has not been established. The patient in the present series who died relapsed twice after achieving apparent complete clinical remission, on the second occasion confirmed by laparoscopy. Following her second relapse laparotomy was performed and she was found to have extensive unsuspected disease throughout the abdomen. In patients with malignant OGCT, as in ovarian carcinomas, it is frequently difficult to assess response to treatment by ultrasound and CT scanning, even with the aid of tumour markers. Accordingly, we feel that a case may be made for the selective use of laparotomy after chemotherapy in high-risk patients with bulky disease, although there are too few data to make firm recommendations.

It is clear that previous chemotherapy or radiotherapy jeopardizes the chance of cure with platinum-containing chemotherapy. As shown in Table 3, 17 patients reported in the literature with NDOGCT relapsing after non-platinum based chemotherapy or radiotherapy only 5 (29%) are alive and disease-free, compared with 87% of pre-

Table 2. Ovarian germ-cell tumours: (excluding dysgerminoma) treatment with platinum-containing combination chemotherapy in relation to stage in previously untreated patients

Authors	Chemotherapy	Stage I	Stage II	Stage III	Stage IV	Total NED*
Julian *et al.* 1980	PVB	—	2/2†	—	—	2/2
Lokey *et al.* 1981	PVB	2/2	—	—	—	2/2
Bradof *et al.* 1982	VABP	2/2	0/1	2/2‡	1/3‡	5/8
Newlands *et al.* 1982	VCR,MTX,B,P, E,A,C,HU,V,Chl	4/4	4/4	6/8		14/16
Wiltshaw *et al.* 1982	PVB	4/4	—	3/3	0/1	7/8
Gershenson *et al.* 1983	PVB	1/1	—	—	—	1/1
Carlson *et al.* 1983	PVB	5/5	—	3/3	—	8/8
Vriesendorp *et al.* 1984	PVB	1/1	1/1	1/1	1/2	4/5
Davis *et al.* 1984	PVB	3/3	1/1	—	—	4/4
Present series§	BEP or CEB	2/2	0/1	3/3	1/1	6/7
Total	24/24 100%	8/10 (80%)	21/27 (78%)		53/61 (87%)	

Numerator = number of patients disease-free. Denominator = number of patients treated.
*NED no evidence of disease.
†One patient had received 300 rad in 2 fractions which has been considered as no previous treatment.
‡Initial stage not given. Stage at time of relapse after surgery only.
§Includes 2 patients with dysgerminoma with raised AFP.

Key to drugs for Tables 3, 4 and 5
P = cisplatin, V = vinblastine, B = bleomycin, E = etoposide, VCR = vincristine, A = actinomycin D, C = cyclophosphamide, Adr = adriamycin, MTX = methotrexate, FU = 5-fluorouracil, Chl = chlorambucil, HU = hydroxyurea

Table 3. Ovarian germ-cell tumours: (excluding dysgerminoma) treatment with platinum-containing combination chemotherapy in previously treated patients

Author	Chemo for relapse	Total NED
Julian *et al.*, 1980	PVB	0/1
Jacobs *et al.*,1982	PVB	1/3
Bradof *et al.*, 1982	VAPB	1/7
Newlands *et al.*, 1982	CX°	0/2
Gershenson *et al.*, 1983	PVB	1/2
Carlson *et al.*, 1983	PVB	1/1
Vriesendorp *et al.*, 1984	PVB	1/1
Total		5/17 (29%)

Numerator = number of patients disease-free.
Denominator = number of patients treated.
CX° = Charing Cross regime—VCR,MTX,BP,E,A,Cy, HU,V,Chl.
Key to drugs—See Table 2.

viously untreated patients receiving platinum as first-line treatment (Table 2).

In conclusion we feel that given the promising results obtained with platinum-containing chemotherapy, all patients with NDOGCT including Stage I should receive chemotherapy since the prognosis was previously poor even in early-stage disease. In view of the fact that the results obtained with BEP are comparable to those obtained using PVB [16] but with less toxicity [13], our policy is to employ this combination in OGCT. With further experience it may be appropriate to substitute carboplatin for cisplatin, which has the advantage of reduced nephrotoxicity and avoids the prolonged hydration necessary with cisplatin.

In contrast, the overall results of surgery and radiotherapy for pure dysgerminoma are good if strict staging criteria are used, Stage IA patients having a unilateral salpingo-oophorectomy and all other stages managed by total abdominal hysterectomy and bilateral salpingo-oophorectomy plus whole abdomen radiotherapy [17–19]. Such an approach with inevitable loss of fertility in all but the earliest stage presentations was appropriate in the era before the advent of chemotherapy but should be reappraised in the light of recent developments in the treatment of testicular seminoma where more than 80% of advanced stage patients are rendered disease-free with platinum-containing chemotherapy and where carboplatin as a single agent appears highly effective [20]. Furthermore there is a substantial failure rate in patients with Stage III disease treated with surgery plus radiotherapy, particularly if peritoneal involvement is present [21]. By analogy with male seminomas,

Table 4. Advanced ovarian dysgerminoma: response to platinum-containing combination chemotherapy

Author	Stage	Previous treatment	Chemotherapy	Post-chemotherapy irradiation	Outcome	Time
Jacobs *et al.*, 1982	III	RT	PVB	—	NED	
Bradof *et al.*, 1982	Rec	RT	VABP	—	NED	48m‡†
Newlands *et al.*, 1982	III	RT	CX°	—	NED	5m*
	III	RT	CX°	—	NED	14m*
	III		CX°	—	NED	33m*
Vriesendorp *et al.*, 1984	IV	—	PVB	—	NED	17m*
Present series‡	III	—	BEP	+	NED	44m†
Total				7/7 100%		

*Time from completion of chemotherapy.
†Time from start of chemotherapy.
‡One patient excluded because platinum omitted.
CX° = Charing Cross regime—VCR,MTX,B,P,E,A,Cy,HU,V,Chl.
Key—see Table 2.

dysgerminomas should be chemosensitive as well as radiosensitive. Hence, chemotherapy should be considered as first-line treatment for disseminated bulky disease, which if necessary could be followed by radiotherapy. In the present series of 2 patients with Stage III pure dysgerminoma were treated with combination chemotherapy folllowed by radiotherapy. The first patient was felt to be at risk of relapse because of the omission of cisplatin and received whole abdominal irradiation with a pelvic boost. In the second patient, who had very extensive pelvic disease, chemotherapy was followed by pelvic irradiation since it was felt there was a high risk of local recurrence. However, recent data in advanced testicular seminoma suggest that post-chemotherapy irradiation may not be necessary [20]. Certainly, if this can be avoided the chances of preserving fertility are much higher.

Table 4 summarizes the limited data reported in the literature on the response of advanced dysgerminomas to platinum-containing chemotherapy showing that all 7 patients are disease-free despite the extensive nature of their disease at presentation. Clearly more information is needed before firm conclusions can be reached but this limited experience suggests that treatment may be safely deferred in the early stage patient so that conservative surgery (USO) with close observation is appropriate in patients with Stage I_A dysgerminoma. Advanced stage patients should be considered for platinum-containing chemotherapy as an alternative to radical surgery and post-operative radiotherapy.

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