

European Journal of Cancer Vol. 31A, No. 11, pp. 1890–1891, 1995.
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0959-8049/95 \$9.50 + 0.00

0959-8049(95)00371-1

Salvage Chemotherapy in Non-dysgerminomatous Germ Cell Tumours of the Ovary

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OVARIAN GERM cell tumours (OGCT) are rare but potentially curable neoplasms that usually affect young females. The patho-

logical classification mainly distinguishes pure dysgerminoma, the female equivalent of seminoma, and tumours other than pure dysgerminoma, the so-called non-seminomatous germ cell tumours. Over the past 20 years, chemotherapy of OGCT has evolved along similar lines to that of testicular germ cell tumours. The first-line treatment of patients with non-dysgerminomatous OGCT currently includes primary surgery and subsequent chemotherapy with etoposide and cisplatin. The results are satisfactory with an overall survival of 80% at 5 years [1]. However, for those patients who have not sustained a complete remission after first-line treatment, the role of salvage chemotherapy has not been clearly studied [2].

From September 1976 to December 1992, 49 patients with non-dysgerminomatous OGCT were treated at Institut Gustave Roussy, France. 10 (20%) failed the primary treatment. 2 patients rapidly died of progressive disease without further therapy. The other 8 patients, 4 who primarily failed first-line

Table 1. Patient characteristics

Patient	Age (years)	Histology	FIGO stage	First-line treatment	Response	Salvage chemotherapy	Response	Status (months)
1	17	Mixed	IV	LO + VAB × 5	PD	Etoposide × 5	PD	DOD (11)
2	23	Mixed	IC	BO + TH + O + VAB × 5	PD	Ifosfamide × 2 PVeBV × 2	PD	DOD (12)
3	24	EST	IV	Biopsy + PVeBV × 6	sCR	Ifosfamide × 2	PD	DOD (18)
4	24	Mixed	IIIC	BO + TH + O + PVeBV × 2 + PEC/ABMT	cCR	VIhP × 4	PD	DOD (34)
5	17	Mixed	IV	LO + EP × 6	cCR	RO + VIP × 4	cCR	NED (24+)
6	26	IT	IC	LO + VAB × 2	PD	VIP × 3	cCR	NED (72+)
7	59	EST	IC	BO + TH + EP × 4	cCR	VelP × 2	PD	DOD (14)
8	51	EST	IIC	BO + TH + CCP × 6	PD	VIC × 4	PD	DOD (22)

EST, endodermal sinus tumour; IT, immature teratoma; LO, left oophorectomy; RO, right oophorectomy; BO, bilateral oophorectomy; TH, total hysterectomy; O, omentectomy; VAB, vinblastine+actinomycin-D+cyclophosphamide+bleomycin+cisplatin; PVeBV, double-dose cisplatin+etoposide+vinblastine+bleomycin; PEC, cisplatin+etoposide+cyclophosphamide; ABMT, autologous bone marrow transplantation; EP, etoposide+cisplatin; CCP, cyclophosphamide+carboplatin+cisplatin; VIhP, etoposide+ifosfamide+double-dose cisplatin; VIP, etoposide+ifosfamide+cisplatin; VelP, vinblastine+ifosfamide+cisplatin; VIC, etoposide+ifosfamide+carboplatin; PD, progressive disease; sCR, surgical complete response; cCR, clinical complete response; DOD, dead of disease; NED, no evidence of disease.

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Received 27 Mar. 1995; accepted 12 Apr. 1995.

treatment and 4 who experienced a relapse after initial complete remission received salvage chemotherapy. Their characteristics are shown in Table 1. The median age was 24 years (range 17–59). Tumour histology included pure immature teratoma (1 patient), endodermal sinus tumour (3 patients) or mixed tumours (4 patients). All but one patient (patient 3) had undergone primary abdomino-pelvic surgery. The first-line chemotherapy regimens included cisplatin in all patients and additional etoposide in 4 patients. In the 4 patients who relapsed after initial complete remission, the interval between the end of primary treatment and relapse was 2, 3, 16 and 17 months in patients 3, 7, 5 and 4, respectively. Sites of relapse were: only the pelvis in patients 3 and 7; pelvis and liver in patient 4; and contralateral ovary and lung in patient 5. Cytoreductive surgery was performed at the onset of salvage treatment in only 1 patient (patient 5). Chemotherapy included a one drug regimen (etoposide or ifosfamide) in 3 patients or ifosfamide-based regimens in 5 patients. Only two clinical complete responses were obtained. These 2 patients are alive without evidence of disease, 24 and 72 months after the end of salvage therapy.

In this series, the salvage protocols were clearly derived from those described in previous studies on testicular germ cell tumours. In the last 15 years, only two drugs, etoposide and ifosfamide, have demonstrated response rates greater than 20% as single agents in the salvage setting. The remarkable efficacy of etoposide rapidly led to its successful evaluation in first-line regimens. Therefore, subsequent studies have focused on the impact of ifosfamide in second-line therapy. Early clinical trials with ifosfamide in heavily pretreated patients suggested definite activity, and provided the basis for further evaluation in a more favourable population [3]. The combination of ifosfamide, cisplatin and etoposide or vinblastine is the current standard treatment after first-line failure [4]. These regimens only induce 15–40% long-term non-progressive disease [4–6]. The use of double-dose cisplatin does not improve these modest results [7]. The role of high dose chemotherapy and autologous bone marrow transplantation is under study in this setting [8].

From this small series, we conclude that the salvage treatment of non-dysgerminomatous OGCT appears to share similar characteristics and outcome to those of testicular germ cell tumours. Only 2 patients among 6 who received combination chemotherapy remain free of disease. Further multicentric studies of the salvage treatment of non-dysgerminomatous OGCT are required in order to draw firm conclusions.

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European Journal of Cancer Vol. 31A, No. 11, pp. 1891–1892, 1995.
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0959-8049(95)00369-X

Lobaplatin in Combination with Methotrexate and Vinblastine in Patients with Transitional Cell Carcinoma of the Urinary Tract—A Pilot Phase I/II Study

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CISPLATIN AND methotrexate are currently considered the most active single agents in transitional cell cancer (TCC), followed by doxorubicin, vinblastine and 5-fluorouracil (5-FU). The most frequently used combination regimens, cisplatin and methotrexate [1], cisplatin, methotrexate and vinblastine (CMV) [2] or cisplatin, methotrexate, vinblastine and doxorubicin (M-VAC) [3] achieve response rates of 40–70% with a considerable toxicity: 20% grade 3 thrombocytopenia, 25% fever in association with leucopenia and 38% decrease of creatinine clearance.

In this study, cisplatin used in CMV regimen was replaced by lobaplatin to reduce renal toxicity. Lobaplatin is a platinum complex, of which *in vitro* and *in vivo* studies have shown superior activity to *cis*- and carboplatin [4, 5]. Lobaplatin as a single agent has been investigated in phase I and II studies [6–9]. The recommended dose is 50 mg/m², day 1, every 3 weeks; the dose limiting toxicity of lobaplatin is thrombocytopenia 2 weeks after drug administration. Leucopenia is less severe than thrombocytopenia with a nadir 3 weeks after lobaplatin administration. There has been no evidence of renal toxicity.

5 patients were treated with the schedule LMV: lobaplatin (50 mg/m²) day 2, methotrexate (30 mg/m²) and vinblastine (4 mg/m²) (LMV(A)) or vinblastine (3 mg/m²) (LMV(B)) on days 1 and 8 of a 3 week cycle. Granulocyte-colony stimulating factor (G-CSF) was given in cases of grade 3 or 4 leucopenia, and platelets were infused when clinically indicated. 3 patients (Nos 1, 3 and 5), with lymph node-positive TCC of the bladder were treated with LMV as inductive chemotherapy. Iliac lymph node metastases were proven by computed tomography (CT)-guided biopsy. One patient (No. 2) received two cycles of LMV because of liver metastases of TCC of the ureter. One patient (No. 4) was treated because of adrenal gland metastasis of a TCC of the bladder.

One patient (No. 3) had a complete response (CR), and received two further cycles of LMV after cystectomy. In 2

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Revised 20 Feb. 1995; accepted 17 Mar. 1995.