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.

1. Williams SD. Current management of ovarian germ cell tumours. *Oncology* 1994, **8**, 53–60.
2. Gershenson DM. Update on malignant ovarian germ cell tumours. *Cancer* 1993, **71**, 1581–1590.
3. Wheeler BM, Loehrer PJ, Williams SD, Einhorn LH. Ifosfamide in refractory male germ cell tumors. *J Clin Oncol* 1986, **4**, 28–34.
4. Loehrer PJ, Lauer R, Roth BJ, *et al.* Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. *Ann Intern Med* 1988, **109**, 540–546.
5. Motzer RJ, Cooper K, Geller NL, *et al.* The role of ifosfamide plus cisplatin-based chemotherapy as salvage therapy for patients with refractory germ cell tumours. *Cancer* 1990, **66**, 2476–2481.
6. Harstrick A, Schmoll HJ, Wilke H, *et al.* Cisplatin, etoposide, and ifosfamide salvage therapy for refractory or relapsing germ cell carcinoma. *J Clin Oncol* 1991, **9**, 1549–1555.
7. Ghosn M, Droz JP, Theodore C, *et al.* Salvage chemotherapy in refractory germ cell tumor with etoposide (VP-16) plus ifosfamide plus high-dose cisplatin. A VIhP regimen. *Cancer* 1988, **63**, 24–27.
8. Droz JP, Pico JL, Kramar A. Role of autologous bone marrow transplantation in germ-cell cancer. *Urol Clin North Am* 1993, **20**, 161–171.

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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/m^2, 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/m^2) day 2, methotrexate (30 mg/m^2) and vinblastine (4 mg/m^2) (LMV(A)) or vinblastine (3 mg/m^2) (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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Table 1. Haematological toxicity

Patient	Toxicity after cycle 1	Grade	Day	Treatment	Toxicity after cycle 2	Grade	Day	Treatment
1	Thrombopenia	0			Thrombopenia	1	15	
LMV(A)	Leucopenia	3	23		Leucopenia	2	12	
2	Thrombopenia	4	14	Platelet infusion: 2 U	Thrombopenia	3	12	Platelet infusion: 1 U
LMV(A)	Leucopenia	4	14	G-CSF: 3 × 480 μg	Leucopenia	3	12	G-CSF: 2 × 480 μg
3	Thrombopenia	3	15		Thrombopenia	1	15	
LMV(A)	Leucopenia	2	12		Leucopenia	1	15	
4	Thrombopenia	2	15		Thrombopenia	0		
LMV(B)	Leucopenia	2	22		Leucopenia	1	12	
5	Thrombopenia	4	13	Platelet infusion: 7 U	Thrombopenia*	3	12	
LMV(B)	Leucopenia	3	15	G-CSF: 7 × 480 μg	Leucopenia*	1	7	G-CSF: 7 × 480 μg

Grade of thrombo-leucocytopenia according to WHO. LMV, lobaplatin, methotrexate, vinblastine.
*Dose of lobaplatin reduced to 40 mg/m².

Table 2

Patient	Toxicity after cycle 3	Grade	Day	Treatment	Toxicity after cycle 4	Grade	Day	Treatment
1	Thrombopenia	1	16		Thrombopenia	3	15	
LMV(A)	Leucopenia	2	12		Leucopenia	3	15	
3	Thrombopenia	4	13	Platelet infusion: 1 U	Thrombopenia*	3	11	
LMV(B)	Leucopenia	3	15	G-CSF: 3 × 480 μg	Leucopenia*	3	11	G-CSF: 4 × 480 μg

Grade of thrombo-leucocytopenia according to WHO. LMV, lobaplatin, methotrexate, vinblastine.
*Dose of lobaplatin reduced to 40 mg/m².

patients (Nos 1 and 2), a partial response (PR) was revealed; No. 1 received two further cycles of LMV after cystectomy, No. 2 refused further chemotherapy. Patient No. 5 had no change and No. 4 had progressive disease.

Toxic effects of the treatment besides mild vomiting, were leucocytopenia and thrombocytopenia (Table 1). An evaluation after eight cycles with LMV(A) revealed a high incidence of leucocytopenia compared to results from clinical studies with lobaplatin as single agent. For vinblastine, considered as the drug with the lowest contribution, to overall efficacy of combination regimens, leucocytopenia is reported to be the main adverse reaction. Therefore, it was reasonable to reduce the vinblastine dose from 2 × 4 to 2 × 3 mg/m². After vinblastine reduction, no further grade 4 leucocytopenia was observed. Lobaplatin dose was reduced in two cycles after severe thrombocytopenia (Table 1).

Serum creatinine, urea and creatinine clearance were measured weekly. A decrease of renal function was not observed in any of the patients, although 2 patients (Nos 2 and 5) were treated in spite of reduced creatinine clearance (71–84 ml/min). This study shows that lobaplatin in combination with methotrexate and vinblastine is a safe therapy with regard to the haematopoietic system and renal function, and that a repetition after 3 weeks is feasible. A randomised study comparing LMV versus CMV is warranted.

1. Splinter TAW, Schröder FH, Denis L, *et al.* Phase-II study of neoadjuvant chemotherapy in T3-4 NO-X MO transitional cell carcinoma of the bladder: a preliminary analysis. *Eur Urol* 1988, **14**, Suppl. 1, 24–26.
2. Harker WG, Meyers FJ, Freiha FS. Cisplatin, methotrexate and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract: a Northern California Oncology Group study. *J Clin Oncol* 1985, **3**, 1463–1470.
3. Sternberg CN, Yagoda A, Scher HI, *et al.* M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988, **139**, 461–469.
4. Rohde D, Sommerhäuser B, Jakse G. Zytotoxizität von Lobaplatin an Harnblasenkarzinomzellinien *in vitro*. *Experimentelle Urologie* 1992, abstr. 140.
5. Voegeli R, Günther E, Aulenbacher P, Engel J, Hilgrad P. Lobaplatin (D-19466). *Drugs of the Future* 1992, **17**, 883–886.
6. Gietema JA, deVries EGE, Sleijfer DT. A phase I study of 1,2-diamminomethyl-cyclobutane–platinum (II)–lactate (D-19466; lobaplatin). *Br J Cancer* 1993, **67**, 396–401.
7. Mross K, Meyberg F, Fiebig HH, *et al.* Pharmacokinetic and pharmacodynamic study with lobaplatin (D-19466), a new platinum complex, after bolus administration. *Oncology* 1992, **15**, 139–146.
8. Fiebig HH, Henβ H, Meyberg F, Aulenbacher P, Burk K, Queiβer W. Phase I clinical trial of lobaplatin (D-19466) after intravenous bolus injection. *Onkologse* 1994, **17**, 142–148.
9. Gietema JA, Guchelaar HJ, Willemse PHB, *et al.* Phase II and pharmacokinetic study with lobaplatin (D-19466) in patients with relapsed ovarian cancer. *Proc Am Soc Cancer Res* 1993, **34**, 204.