cessation in particular shown to be the most cost-effective procedure.

(b) Successful cancer control largely depends upon the quality of family health care in general, because it includes all aspects of medical care.

(c) Special emphasis should now be placed on improving the quality of continuing education of physicians and nurses in primary health care.

(d) Primary prevention in cancer through risk-oriented intervention measures is inseparable from prevention of cardiovascular diseases and some other chronic diseases. Therefore, cooperation between cardiology and oncology in prevention is to be promoted.

(e) Prohibition of the sale of tobacco to minors (those under the age of 16) is an important element in the prevention of smoking in adolescents.

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Letters

Feasibility Trial of a Combination of Vinorelbine, Ifosfamide, Fluorouracil and Folinic Acid (VIF Regimen) in Advanced Urothelial Cancer

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SUBSTANTIAL IMPROVEMENTS have been made in the treatment of advanced urothelial cancer. The most encouraging results are obtained with the M-VAC regimen which offers a high response rate with a substantial complete response rate and about 15% of long-term survivors [1, 2]. Unfortunately, there is no standard salvage regimen for patients who relapse or who are refractory to M-VAC. In addition, in case of impaired renal or cardiac functions there is no standard alternative regimen to M-VAC. In order to develop such an alternative regimen, we have studied the combination of three potentially active drugs: 5-fluorouracil (FU), ifosfamide (I) and vinorelbine (V). The choice of FU was based on the results of several trials [3–5] which suggested some activity against urothelial cancer. Whereas ifosfamide has been extensively investigated in several solid tumours, few clinical trials have been conducted in urothelial cancer. Authors who have performed such studies, especially in the treatment of squamous cell carcinoma of the bladder, report impressive response rates for ifosfamide when used either as single agent or in combination with anthracyclines [6]. V (or nor 5'-anhydrovinblastine) is a new vinca-alkaloïd selected for its improved therapeutic index compared with its parent compound vinblastine. Although this drug has not yet been tested in bladder cancer, it is of particular interest since it showed some activity in patients pretreated with other vinca-alkaloïd containing regimens [7].

We report here the results of a feasibility trial of a combination of V-I-FU and folinic acid (VIF regimen) in advanced stage urothelial cancer.

From January 1990 to March 1991, 14 patients with advanced urothelial cancer were treated in this phase II trial. Patient characteristics are summarised in the Table 1. 4 patients were not pretreated since they could not receive M-VAC because of impaired renal function. All but 1 of the remaining 10 patients had received at least one line of prior cisplatin-containing chemotherapy. The median interval between the last therapy and VIF regimen was 6 months (range, 1–13).

The chemotherapy consisted of: V 25 mg/m^2/day, days 1 and 8; I 2 g/m^2/day, days 1–3; FU 400 mg/m^2/day, days 1–3 and folinic acid 300 mg/m^2/day, days 1–3; repeated every 3 weeks. V was administered in rapid intravenous infusion, I in 1-h infusion in 1 l DW5 with uromitexan 2.4 g/m^2/day, days 1–3 in continuous infusion; FU in a 1-h infusion in 500 ml DW5 and folinic acid in intravenous push 15 min prior to FU infusion.

45 cycles were administered, the median number of cycles being four (range, one to six). In only 27/45 (60%) could the

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Table 1. Patients' characteristics

Total number of patients	14
Age (years)	
Median	63
Range	49–69
Sex (M/F)	12/2
Performance status (WHO)	
0–1	10
2	3
3	1
Primary tumour	
Bladder	9
Ureter	5
Histology	
Transitional cell	13
Squamous cell (partial)	1
Status of disease at inclusion	
Locoregional recurrence with metastases	12
Initially metastatic disease	2
Tumour sites	
Liver	7
Lung	5
Bone	3
Abdominal lymph nodes	6
Peripheral lymph nodes	3
Pelvic lymph nodes	2
Bladder	1
Ureter	2
Peritoneum	2
Pelvic mass	1
Number of tumour sites	
1	3
2	5
> 2	6
Prior treatment	
Surgery	11
Radiation therapy	5
Chemotherapy	10

intermediate day of vinorelbine be administered. The major side-effect was haematological toxicity. We observed neutropenia grade 3: six cycles (15%) in 5 patients and grade 4: 30 cycles (75%) in 12 patients. Eight cycles were delayed and 2 patients required dose reduction. There were 13 neutropenic fevers, but without any infection. 2 patients who experienced severe haematological toxicity died early at 10 and 12 days, respectively, after the first cycle, from irreversible septic shock with WHO grade 4 diarrhoea and mucositis. We also observed four episodes of encephalopathy (one grade 2 and three grade 3) completely and spontaneously reversible after the discontinuation of chemotherapy. 1 patient developed an acute and irreversible renal insufficiency complicated by febrile aplasia and grade 3 encephalopathy. This patient was removed from the study and died 1 month later from progressive disease. 1 patient refused to receive further courses of chemotherapy after the first cycle.

Thus only 10 patients were evaluable for response. There was 1 complete response (CR), 2 partial responses (PR), 4 stabilisations (S) and 3 progressions (P). Two of the three objective responses occurred in previously untreated patients (1 CR + 1 PR) and 1 PR was obtained in a patient who was progressive during a CMV regimen. CR lasted 5 months and PR lasted 4 and 8 months, respectively. All patients died of progressive disease (12 patients) or toxicity (2 patients) with an overall median survival of 5 months (range, 1–9 months).

VIF regimen shows moderate but true efficacy in the treatment of advanced urothelial cancer achieving only 1 CR and 2 PR of short duration in 3 patients who were not candidate to M-VAC regimen. The high incidence of grade 4 neutropenia and febrile aplasia in addition to two toxic deaths clearly demonstrate that this regimen is not feasible. In our opinion, an evaluation of I and of different schedules of modulation of 5-FU merit study in phase II trials. Data about these two drugs are either rare or contradictory and have to be confirmed in well designed phase II studies. I, for example, has never been tested in transitional cell carcinoma. Nazli *et al.* [6] reported impressive results with a response rate of 40% with I alone and more than 60% in combination with epirubicin. On the other hand efficacy of 5-FU is controversial. The Eastern Cooperative Oncology Group [3] reported a response rate of 14% in 64 patients of whom 2 patients failed previously to respond to doxorubicin-containing regimen, whereas in other more limited trials, the efficacy of 5-FU was in the range of 7 to 30% [4, 5].

Studies such as this are essential since there is no standard salvage regimen for patients who fail to respond to M-VAC. Successful reports in this area are rare and disappointingly not reproducible. The most encouraging and impressive results were reported by Logothetis *et al.* [8] who used granulocyte macrophage colony stimulating factor plus escalated dose of M-VAC in patients refractory to cisplatin-containing regimens. Moreover, new drugs such as gallium-nitrate seem to be promising agents, even in patients who have failed prior cisplatin therapy [9, 10].

1. Sternberg CN, Yagoda A, Scher HI, *et al.* MVAC for advanced transitional cell carcinoma of the urothelium: Efficacy and pattern of response and relapse. *Cancer* 1989, **64**, 2448–2458.
2. Boutan-Laroze A, Mahjoubi M, Droz JP, *et al.* MVAC (methotrexate, vinblastin, doxorubicin and cisplatin) for advanced carcinoma of the bladder. The French Federation of Cancer Center experience. *Eur J Cancer* 1991, **27**, 1690–1694.
3. Yagoda A. Chemotherapy of urothelial tract tumors. *Cancer* 1987, **60**, 574–585.
4. Fossa SD, Gudmundsun TE. Single drug chemotherapy with 5FU and adriamycin in metastatic bladder carcinoma. *Br J Urol* 1981, **53**, 320–323.
5. Knight EW, Pagand M, Hahn RG, *et al.* Comparison of 5FU and doxorubicin in the treatment of carcinoma of the bladder. *Cancer Treat Rep* 1983, **67**, 514–515.
6. Nazli G, Khaled H, Abdlewareth A. Epirubucin, ifosfamide combination chemotherapy in invasive bladder cancer. *Proc Am Soc Clin Oncol* 1990, 530.
7. Eghbali H. Etude de phase II Navelbine dans la maladie deHodgkin et les lymphomes chez des malades très lourdement prétraités. In *Navelbine actualités et perspectives*. Pierre Fabre Oncologie, 1990, 257–265.
8. Logothetis C, Dexeus F, Sella A, *et al.* Escalated (Esc) MVAC (MTX 30 mg/m^2, adriamycin 60 mg/m^2, vinblastine 4 mg/m^2, cisplatin 100 mg/m^2) with recombinant human granulocytes macrophage stimulating factor ((rh GM—CSF) schering corp) for patients (pts) with advanced and chemotherapy (CHT) refractory urothelium tumors. A phase I study. *J Clin Oncol* 1990, **8**, 1050–1055.
9. Seidman A, Scher H, Sternberg C, *et al.* Gallium-Nitrate (Ga-N) an active agent in patients with advanced refractory transitional cell carcinoma of the urothelium. *Proc Am Soc Clin Oncol* 1991, 520.
10. Seligman PA, Grawford DE. Treatment of advanced transitional cell carcinoma of the bladder with constant infusion Gallium-Nitrate (Ga-N). *Proc Am Soc Cli Oncol* 1991, 534.