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Timed sequential chemotherapy following ifosfamide-induced kinetic recruitment in refractory ovarian cancer*

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Summary. A total of 22 relapsed or refractory ovarian cancer patients were treated with ifosfamide-containing polychemotherapy. Kinetic analyses were done to evaluate the tumor-cell-recruiting potential of the alkylating agent. Our study shows that ifosfamide can enhance tumor proliferative activity in pretreated ovarian cancers.

Aggressive chemotherapy including cisplatin derivatives has been proven to induce objective responses in 60%–80% of advanced ovarian cancer patients, with a rate of about 25%–30% for complete responses [8, 13, 17, 18]. However, the treatment schedule is generally designed on an empirical basis, regardless of tumor-cell sensitivity.

Several attempts have been made to recruit non-dividing, quiescent cells (representing the majority of the solid-tumor cell population) into the proliferating pool so as to enhance cell susceptibility to cytotoxic agents. Hormones, X-rays and alkylating agents have been used to increase the growth fraction of tumors, followed by cycle-specific drugs, which are given concomitantly with the recruitment peak to improve the therapeutic index of antitumor agents [2, 5–7, 10, 11, 15, 16, 19, 21, 27, 29].

Most kinetic studies have been carried out in haematological malignancies [5, 10, 15, 27–29]. The present study evaluated the kinetic recruitment induced by ifosfamide in 22 ascitic ovarian cancer patients.

Patients and methods

A total of 22 women with ascitic ovarian cancer refractory to (15 patients) or relapsing after (7 cases) front-line cisplatin-containing polychemotherapy were investigated to test cell-kinetic recruitment after i. v. ifosfamide (IFO) administration.

Eight patients received chemotherapy consisting of 1.5 g/m^2 i. v. IFO given on days 1–5 and 40 mg/m^2 methotrexate (MTX) and 600 mg/m^2 5-fluorouracil (5-FU) given on day 12, every 28 days. After a few cycles, the IFO dose was reduced to 1.5 g/m^2 on days 1–3 in heavily pretreated patients because of the delay in bone marrow recovery on day 12.

The remaining 14 patients were treated with 3 g/m^2 IFO, 50 mg/m^2 cisplatin and 45 mg/m^2 Adriamycin on day 1 every 28 days. Sodium-2-mercaptoethane sulphonate (mesna) was given orally at 40% of the IFO dose at 0, 4 and 8 h after IFO infusion to counteract urotoxicity [23]. Tumor cells were collected from ascitic fluid before and after 3, 11–14 and 18–21 days from IFO administration. Kinetic analyses were determinated by means of the thymidine labelling index (TLI) as previously described [7].

Results

Kinetic evaluations of IFO-treated patients are presented in Table 1. A total of 22 patients were evaluated on day 0; 16, on day 3; 20, on days 11–14; and 15, on days 18–21. Analysis of the median value revealed a decrease in TLI 3 days after IFO, a peak value on days 11–14 and a nadir value on days 18–21. No increase in proliferative activity was seen in six patients. Clinical responses included stabilization of disease in 5 patients and progression in 17. Moderate to severe haematological toxicity was observed in almost all cases, with six patients experiencing WBC counts of $<1.5\times 10^6$/l on days 11–14.

Discussion

A close relationship between tumor proliferative activity and sensitivity to cytotoxic drugs has been established [1, 3, 4, 12, 22, 25, 26]. In the present study, IFO was given to evaluate its potential as a recruiting agent and in enhancing cytotoxicity of cycle-specific drugs given concomitantly with the proliferative peak.

In all but six patients, cell-cycle recruitment was noted after IFO exposure. Failures may be explained by drug resistance or by the occurrence of the recruitment peak earlier than days 11–14. Our patients were heavily pre-

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Table 1. TLI evaluation in IFO-treated ovarian cancer patients

Patient number	Median TLI value: Day 0	Day 3	Days 11–14	Days 18–21
22	4.3 (range, 0.6–18.7)	0.35 (range, 0.2–2.2)	8.2 (range, 3.9–1.4)	1.7 (range, 1.2–2.6)

treated or refractory, but it is important to note that leukopenia was not severe enough to prevent the administration of antimetabolites on day 12 in 9 of 19 courses scheduled.

No study has been done to evaluate IFO recruitment in the hemopoietic system; however, haematological toxicity is higher in kinetically designed chemotherapy [9]. A close relationship between tumor proliferative activity and sensitivity to cytotoxic drugs has been claimed [14].

In the present study, IFO showed recruiting activity in pretreated ovarian cancer patients. Tumor kinetic evaluations may lead to a more rational schedule for drug administration and improve the poor results obtained with conventional chemotherapy in refractory patients. Maximal effort should be made to optimize the use of alkylating agents and to exploit the recruiting potential of new molecules such as growth factors.

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