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Epirubicin and ifosfamide in patients with refractory breast cancer and other metastatic solid tumours*,**

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Summary. The combination of ifosfamide (IFO) and epirubicin (EPI) has been found to be an effective regimen in the treatment of metastatic tumours and shows remarkable activity in heavily pretreated breast cancer patients. A combination of EPI (35 mg/m^2 on days 1 and 2) and IFO (1.8–2.5 g/m^2 on days 1–5) was given to 58 patients with refractory breast cancer (n = 23), metastatic sarcomas (n = 15) and other solid tumours (n = 20). Due to extensive prior therapy, the IFO dose had to be adapted to the individual haematological situation. In all, 55 patients were evaluable; we observed 5 complete (CRs) and 16 partial responses (PRs). In addition, 18 patients experienced a minor response (MR) or no change (NC). The median duration of all responses was 6.7 months. Toxicity was generally mild and closely related to previous therapy.

Introduction

Primary or acquired drug resistance remains a major clinical problem, especially in the treatment of advanced refractory breast cancer or other metastatic solid tumours. Since the urotoxicity of ifosfamide (IFO) can be controlled by mesna, the use of increased doses of this drug has led to higher efficacy both in monochemotherapy and in combination regimens. Today IFO shows remarkable activity even in extensively pretreated patients with advanced disease.

Patients and methods

We report on our experience with a combination regimen of epirubicin (EPI) and IFO in 58 patients (55 evaluable) suffering from histologically proven, pretreated breast cancer (n = 23), metastatic sarcomas (n = 15), adenocarcinomas (n = 11) and various other solid tumours (n = 9). All breast cancer patients had been extensively pretreated and had failed cyclophosphamide/methotrexate/5-fluorouracil (CMF) or hormonal treatment; ten had previously received anthracyclines. The median Karnofsky status was 80% and the median age was 52 (range, 20–72) years.

The treatment schedule consisted of 35 mg/m^2 EPI on days 1 and 2 and 2.5 g/m^2 IFO on days 1–5, given every 21–28 days (according to performance status and expected myelotoxicity, which was related to the extent of pretreatment). In patients with a leucocyte count of <1,500/μl or a platelet count of <100,000/μl on day 21, therapy was delayed until day 28. In those with a leucocyte count of 1,500–2,500/μl or a platelet count of 100,000–130,000/μl on day 21, therapy was not delayed but the IFO dose was reduced to 1.8 g/m^2 in the subsequent course (Table 1).

Response was measured by objective criteria and examination of X-ray and computerised tomographic (CT) findings as well as laboratory results [partial (PR) or complete response (CR)] or was evaluated by the improvement in the patients' condition and performance status [minor response (MR)].

Results

Toxicity was generally mild and tolerable for all patients (Table 2). Alopecia (WHO grade 3) occurred in all patients or was present before treatment began. Myelosuppression was mild, but dose modifications (four patients, six courses) or prolongation of therapy-free intervals (eight patients, ten courses) were necessary, especially for heavily pretreated patients. Cardiac side effects such as supraventricular tachycardia were occasionally observed.

None of the breast cancer patients achieved a CR; eight showed a PR, and ten showed an MR or NC. The disease was progressive (PD) in five cases. The CRs in sarcoma patients lasted for 40–52 weeks; all patients subsequently relapsed. Of nine other patients [one thymoma, three carcinoids, six non-small-cell lung cancers (NSCLC)], one (NSCLC) experienced a CR that lasted for 20 weeks. The median time to progression and a summary of all results is shown in Table 3.

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Table 1. Drug schedule

EPI (push)	35 mg/m² on days 1,2
IFO (infusion)	1.8–2.5 g/m² on days 1–5

At the start of the infusion and 4 and 8 h later, patients received i. v. mesna at 20% of the IFO dose. The schedule was repeated every 21–28 days until tumour progression

Table 2. Toxicity of IFO/EPI

Alopecia	(WHO grade 3)	100%
Myelosuppression:		
Leucocytes	(WHO grade 1–2)	45%
	(WHO grade 3)	15%
	(WHO grade 4)	0
Emesis:		
	(WHO grade 1–2)	75%
	(WHO grade 3)	15%
Urotoxicity		23%
Cardiac side effects		10%

Table 3. Response to IFO/EPI and duration of response

	Patients (*n*)	CR	PR	MR/NC	PD	Time to progression (weeks)
Breast cancer	23	-	8	10	5	22
Sarcomas	15	4	6	2	3	32
Adenocarcinomas	11	-	7	2	2	16
Other	9	1	3	1	4	12

Discussion

IFO and IFO-based combinations have shown valuable clinical activity in a wide variety of human solid tumours [3–7]. The present study describes a palliative approach for two categories of patients: (1) extensively pretreated breast cancer patients with the inherent problem of acquired drug resistance, and (2) patients with tumours such as sarcomas and non-breast adenocarcinomas that are rather resistant to conventional treatment regimens or are assumed to be primary-resistant. In spite of the relatively small study group and with the limitations of a retrospective evaluation, our data show both effective palliation in the poor-prognosis breast cancer group (with most patients suffering from visceral disease manifestations) and a significant number of CRs in the non-pretreated sarcoma group.

It would appear from these and other data that IFO needs and deserves further evaluation as first-line chemotherapy in breast cancer. As a second- or third-line agent, alone or in combination, IFO may deserve a trial in most clinical situations involving progressive, inoperable and refractory solid neoplasma. We assume that the additional use of an anthracycline in such situations will in the future be influenced by the presence of the multidrug-resistant phenotype; however, multidrug-resistant tumours may still respond to IFO, as we have previously demonstrated in an experimental tumour system resistant to both anthracyclines and cisplatin [6].

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