Eur J Cancer Clin Oncol, Vol. 24, No. 6, pp. 959–961, 1988.
Printed in Great Britain

0277–5379/88/$3.00 + 0.00

Perspectives and Commentaries

Ifosfamide: an Old Drug Recently Rediscovered

F. CAVALLI

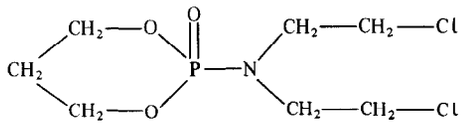
Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

(A COMMENT ON: Bramwell VHC, Mouridsen HT, Santoro A *et al.* Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. *Eur J Cancer Clin Oncol* 1987, **23**, 311–321).

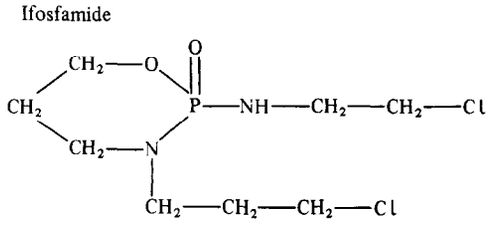
IFOSFAMIDE and cyclophosphamide are alkylating oxazaphosphorines which need to be activated *in vivo*. Ifosfamide (IFO) differs chemically from cyclophosphamide by the transfer of one 2-chloroethyl group from the nitrogen mustard moiety of the molecule to the cyclic phosphamide nitrogen atom of the oxazaphosphorine ring (Fig. 1). In experimental animal tumors the two drugs showed similar spectra of activity, while their acute and chronic toxicities were at least quantitatively somewhat dissimilar [1].

IFO was the subject of a clinical trial in Europe as early as 1977, when it demonstrated activity in a wide range of tumors [1]. Unfortunately, dose-limiting hemorrhagic cystitis and occasional renal failure prevented more widespread use of the drug. In fact, in an effort to circumvent this toxic effect, it was necessary to undertake dose-fractionation for several days as well as various uroprotective measures, such as urine-alkalinization and increased fluid intake. Furthermore, the degree of antitumor activity was not clearly established in many tumor types, mainly because some Phase II trials were based on suboptimal Phase I data. Thus, the history of IFO, along with that of certain other cytotoxic drugs, e.g. etoposide [2], is an example of the delay which suboptimal Phase I data can impose upon a precise evaluation of the antitumor activity of a new drug.

Cyclophosphamide



Ifosfamide



Mesna

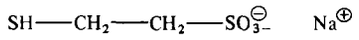


Fig. 1.

Accepted 5 November 1987.

THE REDISCOVERY OF IFOSFAMIDE

The recent (1980) development of mesna (sodium 2 mercapto-ethane-sulphonate), a thiol compound (Fig. 1) which detoxifies the urotoxic oxazaphosphorine metabolite, acrolein, has permitted the use of higher doses of IFO, with myelosuppression now being the dose-limiting toxicity [3]. Administration of high single-dose infusions of up to 5–8 g/m^2/24 h is now feasible without serious problems, under protection of continuous mesna infusion, and this explains the renewed clinical interest in IFO. The drug has already found its way into combination chemotherapy, mainly in non-small-cell lung cancer [4], breast cancer [1] and lymphomas [5]. However, in most combinations it is very difficult to evaluate its relative merit.

Several European investigators, primarily in Germany, published early reports of impressive single-agent activity of IFO in refractory testicular

cancer [6]. Their data were then confirmed at Indiana University, where a response rate of 23% was found in 30 patients with advanced disease [7]. Since then ifosfamide has been incorporated with cisplatin and etoposide in a 'standard' salvage therapy for patients with refractory germ cell tumor [8]. Interesting and sometimes quite provocative results were reported in the treatment of malignant melanoma and renal cell cancer [1]. These results, however, need to be confirmed in much larger series of patients. Also of interest is a recent report of remarkable IFO activity in the treatment of pancreatic cancer: a response rate on the order of 22% among 27 evaluable patients warrants further trials in this important tumor type using this drug alone and/or in combination with other agents [9]. Notwithstanding its reported activity in previously untreated patients [1], ifosfamide proved to be totally inactive in patients with advanced pretreated ovarian cancer [10]. In contrast, six responses were observed among 18 patients with recurrent osteosarcoma, all but one of whom had previously been treated with various cytotoxic agents [11]. Soft tissue sarcomas represent one of the tumor types for which IFO has elicited great interest. As early as 1975 the drug was reported in German literature to have considerable activity in soft tissue sarcomas [12]. During recent years there has been increasing interest in ifosfamide for the treatment of this tumor category, a fact which is demonstrated by the publication of a considerable number of papers dealing with this drug alone or in combination with other drugs [13].

IS IFO SUPERIOR TO CYCLOPHOSPHAMIDE?

It is almost always impossible to make historical comparison between two derivatives on the basis of single-agent activity in Phase II trials. This is particularly true for IFO and cyclophosphamide, since two equitoxic regimens have yet to be clearly established. Randomized Phase II trials could perhaps resolve this impasse. One of the very few trials comparing IFO and cyclophosphamide in the early phase was carried out in 36 patients with non-small-cell lung cancer with a response rate of 29% for IFO and 5% for the parent compound [14]. Since conclusions can obviously not be drawn on the basis of such a limited number of patients, there was considerable interest in the randomized comparison carried out by the EORTC in soft tissue sarcoma, the final report of which was recently published in this Journal [15]. The 171 patients who were accrued to that trial were given either 5 g/m^2 of IFO or 1.5 g/m^2 of cyclophosphamide; 135 of the patients are evaluable. Although the response rate to IFO (18%) was superior to that to cyclophosphamide (8%), the difference ($P = 0.13$ for response rate, 0.04 for linear trend) was not statistically significant, particularly when adjustments for prognostic factors such as sex and previous chemotherapy were made. Both drugs were active in previously untreated females, but virtually inactive in males or those who had received previous chemotherapy.

The response rate for IFO was disappointing by comparison with other recent studies using an identical dose schedule and reporting remission rates between 38% and 50% [16]. The probable main reason of this inconsistency is that in the EORTC study only 4% of the patients had dose escalation, stipulated by hematological feasibility. This non-compliance with the protocol compromised the comparison between the two drugs, since cyclophosphamide was statistically significantly more myelosuppressive than IFO. It is conceivable that had two equitoxic regimens been used, the difference in response rates would have been amplified: only a few additional responses with IFO would have sufficed to render the difference statistically significant.

In conclusion, this EORTC study emphasizes once again the necessity for a large patient population, even in trials simply comparing two single agents. It also underscores the basic fact that such comparisons are virtually impossible as long as Phase I data and early Phase II results are insufficient to serve as a basis for planning equitoxic regimens. In other words, mesna has not solved all of the methodological problems related to ifosfamide.

REFERENCES

1. Brade WP, Herdrich K, Varini M. Ifosfamide—pharmacology, safety and therapeutic potential. *Cancer Treat Rev* 1985, **12**, 1–47.
2. Cavalli F. Etoposide. A critical review of its activity. *Cancer Chemother Pharmacol* 1982, **7**, 81–85.
3. Sheef V, Klein HO, Brock N *et al.* Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: preliminary results. *Cancer Treat Rep* 1979, **63**, 501–505.
4. Drings P, Stiefel P, Kleckow M *et al.* Ifosfamide combination chemotherapy in non-small cell lung cancer. 13th International Congress of Chemotherapy, Vienna, 1983, Symposium SY 83, part 210, 33–39.
5. Cabanillas F, Hagemeister FB, Bodey GP, Freireich E. IMVP-16: an effective regimen

for patients with lymphoma who have relapsed after initial combination chemo-therapy. *Blood* 1982, **60**, 693–697.
6. Hunter HL, Harrison EE. The anticancer spectrum of ifosfamide. *Semin Oncol* 1982, **9**, 96–100 (suppl.).
7. Wheeler BM, Loehrer PJ, Williams SB *et al.* Ifosfamide in refractory male germ cell tumors. *J Clin Oncol* 1986, **4**, 28–34.
8. Loehrer PJ, Einhorn LH, Williams ST. VP-16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. *J Clin Oncol* 1986, **4**, 528–536.
9. Loehrer PJ, Williams SD, Einhorn LH, Ansary R. Ifosfamide: an active drug in the treatment of adenocarcinoma of the pancreas. *J Clin Oncol* 1985, **3**, 367–372.
10. Jungi WF, Sessa C, Engler W *et al.* Phase II trial with high dose ifosfamide + mesna in advanced pretreated ovarian cancer. *Proc ASCO* 1985, **4**, 115.
11. Marti C, Kroner T, Rehmagen W, Berchtold W, Cerrhati M, Varini M. High-dose ifosfamide in advanced osteosarcoma. *Cancer Treat Rep* 1985, **69**, 115–117.
12. Hoefer Janker H, Scheef V, Guenther U, Hulz W. Erfahrungen mit der fraktionierten Iphosphamide Stosstherapie bei generalisierten malignen Tumoren. *Med Welt* 1975, **26**, 972–979.
13. Santoro A, Bonadonna G. Soft tissue and bone sarcomas. In: Pinedo HM, Chabner BA, eds. *Cancer Chemotherapy/8. The EORTC Cancer Chemotherapy Annual.* Elsevier, Amsterdam, 1986, vol. 8, 495–510.
14. Posey LI, Morgen LR, Carter RD *et al.* A comparison of cyclophosphamide and ifosfamide in advanced bronchogenic carcinoma. *Proc AACR* 1978, **19**, 388.
15. Bramwell VHC, Mouridsen HT, Santoro A *et al.* Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. *Eur J Cancer Clin Oncol* 1987, **23**, 311–321.
16. Bramwell VHC, Crowther D, Deakin DP, Swindell R, Harris M. Combined modality management of local and disseminated adults of tissue sarcomas: a review of 257 cases seen over 10 years at the Christie Hospital and Holt Radium Institute, Manchester. *Br J Cancer* 1985, **51**, 301–318.