*Anti-Cancer Drugs 1995*, **6**, pp. 604–607

# Short report

# Stability of ifosfamide in solutions for multiday infusion by external pump

**Leonello Leone,[1] Alessandro Comandone,[2] Cristiano Oliva,[2] Paolo Bussi,[1] Franca Goffredo,[3] Sergio Bretti[2] and Cesare Bumma[2]**

[1]Laboratorio Analisi, Ospedale Regina Margherita, Torino, Italy. [2]Divisione di Oncologia Medica, Italé and [3]Servizio di Farmacia, Ospedale San Giovanni Antica Sede, Via Cavour 31, 10123 Torino, Italy. Tel: (+39) 11 5754839; Fax: (+39) 11 5754891.

**The stability of ifosfamide in Ringer lactate buffer solution either alone or mixed with mesna at 37°C for a 7-day period was analyzed by HPLC. This study was performed to investigate the feasibility of continuous infusion of ifosfamide by a multiday pump in order to reduce the toxicity and to increase the production of active alkylating metabolites of the parent drug. The total decay of ifosfamide activity did not exceed 3.2% at day 7. We conclude that ifosfamide can be safely delivered in a 7-day infusion with no significant loss of activity.**

*Key words:* Ifosfamide, infusion, pump, stability.

## Introduction

Ifosfamide (Holoxan®; Asta Medica, Frankfurt, Germany) is an oxazophosphorine agent with good activity against many human tumors.[1]

As a single agent the drug has shown a good activity in advanced soft tissue sarcomas with objective response rates of 22–43% in non-randomized studies (6–16% complete).[2,3] In controlled studies the percentage of responses falls to 21%, but nevertheless ifosfamide is the second most active drug in these neoplasms.

In testicular cancer (seminomas and non-seminomas) the drug has been used in salvage chemotherapy[4] in refractory or relapsing tumors after cisplatin-based treatment. The patients received 1.2 g/m$^2$ ifosfamide for five consecutive days with 25% of evaluable responses in non-seminomas and 87% in seminomas.[5]

Ifosfamide has also been used in advanced small cell lung cancer instead of its analog cyclophosphamide.[6] Various regimens including ifosfamide, doxorubicin and/or etoposide showed a range of activity of 16–77% with 11–72% of complete responses. Unfortunately no difference in overall survival with other schedules was seen.

In non-small cell lung cancer a response rate of 5–35% with single-agent ifosfamide prompted its inclusion in combination treatment. In comparative studies of ifosfamide plus vindesine and cisplatin versus mytomicin plus vindesine and cisplatin, a 20% response rate was obtained for the first treatment versus 26% for the latter.[7]

New promising areas of investigation are Ewing sarcomas (26% RR as a single agent) and sarcomas of the bone (42% RR as a single agent).[8,9]

Ifosfamide is a prodrug metabolized in the liver, by cytocrome P-450, to 4-OH-ifosfamide and isophosphoramide mustard as active drugs.[1]

Its main toxicity is urological, caused by acrolein as a terminal metabolite. Mesna (sodium-2-mercaptoethansulfonate), a thiol compound, combining with the double bond of acrolein to form non-toxic compounds, can prevent urothelial toxicity.[2] Other important side-effects of ifosfamide are myelosuppression, renal toxicity, neurotoxicity with drowsiness, confusion and lethargy, and nausea and vomiting.[1,10]

Ifosfamide as well as cyclophosphamide has an increased therapeutic index when administered in fractioned doses over several days; maximal fractionation can be obtained by continuous infusion.[11–14]. Moreover, many authors have shown better tollerability using continuous infusion, with less neurotoxicity.[10–14]

The feasibility of high-dose ifosfamide administration in continuous infusion has been demonstrated, reaching a top dose of 18 g/m$^2$ in 4-day

Correspondence to A Comandone

therapy.[2] Moreover high-dose ifosfamide leads to a higher activity in many neoplasms, such as soft tissue sarcomas and metastatic osteosarcomas, than conventional doses of the same drug.[2,13]

Thusfar, the continuous infusion of ifosfamide has been restricted to inpatient use only, because long-term stability data on ifosfamide solution are very few[15] and hospitalization allows a frequent change of the ampule containing the drug.

To avoid costly hospitalization and therefore to improve the quality of life of the patients, especially when ifosfamide regimens are used in metastatic disease, outpatients administration is a valid alternative and should be encouraged.

The aim of our study was to determine the stability of different kinds of ifosfamide solutions with or without mesna, applied for several days by portable pumps for outpatients. HPLC was applied for the analysis.

## Materials and methods

### Experimental design

Three multiday infusors (Baxter, Deerfield, MI) with a fluid volume of 60 ml for 5 days (0.5 ml/h) and two glass vials were filled on day 1 in the Pharmacy of the Ospedale San Giovanni AS in Torino with a solution containing ifosfamide (41.7 g/l), the uroprotective agent mesna (33.3 g/l) and Ringer lactate buffer (pH 7.26). The samples were named E1, E2 and E3 for solution infusors, and A and B, respectively, for glass vials solutions.

Samples E1, E2, E3 and A were stored at 37°C in a dark environment; sample B (control) was spiked into 20 aliquots of 10 ml each and frozen at −20°C until analyzed.

From day 1 to 4 and from 7 to 9, three aliquots of each sample were analyzed in random order.

### Chromatographic method

Analysis was performed in the Laboratory of Ospedale Regina Margherita in Torino.

The method was derived from a published method used for cyclophosphamide analysis[16] with minor modifications. Briefly, we used a Perkin-Elmer liquid chromatography system configured with a Series 4 solvent delivery pump, an autosampler model ISS 100, a recorder-integrator model LCI 100 and a UV-vis detector model LC-95 set at 190 nm (Perkin-Elmer, Norwalk, CT). The analytical column was Superspher 60 RP-8, 125 × 4 (Merck, Darmstad, Germany) and the mobile phase was acetonitrile: monobasic potassium phosphate 20 mM (pH 4.7) (17.5:82.5). The analyses were performed isocratically with a flow rate of 1 ml/min. The elution time of ifosfamide was 7 min.

### Statistical analysis

Peak areas of ifosfamide of samples E1, E2, E3 and A were expressed as percentage of the daily average peak area of sample B (control). The resulting 84 values (4 samples × 3 replicates × 7 days) were then submitted in a two-way analysis of variance (ANOVA) and to a linear regression analysis (percentage of area versus time), according to standard statistical methods.[17]

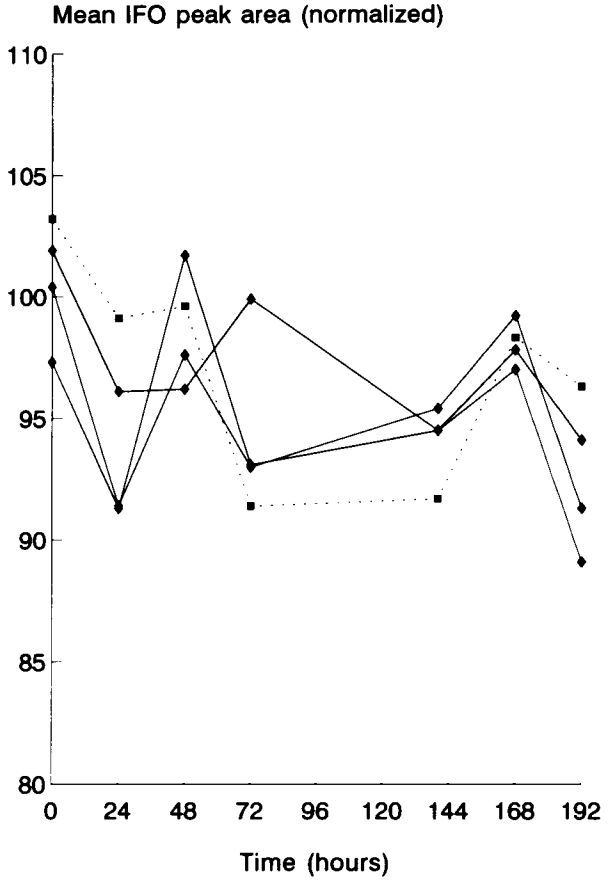


**Figure 1.** Stability of ifosfamide in multiday infusion: the lines represent the median activity of the drug of each sample. Solid lines: samples solution in multiday pumps. Dotted line: glass vials containing ifosfamide and mesna.

**Table 1.** Two-way ANOVA of ifosfamide peak area

| Source of variation | d.f. | $\bar{x}^2$ | $F$ | $p$ |
|---|---|---|---|---|
| Time | 6 | 111.55 | 6.27 | $<0.001$ |
| Sample | 3 | 28.06 | 1.57 | NS |
| Time × sample | 18 | 22.97 | 1.29 | NS |
| Error | 56 | 17.8 | | |

## Results

The results are summarized in Figure 1, where each point represents the average from three replicates of each sample.

The observed dispersion of the data may be due to different sources of variation: analytical imprecision, differences between samples, decrease with time, etc. In order to judge if the effect of time is significant, we separated the components of variance, according to the method of ANOVA. The results (Table 1) indicate that only the variance due to time was greater than the error, i.e. the analytical imprecision ($p < 0.001$). Neither the variance due to the difference between samples nor the interaction 'time × sample' contributed significantly to the overall variance.

As expected, due to the results of ANOVA, the regression of the ifosfamide peak area (normalized) versus time indicated a slope statistically different from zero: $y = 98 - 0.0193 \cdot \text{Time (h)}$ ($s_b = 0.0078$; $t_b = 2.47$, $p < 0.01$, $n = 84$). As a result, the mean decrease of ifosfamide concentration, during 7 days storage at 37°C, can be estimated as 3.2% (95% confidence interval: 0.6–5.8%).

## Discussion

The main toxic effect of ifosfamide occurs in the urothelium, causing hemorragic cystitis and renal failure, but this can be abolished by the simultaneous use of mesna that binds and inactivates the acrolein.[1] Mielotoxicity can be prevented by using G-CSF or GM-CSF or fractionating the dose of the drug.[13,14] Fractionation is therefore important to enhance drug activity and continuous infusion is theoretically the best way to reach this aim.[10,13,14]

Before our study very few data were available to determine the stability of the ifosfamide over several days of infusion by a multiday pump.[15] In addition, in order to reach a safe and practical clinical use in outpatient administration, we mixed, in the same multiday infusor, a solution containing ifosfamide, mesna and Ringer lactate.

The results of our study show that at 37°C in a dark environment, the loss of ifosfamide activity can be estimated as 3.2% over 7 days.

We are sure that the method used is indicative of stability, as stated before by Radford *et al.*[15] We confirm that neither evaporation nor concentration of the solution were recorded. This is important because a loss of solvent would determine a higher concentration of ifosfamide in the vials, causing a confounding decrease of the initial amount of the drug.

In conclusion we confirm that continuous infusion of ifosfamide is an interesting form of administration of the drug. Continuous infusion is feasible also in outpatient administration, because ifosfamide in Ringer lactate solution and mixed with mesna in multiday infusors is stable for 7 days at 37°C.

## References


1. Dechant KL, Brogden RN, Faulds D, *et al.* Ifosfamide/mesna: a review of its antineoplastic activity, pharmacokinetic properties and therapeutic efficacy in cancer. *Drugs* 1991; **42**: 428–67.
2. Elias AD, Eder JP, Antman KH, *et al.* High-dose ifosfamide with mesna uroprotection: a phase I study. *J Clin Oncol* 1990; **8**: 170–8.
3. Toma S, Coialbu T, Biassoni L, *et al.* Epidoxorubicin plus ifosfamide in advanced and or metastatic soft tissue sarcomas. *Cancer Chemother Pharmacol* 1990; **26**: 453–6.
4. 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 tumour. *Cancer* 1990; **66**: 2476–81.
5. Cleum C, Hartenstein R, Willich N, *et al.* Combination chemotherapy with vinblastine, ifosfamide and cisplatin in bulky seminoma. *Acta Oncolog* 1989; **28**: 231–5.
6. Bidoli P, Spinazzè S, Santoro A, *et al.* Pilot study with adriamicin and ifosfamide in small cell lung cancer. *Tumori* 1989; **75**: 34–37.
7. Rosell R, Rabat Esteve A, Moreno I, *et al.* A randomized study of two vindesine plus cisplatin containing regimens with the addition of mytomicin or ifosfamide in patients with advanced non-small cell lung cancer. *Cancer* 1990; **65**: 1692–9.
8. Bacci G, Picci P, Ruggieri P, *et al.* Histological response of osteosarcomas of the extremity to multiagent regimens in which cisplatinum was delivered intraarterially or intravenously. In *Proc Vth Int Congr on Anti-Cancer Chemotherapy* 1995: O 756, 165.
9. Pratt CB, Douglass EC, Goren MP, *et al.* Ifosfamide in pediatric malignant solid tumours. *Cancer Chemother Pharmacol* 1989; **4**: S24–7.
10. Cerny T, Castiglione M, Brunner K, *et al.* Ifosfamide by continuous infusion to prevent encephalophaty. *Lancet* 1990; **35**: 175.
11. Bramwell VHC, Mouridsen HT, Van Oosterom 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**: 311–21.

12. Loeffler TM, Weber FW, Hausamen TU. Ambulatory high-dose 5-day continuous infusion ifosfamide combination chemotherapy in advanced solid tumors: a feasibility study. *J Cancer Res Clin Oncol* 1991; **117** (Suppl 4), 125–8.
13. Toma S, Palumbo R, Comandone A, *et al.* Ambulatory high dose ifosfamide continuous infusion with mesna uroprotection and G-CSF in advanced pretreated solid tumours: feasibility, compliance and effectiveness. *Ann Oncol* 1994; **5** (Suppl 8): 453.
14. Anderson H, Prendiville J, Swindell R, *et al.* A randomised study of intravenous bolus versus continuous infusion of ifosfamide and doxorubicin with oral etoposide for small cell lung cancer. *J Cancer Res Clin Oncol* 1991; **117** (Suppl 4): 139–40.
15. Radford JA, Marginson JM, Tatcher N, *et al.* The stability of ifosfamide in acquous solution and its suitability for continuous 7-day infusion by ambulatory pump. *J Cancer Res Clin Oncol* 1991; **117** (Suppl 4): 154–6.
16. Rustum AM, Hoffman NE. Determination of cyclophosphamide in whole blood and plasma by reversed-phase high performance liquid chromatography. *J Chromatogr* 1987; **422**: 125–34.
17. Dixon WJ, Nassey FJ. *Introduction to statistical analysis.* New York: McGraw Hill 1969.
18. Rowland CG, Bradford E, Adams P, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **8**: 468.

*(Received 30 April 1995; received in revised form 23 May 1995; accepted 25 May 1995)*