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Comparison of Continuous Infusion and Bolus Administration of Ifosfamide in Children

A.V. Boddy, S.M. Yule, R. Wyllie, L. Price, A.D.J. Pearson and J.R. Idle

The pharmacological effects of ifosfamide (IFO) are dependent on its metabolism which may vary between different modes of administration. This was studied in 17 patients who received both a continuous infusion (9 g/m² over 72 h) and repeated bolus administration (3 g/m² every 24 h for 3 days). Concentrations of IFO and its metabolites were determined in plasma and urine. There was up to 70% less of the dechloroethylated metabolites in plasma following bolus administration compared to continuous infusion. Since dechloroethylation results in the formation of the toxic metabolite chloroacetaldehyde, this difference in metabolism may have an impact on the toxicity of IFO. There were no other consistent differences between the two modes of administration. Auto-induction of IFO metabolism, with an increase in dechloroethylated metabolites, was observed for both modes of administration. In conclusion, apart from dechloroethylation, there is little difference between these two modes of administration. However, during multiple cycles of IFO therapy such differences could have a significant effect.

Key words: ifosfamide, pharmacokinetics, metabolism, bolus, infusion
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INTRODUCTION

IFOSFAMIDE (IFO), an alkylating antitumour agent used in the treatment of a number of malignancies, is most commonly administered as a continuous infusion, often over several days [1–3]. This mode of administration is adopted to minimise toxicity [4] and to avoid possible saturation of drug metabolism [5, 6]. This is particularly important since the action of IFO is dependent on its metabolism (Figure 1). There is evidence that fractionation of IFO doses over several days produces an improvement in therapeutic outcome [5], although, in at least one study, continuous infusion was less effective than repeated bolus administration [4]. No systematic comparison has been made between continuous infusion, which usually requires prolonged hospitalisation or sophisticated infusion pumps [7], and repeated bolus administration at the same dosing rate. The latter dosing regimen may allow out-patient therapy with increased convenience for patients and medical staff, if sufficient hydration and Mesna administration can be maintained.

Oxazaphosphorines, such as IFO, are prodrugs which require metabolic activation to exert their antitumour effect [8]. Specifically, activation of IFO has been shown to be dependent on an initial hydroxylation reaction, mediated by the cytochrome P450 enzyme CYP3A4 [9, 10]. This is followed by a sequence of spontaneous reactions resulting in the liberation of the alkylating species, isophosphoramide mustard (IPM). Oxidation of an intermediate in this reaction by an aldehyde dehydrogenase (ALDH) enzyme produces the inactive carboxy metabolite, carboxyifosfamide (CX) [11]. Another P450-mediated route of metabolism is oxidative dechloroethylation of IFO, which results in the formation of inactivated metabolites, 2- and 3-dechloroethylifosfamide (2-DCI and 3-DCI) and the toxic species chlo-

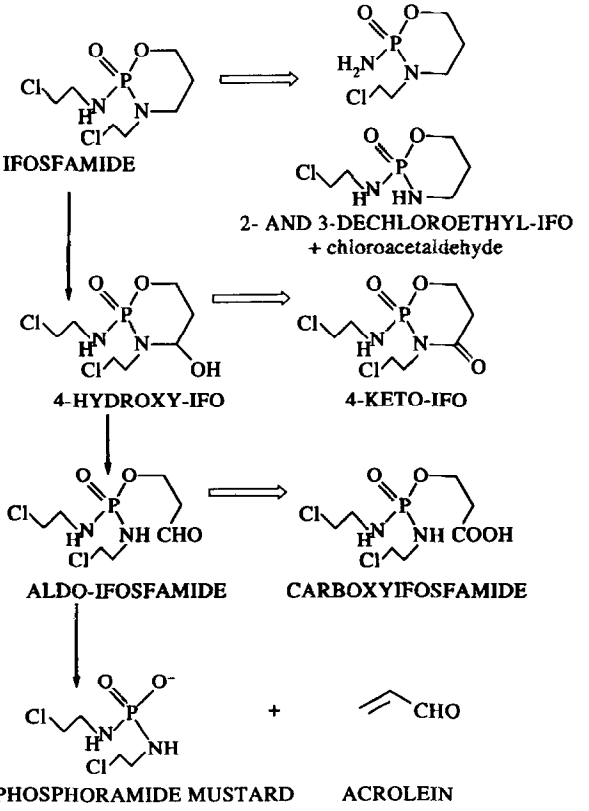

Figure 1. The metabolic pathways of ifosfamide.

Correspondence to A.V. Boddy at the Cancer Research Unit, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH, U.K.
J.R. Idle is at the Department of Pharmacological Sciences; and S.M. Yule, R. Wyllie, L. Price and A.D.J. Pearson are at the Department of Child Health, The Medical School, University of Newcastle upon Tyne, NE2 4HH, U.K.
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roacetaldehyde. This latter route of metabolism has been associated with renal [12] and CNS toxicity [13] and has also been shown to be mediated by CYP3A4 [10].

The pharmacological effects of IFO are thought to be dependent on the relative contributions of these metabolic pathways *in vivo* [8]. Thus, variations in metabolism due to different modes of administration could lead to variations in both therapeutic and toxic effects. This could be due to saturation of metabolism during bolus administration or to differences in the known auto-induction of IFO [14]. Such differences in metabolism could result in different patterns of acute toxicity, or, if maintained throughout repeated administration over several months, in differences in chronic toxicity or therapeutic effect.

In previous publications, we have determined the inter-[15] and intra-individual [16] variability in IFO metabolism in a group of paediatric patients. In the present study, we compared continuous infusion and bolus administration in terms of their influence on IFO metabolism by measuring parent drug and metabolite concentrations in plasma and urine. In addition, we determined the time-course of alteration in IFO pharmacokinetics and metabolism following repeated bolus administration.

PATIENTS AND METHODS

IFO and its metabolites were obtained from Asta Medica AG (Frankfurt, Germany). Cyclophosphamide and 4-nitrobenzylpyridine (NBP) were purchased from Sigma (Poole, U.K.). All other reagents were of appropriate analytical grade.

17 patients, five females, were being treated for soft tissue sarcoma with up to 15 courses of IFO every 3 weeks (Table 1). One patient was studied during a second cycle of IFO therapy following relapse. Ages ranged from 8 months to 16 years. Patients received IFO either as a continuous intravenous infusion (Gemini PC-2 volumetric infusion pump, Imed, San Diego, California, U.S.A.) at a dose of 3 g/m^2 each day for 3 days or as the equivalent dose over 1 h every 24 h for 3 days. Ifosfamide administration was always accompanied by 3l/m^2 of hydration each day and Mesna (3 g/m^2 per day), infused during and for 12 h after IFO administration. Other chemotherapy included etoposide, vincristine and actinomycin D. Concomitant drugs for each patient did not vary between the different courses studied. With the exception of patient 6, no drug interactions with IFO metabolism were identified in previous studies. Patient 6 was treated with a constant dose of carbamazepine, a known inducer of P450 enzymes [17] and was found to have a clearance twice that of other patients studied. Patients' renal function (glomerular filtration rate, GFR, by ^{51}Cr EDTA clearance), was measured for at least one and usually for both courses of IFO. The study was approved by the joint ethical committee of the University of Newcastle upon Tyne and the Newcastle Health Authority, UK. 9 of the patients had been included in our previous studies of inter- and intra-subject variation of IFO metabolism.

Continuous infusion and bolus administration were studied in a randomised order on different courses up to 12 months apart. Intervening courses were all administered as continuous infusions. Blood samples (3–5 ml depending on the size of the child) were collected immediately before the infusion, at 3, 6, 12, 18, 24, 36, 48 and 60 h after the start of the infusion, at the end of the infusion and at 1, 2, 4, 6, 12, 18 and 24 h after the end of the infusion. Sampling times for bolus administration were immediately before and at 0.5, 1, 2, 4, 6, 12, 18 and 24 h after each dose, repeated for the 3 days of the study. Blood was anticoagulated with EDTA and plasma separated and frozen immediately at −20°C prior to analysis. Urine was collected from the older children at 6-h intervals throughout the infusion and for 24 h after. Each passage of urine was stored at 5°C until the end of the collection period. The volume of each urine collection was measured and an aliquot frozen at −20°C for subsequent analysis.

Concentrations of IFO, IPM, CX, 2-DCI and 3-DCI were determined in urine and plasma using a quantitative thin-layer chromatography photography densitometry technique [18]. Briefly, urine (1 ml) and plasma (0.75 ml) samples, with 50 μl of internal standard (cyclophosphamide 500 μg/ml in methanol), were extracted and applied to silica gel TLC plates (E. Merck, Darmstadt, Germany). After chromatography and visualisation, the plates were photographed. The negative was enlarged to the exact size of the original plate and the photographs of the plates

Table 1. *Patients' characteristics*

Patient no.	Sex	Age (years)		BSA (m^2)		Weight (kg)		Course		GFR (ml/min)	
		Inf	Bol	Inf	Bol	Inf	Bol	Inf	Bol	Inf	Bol
1	M	4.2	5.0	0.60	0.70	14.3	14.5	2	5	80	110
2	M	16.0	16.2	1.50	1.50	47.7	45.2	3	5	148	148
3	M	7.0	7.1	0.90	0.90	20.6	21.0	2	3	130	130
4	M	3.8	4.0	0.60	0.60	14.8	14.4	2	6	100	121
5	M	1.9	2.3	0.50	0.50	11.4	11.5	2	8	115	101
6	M	0.8	0.9	0.28	0.33	8.3	9.6	3	6	126	126
7	F	3.8	3.9	0.65	0.65	17.1	18.3	2	3	189	189
8	F	5.1	5.0	0.70	0.70	16.8	16.7	4	3	113	113
9	M	1.0	1.1	0.42	0.42	9.1	9.1	1	2	155	209
10	M	5.0	4.9	0.80	0.80	20.4	21.8	3	2	176	143
11	F	4.3	4.0	0.70	0.70	17.9	16.5	8	4	99	155
12	M	6.8	8.4	0.90	0.90	24.2	24.2	5	16	184	122
13	F	1.6	1.7	0.45	0.45	8.4	7.7	3	4	112	112
14	M	16.5	16.9	1.85	1.85	68.2	65.0	6	10	181	181
15	F	6.4	6.1	0.80	0.80	21.3	22.1	3	2	117	92
16	M	10.9	10.0	1.00	1.00	27.2	27.7	4	3	104	104
17	M	12.5	12.8	1.10	1.10	30.7	30.7	3	8	128	128

BSA, body surface area; GFR, glomerular filtration rate normalised to a BSA of 1.73 m^2; Inf, infusion; Bol, bolus; M, male; F, female.

were scanned. The peak areas for IFO and metabolites were divided by the area under the internal standard (cyclophosphamide) peak and the peak area ratio used for calibration. Each plate contained samples and at least six tracks derived from spiked urine or plasma containing known concentrations of authentic standards (2–50 μg/ml). Calibration curves were obtained for IFO and each of the metabolites and used to determine the concentrations in patient urine and plasma samples.

A non-compartmental approach was used to estimate clearance (Cl) from concentrations of IFO in plasma for infusion and each day of bolus administration. A monoexponential equation was fitted to the postinfusion and bolus data to estimate half-life ($t_{\frac{1}{2}}$) and volume of distribution (V_β) for each subject. Volume of distribution at steady state (V_{dss}) was calculated for each day of bolus administration, but could not be calculated from infusion data due to time-dependent kinetics. Exposure of each patient to IFO and each of its metabolites was expressed as the area under the plasma concentration–time curve (AUC) for that species. AUCs were calculated for infusion and for each day of bolus administration. There was no residual plasma concentration of parent drug or metabolites prior to the next dose. Total AUC for each metabolite following bolus administration was calculated as the sum of AUCs for each day. Recoveries of IFO and metabolites in urine were expressed as a percentage of the total administered dose for both infusion and bolus administration. Both AUC and percentage of dose were corrected for molecular weight. The ability of IFO to induce its own metabolism was measured as the percentage change in parent drug or metabolite concentration between 24 h and the end of the infusion or percentage change in AUC between day 1 and day 3 of bolus administration.

Pharmacokinetic and metabolite parameters were compared using a paired *t*-test. Correlations among pharmacokinetic and metabolite parameters were analysed using normal linear regression. The influence of patients' characteristics and study effects was determined by regression analysis based on the influence of course and the order of study.

RESULTS

Ifosfamide therapy was well tolerated by all the patients studied except patient 9 whose treatment was stopped after nine courses due to severe renal toxicity. Whilst haematological or gastrointestinal toxicities were monitored throughout treatment, no direct comparisons could be made between the two modes of administration because of differing concomitant chemotherapy and cumulative myelosuppression. All subjects have now completed chemotherapy, with 11 children disease free at 19–49 months (median 30 months) following diagnosis. Six children have died from disease recurrence after completing chemotherapy. There were no toxic deaths.

IFO and its metabolites could be detected in the plasma of all patients studied and in the urine where available, except for CX and 2-DCI which were detectable in urine, but not in plasma for 2 patients. Following both continuous and bolus administration, induction of IFO metabolism was observed, resulting in lower parent drug concentrations and higher concentrations of the dechloroethylated metabolites at the end of infusion or on the third day of bolus administration (Figures 2 and 3). Pharmacokinetic and metabolite parameters for the two modes of administration are given in Table 2. Patient characteristics such as GFR had no significant effect on pharmacokinetics or metabolism during either mode of administration.

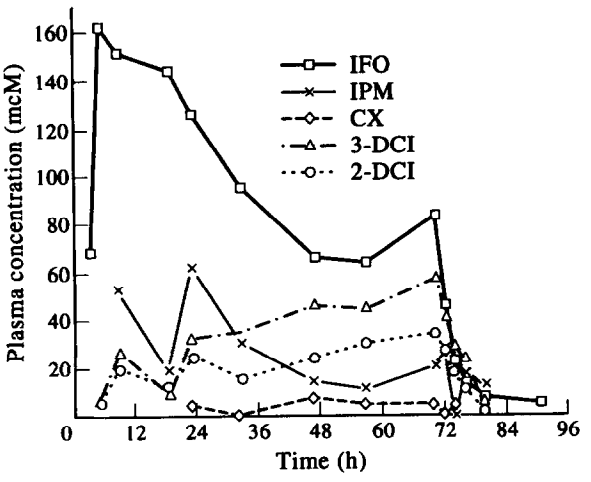

Figure 2. Plot of plasma concentration (μmoles/l) against time for ifosfamide and its metabolites following a 72-h infusion in a representative patient.

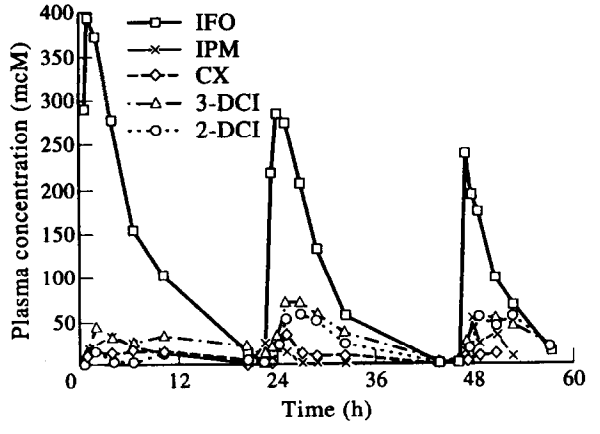

Figure 3. Plot of plasma concentration (μmoles/l) against time for ifosfamide and its metabolites following repeated bolus administration in a representative patient (as in Figure 1).

With regard to the repeated bolus administration, the nature of the auto-induction phenomenon can be clearly seen (Figure 3, Table 3). There is no notable change in V_{dss} from day 1 to day 3, but Cl increases and half-life decreases correspondingly from day 1 to day 2, with no further significant change between days 2 and 3. The AUC of IFO decreases on the same time course, matched by an increase in the AUC of the two DC metabolites (Table 3). The degree of induction (expressed either as increase in DC metabolites or decrease in IFO) did not differ significantly between infusion and bolus administration. This induction phenomenon meant that it was difficult to make comparisons between pharmacokinetic parameters for bolus and infusion (Table 2). The Cl value for a continuous infusion is an average value over the entire study period, whereas that calculated for each of the 3 days of bolus administration is averaged over the 24 h between doses. Similarly, the half-life calculated following the end of the infusion is determined by the induction of IFO metabolism produced by 72 h of continuous exposure to the drug. This cannot be compared to that obtained from the three bolus doses, although for each patient these values tend towards that seen following infusion. Finally, the volume of distribution at steady state cannot be calculated following the infusion

Table 2. Pharmacokinetics and metabolism of ifosfamide administered as a continuous infusion or as three bolus doses

Parameter	Infusion	Bolus	P
Cl	5.48 ± 2.68	3.81 ± 1.08	
V_β	670 ± 390	1070 ± 370	
Half-life	2.07 ± 0.72	3.18 ± 1.49	
AUC IPM	1.78 (0.24–3.46)	1.19 (0.23–4.16)	NS
AUC CX	0.58 (0–2.30)	0.49 (0–1.19)	NS
AUC 3-DCI	1.96 (0.81–7.17)	1.64 (0.57–4.56)	0.02
AUC 2-DCI	0.99 (0.19–3.80)	0.69 (0–1.75)	NS
AUC IFO	6.39 (2.30–10.86)	6.22 (4.83–12.21)	NS
REC IPM	6.6 (3.6–13.9)	7.3 (3.2–18.7)	NS
REC CX	8.8 (5.4–17.5)	9.9 (4.3–17.8)	NS
REC 3-DCI	7.8 (6.1–27.2)	7.3 (5.9–9.8)	NS
REC 2-DCI	5.0 (2.9–19.3)	4.6 (3.4–7.5)	NS
REC IFO	15.4 (9.8–25.8)	19.6 (7.5–42.3)	NS
REC Total	43.7 (23.8–83.4)	52.3 (37.9–69.0)	NS

Parameters from bolus and infusion compared by paired *t*-test ($P<0.05$ assumed significant).
Pharmacokinetic parameters (mean ± S.D.) given for illustration. Comparison is not possible due to time-dependent metabolism.
Bolus parameters are from day 1 (Cl, l/h/m^2), or day 3 (V_β, l/kg and half-life, h).
Areas under plasma concentration time curves (AUC, mM.h) are the sum of all three doses for bolus administration.
Recoveries of parent drug or metabolites in urine (REC, % of dose) are the sum of all collections during and for 24 h after drug administration for both infusion and bolus administration. Recoveries and AUCs are given as median (range). Urine data from 11 patients.
Cl, clearance; V_β, volume of distribution; IPM, isophosphoramide mustard; CX, carboxyifosfamide; DCI, dechloroethylifosfamide; IFO, ifosfamide; NS, non-significant.

because of the time variance in Cl. Calculation of V_β from Cl and postinfusion elimination rate constant is very dependent on the latter parameter and so on the degree of auto-induction. V_{dss} can, however, be calculated for each of the three bolus doses. Clearance following infusion is very similar to that seen on day 2 of bolus administration (Tables 2 and 3).

The AUC of the 3-DC metabolite following continuous infusion was higher than that following the three bolus doses ($P = 0.02$). The AUC of the 2-DC metabolite also tended to be higher following infusion, but this difference was not significant. Overall, the difference in total DC metabolite concentrations between infusion and bolus administration was as much as 70% of the infusion AUC (Figure 4), but 3 patients (numbers 2, 11 and 16) had higher AUCs of DC metabolites following bolus administration. There were no other differences in plasma concentrations or recovery in urine for parent drug or the other metabolites. Concurrent drug treatment was not considered as a source of variation between infusion and bolus administration as therapy did not differ markedly between the courses studied. Only carbamazepine had a significant effect on IFO pharmacokinetics and metabolism (patient 6), as we have reported previously.

DISCUSSION

Although the oxazaphosphorines, IFO and cyclophosphamide, have been used for many years, the design of dosage regimens is largely empirical and based on arbitrary dose fractionation. Little is known about how prolonged treatment affects the metabolism of these drugs, or if changes in metabolism may be indicators of acute or chronic toxicity or of therapeutic efficacy. Previous studies have characterised the metabolism of IFO in a particular individual using the same mode of administration (either infusion or bolus) [15, 19, 20]. In the present study, we investigated potential differences in IFO metabolism between administration as a continuous infusion and repeated bolus administration in the same patient. Comparing metabolite levels in plasma and cumulative recovery in urine, there is no apparent difference between these two modes of administration, other than a smaller degree of dechloroethylation following bolus administration. This could be the result of saturation of this pathway at the higher concentrations achieved

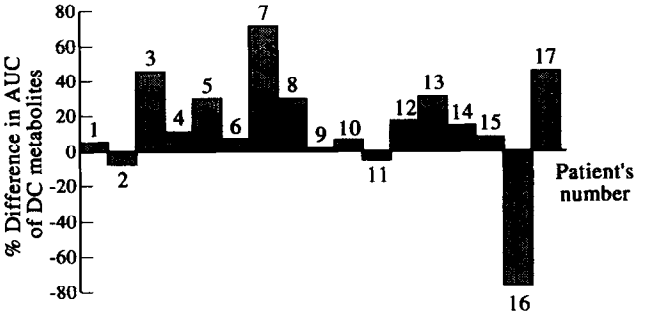

Figure 4. Difference between total area under the curve (AUC) for dechloroethylated metabolites for bolus administration compared to infusion (positive number indicates infusion>bolus).

Table 3. Pharmacokinetics and metabolism of ifosfamide on 3 successive days of bolus administration

Parameter	Bolus Day 1	Bolus Day 2	Bolus Day 3	P 1 vs 2	P 1 vs 3	P 2 vs 3
Cl	3.81 ± 1.08	5.63 ± 1.89	6.34 ± 1.81	0.00001	0.00002	NS
V_{dss}	810 ± 240	810 ± 240	870 ± 230	NS	NS	NS
Half-life	4.73 ± 2.31	3.35 ± 1.25	3.18 ± 1.49	0.008	0.001	NS
AUC IPM	0.37 (0.03–3.12)	0.38 (30–0.94)	0.24 (0.01–0.84)	NS	NS	NS
AUC CX	0.16 (0–0.41)	0.16 (0–0.48)	0.19 (0–0.64)	NS	NS	NS
AUC 3-DC	0.47 (0.16–1.12)	0.69 (0.26–1.98)	0.61 (0.15–1.57)	0.01	0.02	NS
AUC 2-DC	0.19 (0–0.55)	0.37 (0–0.82)	0.26 (0–0.74)	0.0007	0.01	NS
AUC IFO	2.82 (2.07–6.15)	1.97 (1.25–3.75)	1.79 (1.08–3.16)	0.00001	0.00007	NS

See footnotes to Table 2 for explanation of parameters and abbreviations. V_{dss}, volume of distribution at steady-state.
Parameters were calculated separately for each day of administration and compared using a paired *t*-test.

following bolus administration. However, there was no corresponding difference in the products of the oxidation reaction (IPM and CX), despite indications that these two pathways are mediated by identical or linked P450 enzymes [10]. Also, this difference in dechloroethylation had no significant effect on plasma concentrations or urine recovery of parent drug. This analysis assumes that there is no intrasubject variation in the rate of elimination of the dechloroethylated metabolites themselves. We recently investigated intrasubject variation in IFO metabolism and found that while there were no significant, consistent changes with repeated therapy, there was a large degree of unexplained variation between cycles [16], in particular a decrease of dechloroethylated metabolites in later courses. A similar degree of variation has also been reported for cyclophosphamide [21]. Therefore, it is possible that intrasubject variation is masking differences between infusion and bolus administration. To some extent, this was avoided in the present study by randomising the order of bolus and infusion treatment. However, to fully investigate such a phenomenon it would be necessary to repeatedly measure drug and metabolites in several cycles using both modes of administration.

The clinical significance of the relatively minor difference in IFO metabolism between bolus and infusion dosing is hard to determine. Dechloroethylation results in formation of an equimolar quantity of chloroacetaldehyde, which has been linked with the toxic effects of IFO, particularly encephalopathy [13]. These results would seem to suggest that bolus administration is safer relative to infusion in that less dechloroethylation occurs. However, this conflicts with the previous clinical studies [4, 5, 22] and until the precise mechanism of IFO toxicity is determined, this result should be interpreted with caution. A comparison of different ways of administering IFO is hampered by dependence of metabolism on both acute and chronic prior exposure and the significant degree of intra-subject variation in metabolism.

Ifosfamide induces its own metabolism, resulting in complicated pharmacokinetics [23, 24]. The estimate of Cl obtained by non-compartmental analysis is an average over the time course of administration and the half-life determined at the end of the infusion reflects the maximally induced rate of elimination. The Cl estimates for each of the 3 days of bolus administration are more representative of a clearance value relevant to the administered dose. The clear increase in Cl and decrease in half-life from day 1 to day 2 show that auto-induction of IFO metabolism occurs very quickly, but reaches a maximum after day 2. That there is no change in volume of distribution during the 3 days of bolus administration means that the changes in clearance are due to an increased rate of elimination, presumably by increasing the amount or activity of drug-metabolising enzyme available. In the present study, this increase in metabolism appears to be due to an increase in *N*-dechloroethylation, with increased production of 3-DCI and 2-DCI metabolites. It has previously been reported that the 4-hydroxylation pathway is also induced when repeated doses of IFO are administered over 5 days [25], although the time course of auto-induction was not investigated. The products of 4-hydroxylation (IPM and CX) did not increase on repeated dosing in our study, but it may be that the time-course of induction of this reaction differs from that of the *N*-dechloroethylation reaction. Another study of IFO metabolites in urine reported an increase in IPM and CX excretion during 3 days of treatment [20].

In conclusion, we compared the metabolism of IFO when given as either a continuous infusion or as consecutive bolus doses in the same patient. Although there were some minor differences in metabolism between the two modes of administration, the significance of this for the acute and chronic toxicities and for the therapeutic effect of IFO are not known. Auto-induction of IFO metabolism was demonstrated to occur in the first 2 days of treatment and to involve the *N*-dechloroethylation pathway.

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Feature Articles

Therapy of Carcinoma of the Oesophagus: Either Attempt it Not or Succeed

J.A. Ajani

CARCINOMA OF the oesophagus is endemic in certain parts of China, Russia, Iran, Brazil, South Africa and France. However, in the western world, it remains uncommon accounting for approximately 1% of all malignancies. In the U.S.A., approximately 11 300 new cases and 10 200 deaths were estimated, in 1993, to be the result of carcinoma of the oesophagus and gastro-oesophageal junction [1]. Approximately half the patients have local-regional disease at diagnosis, while the other half have more widespread cancer, usually beyond potential cure. T3- or T4- and N-positive lesions, according to the TNM classification, are present in 70% of patients. Thus, the prognosis remains poor and the 5-year survival rates have remained under 10% for the past four decades.

An intriguing aspect of this malignancy has been the dramatic increase in the incidence of adenocarcinoma of the oesophagus and proximal stomach. Particularly in the U.S.A., this increase has been observed in the past 15 years, and has superseded the increases in non-Hodgkin's lymphoma, melanoma and brain tumours [2]. The incidence of squamous carcinoma of the oesophagus has declined. Adenocarcinoma of the oesophagus and gastrooesophageal junction appears to afflict predominantly Caucasian males in their 50s and early 60s. The lifestyle of patients developing adenocarcinoma appears different from that of patients with squamous cell carcinoma, in that alcohol and tobacco abuse are infrequent. Nevertheless, the aetiologic factors for this rapid rise in incidence of adenocarcinoma have not yet been determined. Similarly, an increase in adenocarcinoma of the upper gastrointestinal tract has also been reported in Europe [3–5].

Successful efforts in the detection and treatment of early carcinoma can substantially improve therapy outcomes. Faced with more advanced primary tumours in patients in the western world, surgery produces mediocre results, in need of much improvement. Surgery, however, results in a consistent cure rate approaching 15% [6, 7]. Many prominent surgical groups worldwide now favour radical lymphadenectomy, although this issue remains as unsettled for patients with carcinoma of the oesophagus as it is for patients with gastric carcinoma. Two obstacles define the failure of surgery to cure more patients: (i) a curative resection rate that varies from 55 to 65% (this is partly due to inadequacy of clinical staging), and (ii) subsequent distant as well as local relapses. The surgical mortality has declined over the past 15 years and remains well under 5% in the hands of the surgical groups that perform oesophageal surgery quite frequently. The Ivor-Lewis oesophagogastrectomy is preferred by more groups than the transhiatal approach.

Recent investigations with endoscopic ultrasonography have provided an accurate appraisal of tumour stage, particularly the T stage [8], compared to those obtained by either computerised tomography or magnetic resonance imaging. Substantial further improvements in staging will be slow, but will probably involve antibody-mediated imaging or positron emission tomographic scanning.

Radiotherapy has played a substantial palliative role in the management of carcinoma of the oesophagus. However, radiotherapy alone, given either prior to surgery, after surgery or as definitive therapy, has not demonstrated a consistent survival advantage for patients with local-regional carcinoma. Thus, radiotherapy alone is recommended only when the patient is not suitable for surgery, and chemotherapy is contra-indicated.

Correspondence to J.A. Ajani at the Department of Gastrointestinal Medical Oncology and Digestive Diseases, U.T.M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas 77030-4095, U.S.A.
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