Anti-Cancer Drugs 1997, **8**, pp. 42–47

Plasma pharmacokinetics of idarubicin and its 13-dihydro metabolite—a comparison of bolus versus 2 h infusion during a 3 day course

Staffan Eksborg, Magnus Björkholm,[1] Robert Hast[2] and Eva Fagerlund
Karolinska Pharmacy and [1]Department of Medicine, Karolinska Hospital, Stockholm, Sweden.
Tel: (+468) 729 53 30; Fax: (+468) 30 73 46. [2]Department of Medicine, Danderyd Hospital, Danderyd, Sweden.

The plasma pharmacokinetics of a second generation anthracycline derivative, idarubicin (Ida), have been studied in 17 patients with acute myelocytic leukemia (AML) and high risk features. The drug (10 mg/m^2) was given in a randomized cross-over design as 3 min and 2 h infusions for three consecutive days. Cytosine arabinoside (Ara-C, 1 g/m^2) was given on days 1–4. The plasma concentration time course of Ida was most properly described by the three-compartment pharmacokinetic model, independent of administration time. The maximum plasma concentration (C_{max}) of Ida was reduced by a factor of 3 by increasing the infusion time from 3 min to 2 h. The pharmacokinetic pattern of the active metabolite idarubicinol (IdaOH) was only to a minor extent affected by the longer infusion time. The time course of IdaOH following each dose of Ida was accurately described by the one-compartment model with a first-order formation phase. The area under the plasma concentration versus time curves (AUC) of Ida and IdaOH were not affected by the administration time. Following Ida in combination with Ara-C, the median duration of leukopenia ($< 1.0 \times 10^9$/l) was 14 days (range 5–56) and of thrombocytopenia ($< 50 \times 10^9$/l) was 22 days (range 7–120). The large majority of patients developed infectious complications. Two patients with MDS-AML showed a good response. The results of the present study give no evidence of reduced hematologic toxicity by increasing the administration time of Ida from 3 min to 2 h. However, minimizing C_{max}, by administration of Ida as prolonged infusion during a 3 day course, might be clinically important in order to reduce cardiotoxicity and hopefully to increase anti-tumor efficacy through an increased accumulation of Ida and IdaOH in leukemic cells.

Key words: Idarubicin, infusion, leukemia, pharmacokinetics.

Introduction

Anthracycline glycosides have been successfully used for the treatment of a variety of neoplastic diseases, including acute leukemia. Idarubicin (4-demethoxy-daunorubicin, Ida) is a second generation drug within this class. The pharmacodynamic and pharmacokinetic properties and the therapeutic potential of Ida have been reviewed.[1] It was stated that Ida is 10-fold more cytotoxic than daunorubicin. This observation is thought to be due to the greater accumulation of Ida in leukemic cells as compared to daunorubicin. Moreover, Ida has a higher binding capacity to DNA as compared to daunorubicin, which may result in Ida having a stronger activity in inducing DNA strand breaks than daunorubicin.[2] Animal toxicity tests demonstrated decreased cardiotoxicity of Ida as compared to daunorubicin and doxorubicin.[1] A cumulative dose of Ida beyond which the incidence of cardiotoxicity rapidly increases has, however, as yet not been determined in man.

In general, the anthracyclines are administered as i.v. bolus injections. However, administration as prolonged infusion is sometimes considered to be advantageous as compared to bolus administrations. Hence, the risk for fatal cardiomyopathy is reduced by administration of doxorubicin as prolonged infusion.[3–5] Even some other side effects, including nausea, vomiting and hematological toxicity, and possibly also alopecia, are reduced.[6–8] These effects have been associated with the reduction of the plasma peak concentration caused by the increase of the infusion time.

The cytostatic efficacy of the anthracyclines *in vitro* and *in vivo* has been correlated with the drug exposure,[9] expressed as the area under the (plasma) concentration versus time curve (AUC). The observed increase of anthracycline accumulation in human leukemic cells with increasing infusion time[10] might improve the therapeutic efficacy.

The anthracycline antibiotics are extensively metabolized to their corresponding 13-dihydro-deriva-

Financial support from Farmitalia Carlo Erba, Täby, Sweden, is gratefully acknowledged.

Correspondence to S Eksborg

tives. The amount of formed 13-dihydro metabolite is increased with increasing lipophilic character of the anthracycline drugs. The anti-leukemic effect of Ida treatment is most likely to a great extent caused by the formed metabolite, idarubicinol (IdaOH), since this metabolite, strongly cytotoxic against HL60 cells, persists in blood for prolonged periods after administration of Ida.[1,11]

In this study we compared the pharmacokinetic pattern of Ida and IdaOH during a 3 day course with the drug given as a short time (3 min) and a prolonged (2 h) infusion, with the aim of finding a pharmacokinetic rationale for the clinical use of extended infusion times. Plasma concentrations of Ida and IdaOH were quantified with reversed-phase liquid chromatography using fluorometric detection.

Material and methods

Patient population

Seventeen patients with acute myelocytic leukemia (AML) with previously untreated (elderly patients and AML evolving from a myelodysplastic syndrome, MDS), relapsing or refractory disease above the age of 45 years were included. A performance status below ECOG 3 and patient consent were required. Patients with significant cardiovascular, hepatic and renal impairment were not included.

There were eight women and nine men with a median age of 70 years (range: 49–83 years). The distribution according to the FAB classification was M1 = 4, M2 = 9, M5 = 3 and M6 = 1. Six patients were previously untreated and four patients had received two or more anti-leukemic chemotherapy regimens.

All patients were randomized in a cross-over design to start their Ida treatment with either a 3 min or a 2 h infusion. Twelve of the patients were given both 3 min and 2 h infusions, with at least a 3 week interval between the study periods. Due to disease progression/death, four of the patients were only given the 2 h infusion, while one patient was treated only with the 3 min infusion.

Treatment schedule

Ida (10 mg/m^2) was given as a short time (3 min) or prolonged (2 h) infusion on days 1, 2 and 3. Cytosine arabinoside (Ara-C), 1 g/m^2 (1 h), was given i.v. on days 1–4.

Plasma samples

Blood samples (5 ml) were collected in glass test tubes (Vacutainer®) containing 250 IU of heparin (freeze-dried). The samples were immediately centrifuged to separate the plasma fractions, which were stored at −70°C until analysis.

After the 3 min infusion of Ida blood samples were drawn at 5, 15, 30, 45 min, and 1, 2, 3, 6, 12 and 24 h after dose 1 and 3.

During the 2 h infusion blood of Ida samples were drawn at 15, 30, 45, 60, 75, 90 and 110 min after start of the infusion on day 1 and 3. After the end of the 2 h infusion blood samples were drawn at 5, 15, 30 and 45 min, and 1, 2, 3, 4, 6 and 24 h on day 1 and 5, and 15 min and 24 h on day 3.

Analytical procedure

Ida and IdaOH were assayed by an analytical procedure based on reversed-phase liquid chromatography with fluorometric detection.[12]

Briefly, 1 ml of plasma sample was mixed with the internal standard (4′-*epi*-adriamycin) dissolved in phosphate buffer (pH 7.4) and transferred into a SepPak C_{18} extraction column. After rinsing with 5 ml of phosphate buffer, Ida and IdaOH were eluated with 4 ml of methanol. The eluate was evaporated and redissolved in phosphate buffer (pH 7) and injected into a Nova-Pak Phenyl Cartridge. Acetonitrile, 35% in phosphoric acid, 0.01 M was used as mobile phase. The fluorometric detector was operating at 486/600 nm.

The yield was higher than 90% and the precision better than 13% (relative standard deviation) at concentrations exceeding 0.6 ng/ml. The precision was better than 6% when the sample concentrations exceeded 20 ng/ml.

Pharmacokinetic evaluation

Pharmacokinetic modelling of *median* plasma concentration data were performed by the PC-NONLIN program (version 2.0).[13] The number of exponential terms describing the plasma concentration time course of Ida was evaluated by the *F* ratio test.[14] The time course of IdaOH following each dose of Ida was fitted to a one-compartment model with a first-order formation phase. The Mltdose program (version 2.1)[15] was used for simulations of plasma concentration-time curves for Ida and IdaOH.

We used non-compartmental principles for phar-

macokinetic evaluation of Ida and IdaOH in the *individual* patient. C_{max} values of Ida after the short time infusion were obtained by extrapolation of concentration data to the end of the infusion period. AUC values were calculated from determined plasma concentrations using the trapezoidal rule.

Statistics

Median values and their 95% confidence intervals (95% CI) were calculated according to principles given by Tukey.[16]

Comparison of paired data was performed by the Pitman randomization test based on Wilcoxon matched-pairs signed-ranks test.[17]

Results

The patient's actual doses of Ida were within the range 14.9–19.0 mg (median value 17.9 mg), corresponding to 9.2–10.5 mg/m^2, i.e. close to the scheduled dose. All the 12 patients treated with 3 min and as well as with 2 h infusions obtained the same dose on both occasions.

Median values of measured plasma concentrations of Ida and IdaOH after 3 min and 2 h drug infusions are given in Figures 1 and 2, respectively. Results from pharmacokinetic modeling, included in the figures, showed a close correlation between estimated and determined plasma concentrations.

The plasma concentration–time course of Ida was most properly described by the three-compartment pharmacokinetic model, independent of administration time.

After short time infusion of Ida its high initial plasma concentration decreased, the half-life time of the distribution phase being 6.8 min. One hour after administration the plasma concentration was only 10% of its maximum value. The terminal half-life time of Ida was 17.3 h.

During the 2 h infusion of Ida its plasma concentration increased rapidly. After cessation of the infusion there was initially a drastic decrease of the plasma concentration as previously observed after the short time infusion. The terminal half-life time was 17.4 h.

The results in Figure 1 show that the maximum plasma concentration of Ida was reduced by a factor of 3 by increasing the infusion time from 3 min to 2 h. The AUC of Ida was not affected by the infusion time. Figure 1 also demonstrates that Ida is accumulated in plasma by the repeated administration of the drug on days 1, 2 and 3, albeit only to a minor extent.

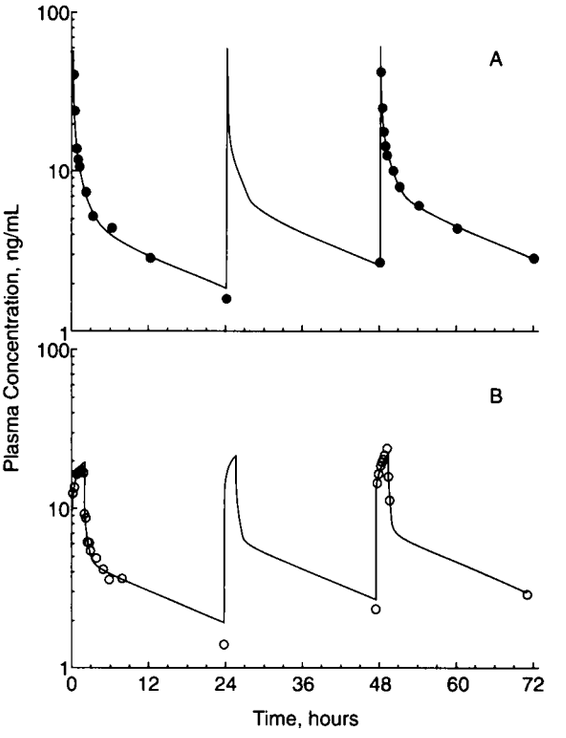

Figure 1. Plasma pharmacokinetics of Ida during a 3 day course. Median values of measured plasma concentrations of Ida administered as a 3 min infusion (A) and as a 2 h infusion (B). The results from pharmacokinetic modeling are given by the solid lines.

The pharmacokinetic pattern of IdaOH (Figure 2) was almost unaffected by increasing the infusion time of Ida from 3 min to 2 h. The time course of IdaOH following each dose of Ida was accurately described by the one-compartment model with a first-order formation phase.[18] The rapid increase of the IdaOH plasma concentration for a period of 2 h was followed by an elimination phase with a half-life time of 95 h or greater.

The results in Figures 1 and 2 demonstrate that IdaOH is accumulated in plasma to a greater extent than Ida by repeated administration of the drug.

The plasma concentration of IdaOH exceeded the concentration of Ida 2.5 h after the end of drug administration on day 1 and somewhat earlier on day 3. The AUC values of IdaOH were about 1.4 times higher than the AUC values of Ida. The difference was more pronounced ($p = 0.02$) on day 3 after administration of Ida as a 3 min infusion. Administration of Ida as short time infusions resulted in peak concentrations approximately 15 times high-

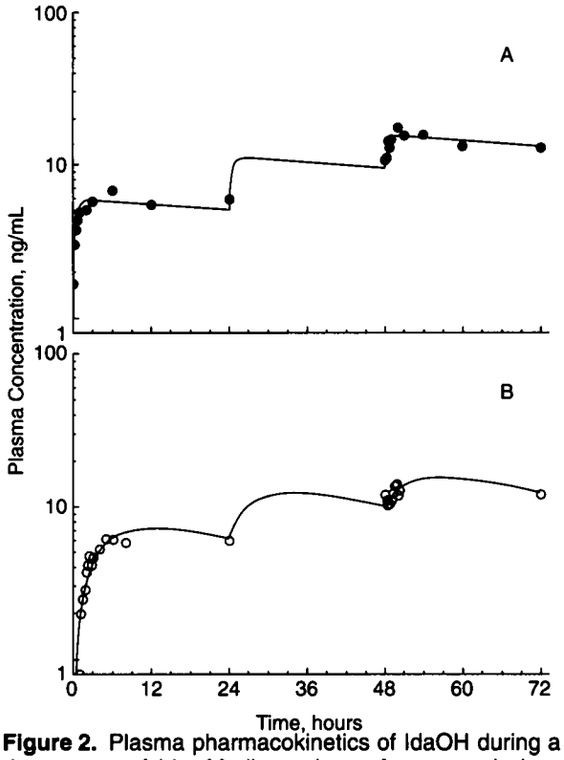

Figure 2. Plasma pharmacokinetics of IdaOH during a 3 day course of Ida. Median values of measured plasma concentrations of IdaOH after administration of Ida as a 3 min infusion (A) and as a 2 h infusion (B). The results from pharmacokinetic modeling are given by the solid lines.

er than for IdaOH. The differences in C_{max} of Ida and IdaOH after administration of Ida as a 2 h infusion were almost negligible.

The AUC and C_{max} values of Ida and IdaOH showed a large inter-patient variability as illustrated in Table 1.

Following Ida in combination with Ara-C, the median duration of leukopenia ($< 1.0 \times 10^9$/l) was 14 days (range 5–56) and of thrombocytopenia ($< 50 \times 10^9$/l) was 22 days (range 7–120). The large majority of patients developed infectious complications. Two patients with MDS-AML showed a good response.

One patient with MDS-AML showed a bone marrow morphology consistent with MDS 3 following the first and second courses of Ida and Ara-C. Another patient with MDS-AML (FAB M6) disease had a bone marrow picture following regeneration after the first course showing MDS 2. The remaining patients except one, who received two courses as consolidation treatment, had no or only a transient reduction of the number of leukemic cells in the bone marrow.

One male patient developed atrial flutter following the first course of Ida and Ara-C. He had previously been treated with both daunorubicin and mitoxantrone.

There was no significant difference in the hematological toxicity profile between 'long' or 'short' time Ida administration.

Discussion

Pharmacokinetic modeling confirmed previous findings that a three-compartment model is suitable for describing the plasma concentration–time course of Ida after the short time infusions.[1,12] This pharmacokinetic model is also suitable for describing the plasma concentration–time course of Ida after prolonged infusions. Our findings that the AUC values of neither Ida nor IdaOH were affected by the

Table 1. Pharmacokinetics of Ida and IdaOH

Drug	Day	AUC[a]		C_{max}[b]	
		3 min	2 h	3 min	2 h
Ida	1	103.0	103.7	88.4	22.9
		84.5–122.1	81.2–123.0	63.0–288.4	18.8–29.8
IdaOH	1	138.5	135.9	6.90	6.95
		110.8–174.4	94.8–201.7	5.40–9.60	4.55–9.35
Ida	3	162.0	201.1	309.3	28.3
		135.4–211.7	174.8–300.8	59.3–624.0	22.8–84.1
IdaOH	3	330.4	323.9	16.8	15.0
		270.1–384.9	247.1–416.1	14.0–19.0	11.5–22.5

All data are expressed as median values and 95% CI.
[a]AUC is expressed in ng·h/ml.
[b]C_{max} is expressed in ng/ml.

administration time support the assumption of linear pharmacokinetics.

The pharmacokinetics of the active metabolite IdaOH was most accurately described by the one-compartment model with a first-order formation phase. This is in contrast with previous findings,[18] where a zero-order formation phase was utilized in the pharmacokinetic modeling.

The plasma concentration of IdaOH was maintained at almost a constant concentration over a prolonged period of time on repeated administration of Ida for three consecutive days. However, the AUC ratio IdaOH/Ida was considerably lower after i.v. administration than observed after oral administration, 1.4 and 5, respectively.[1,12] Still, it is most likely that IdaOH makes an important contribution to the therapeutic effect of i.v. administration of Ida to patients with AML.

The results in Table 1 are in agreement with earlier findings of a wide pharmacokinetic variability of anthraquinone glycosides. Hence, the dose normalized AUC and C_{max} of adriamycin show a more than 10-fold inter-individual variation.[7,12] The clinical relevance of the difference in pharmacokinetics is still an unresolved issue and a matter of controversial debate. In breast cancer patients we observed that side effects like alopecia, nausea and vomiting increased with increasing maximum plasma concentration of epirubicin, 60 mg/m^2 administered as a 2 h constant rate infusion,[12] while there was no obvious correlation with clinical response.

The use of prolonged anthracycline infusions is associated with an increased accumulation of anthracyclines in leukemic cells,[10,19,20] even though these findings have been questioned by Muller *et al.*[21] Their conclusions are, however, based on pharmacokinetic data using different drug combinations for infusion and bolus therapy.

Thus, in addition to a potential increase of the anti-leukemic effect, the use of prolonged infusions may reduce side effects. Peak left ventricular tissue concentration of the doxorubicin seems to be correlated with peak plasma concentration.[22] It has been suggested that cardiotoxicity following anthracycline therapy might be related to the peak plasma and/or cardiac concentrations of intact drugs and/or their 13-dihydrometabolite.[22]

We have previously studied the pharmacokinetic effects by varying the infusion time of doxorubicin, an anthraquinone glycoside considerably less lipophilic than Ida.[23] The maximum plasma concentration of doxorubicin was decreased by a factor of about 10 using 2 h infusions as compared to bolus injections. The results of the present study show that the reduction in C_{max} by prolongation of the infusion time is much less pronounced for Ida. It is, however, possible to administer Ida as a 3 day course to further decrease C_{max}, as Ida and IdaOH are accumulated only to a minor extent in plasma by repeated daily administration.

Clinical evaluation has proved that infusion therapy with anthracyclines is effective in the treatment of AML as well as solid tumors.[6,24] The decrease in side effects associated with anthracycline infusion therapy as compared to bolus administration might permit an increase of the dose intensity. An increase of the anthracycline dose intensity has resulted in an increasing response rate in advanced breast cancer,[25,26] large-cell lymphoma,[27] sarcoma[28] and children with acute lymphoblastic leukemia.[29] The results in the present study give no evidence of reduced hematological toxicity by increasing the administration time of Ida from 3 min to 2 h. However, it is difficult to evaluate toxicity between short- and long-term infusions, since the patients also received Ara-C each day. Still, minimizing C_{max}, by administration of Ida as prolonged infusion during a 3 day course, might be clinically important in order to reduce cardiotoxicity and hopefully to increase anti-tumor efficacy due to an increased accumulation of Ida and IdaOH in leukemic cells.

References

1. Hollingshead LM, Faulds D. Idarubicin—a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs* 1991; **42**: 690–719.
2. Fukushima T, Ueda T, Uchida M, Nakamura T. Action mechanism of idarubicin (4-demethoxydaunorubicin) as compared with daunorubicin in leukemic cells. *Int J Hematol* 1993; **57**: 121–30.
3. Carrió I, Lopez-Pousa A, Estorch M, *et al.* Detection of doxorubicin cardiotoxicity in patients with sarcomas by Indium-111-antimyosin monoclonal antibody studies. *J Nucl Med* 1993; **34**: 1503–7.
4. Legha SS, Benjamin RS, Mackay B, *et al.* Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med* 1982; **96**: 133–9.
5. Shapira J, Gotfried M, Lishner M, Ravid M. Reduced cardiotoxicity of doxorubicin by a 6-hour infusion regimen. A prospective randomized evaluation. *Cancer* 1990; **65**: 870–3.
6. Anderson H, Prendiville J, Thatcher N, Radford JA, Swindell R. A randomized 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**: S139–40.
7. Eksborg S, Hardell L, Bengtsson N-O, *et al.* Epirubicin as a single agent therapy for the treatment of breast

cancer—a pharmacokinetic and clinical study. *Med Oncol Tumour Pharmacother* 1992; **9**: 75–80.
8. Hortobagyi GN, Frye D, Buzdar AU, *et al.* Decreased cardiac toxicity of doxorubicin administered by continuous intravenous infusion in combination chemotherapy for metastatic breast carcinoma. *Cancer* 1989; **63**: 37–45.
9. Eichholz-Wirth H. Dependence of the cytostatic effect of adriamycin on drug concentration and exposure time *in vitro*. *Br J Cancer* 1980; **41**: 886–91.
10. Paul C, Tidefelt U, Liliemark J, Peterson C. Increasing the accumulation of daunorubicin in human leukemic cells by prolonging the infusion time. *Leukemia Res* 1989; **13**: 191–6.
11. Fukushima T, Kawai Y, Urasaki Y, Yoshida S, Ueda T, Nakamura T. Influence of Idarubicinol on the antileukemic effect of idarubicin. *Leukemia Res* 1994; **18**: 943–7.
12. Eksborg S, Söderberg M, Nilsson B, Antila K. Plasma pharmacokinetics of Idarubicin and its 13-hydroxymetabolite after intravenous and oral administration under fasting and non-fasting conditions. *Acta Oncol* 1990; **29**: 921–5.
13. Statistical Consultants Inc. PC-NONLIN and NONLIN84: software for the statistical analysis of nonlinear models. *Am Statistician* 1986; **40**: 52.
14. Boxenbaum HG, Riegelman S, Elashoff RM. Statistical estimations in pharmacokinetics. *J Pharmacokinet Biopharm* 1974; **2**: 123–48.
15. Thompson GA, Shumaker RC. Multidose—a multiple-dose simulation program for linear systems characterized by exponential functions. *Drug Metab Rev* 1990; **21**: 463–9.
16. Daniel WW. *Applied non-parametric statistics*. Boston, MA: Houghton Mifflin 1978.
17. Dallal GE. Pitman: a fortran program for exact randomization tests. *Computers Biomed Res* 1988; **21**: 9–15.
18. Leoni F, Giuliani G, Pascarella A, *et al.* Attenuated-dose idarubicin in acute myeloid leukemia of the elderly: pharmacokinetic study and clinical results. *Br J Haematol* 1995; **90**: 169–74.
19. de Vries EGE, Greidanus J, Mulder NH, *et al.* A phase I and pharmacokinetic study with 21-day continuous infusion of epirubicin. *J Clin Oncol* 1987; **5**: 1445–51.
20. Speth PAJ, Linssen PCM, Boezeman JBM, Wessels HMC, Haanen C. Leukemic cell and plasma daunomycin concentrations after bolus injection and 72 h infusion. *Cancer Chemother Pharmacol* 1987; **20**: 311–5.
21. Muller C, Chatelut E, Gualano V, *et al.* Cellular pharmacokinetics of doxorubicin in patients with chronic lymphocytic leukemia—comparison of bolus administration and continuous infusion. *Cancer Chemother Pharmacol* 1993; **32**: 379–84.
22. Cusack BJ, Young SP, Driskell J, Olson RD. Doxorubicin and doxorubicinol pharmacokinetics and tissue concentrations following bolus injection and continuous infusion of doxorubicin in the rabbit. *Cancer Chemother Pharmacol* 1993; **32**: 53–8.
23. Eksborg S, Strandler H-S, Edsmyr F, *et al.* Pharmacokinetic study of IV infusions of adriamycin. *Eur J Clin Pharmacol* 1985; **28**: 205–12.
24. Lewis JP, Meyers FJ, Tanaka L. Daunomycin administrated by continuous intravenous infusion is effective in the treatment of acute nonlymphocytic leukemia. *Br J Haematol* 1985; **61**: 261–5.
25. Focan C, Andrien JM, Closon MT, *et al.* Dose–response relationship of epirubicin-based first-line chemotherapy for advanced breast cancer: a prospective randomized trial. *J Clin Oncol* 1993; **11**: 1253–63.
26. Neri B, Pacini P, Algeri R, *et al.* Conventional versus high-dose epidoxorubicin as single agent in advanced breast cancer. *Cancer Invest* 1993; **11**: 106–12.
27. Kwak LW, Halpern J, Olshen RA, Horning SJ. Prognostic significance of actual dose intensity of diffuse large-cell lymphoma: results of a three-structured survival analysis. *J Clin Oncol* 1990; **8**: 963–77.
28. Smith MA, Ungerleider RS, Horowitz ME, Simon R. Influence of Doxorubicin dose intensity on response and outcome for patients with osteogenic sarcoma and Ewing's sarcoma. *J Natl Cancer Inst* 1991; **83**: 1460–70.
29. Gaynon PS, Steinherz PG, Bleyer WA, *et al.* Association of delivered drug dose and outcome for children with acute lymphoblastic leukemia and unfavorable presenting features. *Med Pediatr Oncol* 1991; **19**: 221–7.

(Received 8 October 1996; accepted 29 October 1996)