Phase I and Clinical Pharmacological Study of 4-Demethoxydaunorubicin (Idarubicin) in Children with Advanced Cancer

Charlotte T. C. Tan, Counce Hancock, Peter Steinherz, David M. Bacha, Laurel Steinherz, Enrique Luks, Naomi Winick, Paul Meyers, Anna Mondora, Ester Dantis, Donna Niedzwiecki, and Yee-Wan Stevens

ABSTRACT

We conducted a phase I and pharmacokinetic study of i.v. idarubicin, a new anthracycline analogue, in 42 evaluable children 1–19 years old. Twenty-seven had leukemia and 15 had various solid tumors. The drug was administered in escalating doses of 10 to 40 mg/m²/course in 3 equal fractions over 3 consecutive days at 14- to 21-day intervals. Myelo-suppression and mucositis were the limiting toxicities for short-term administration. Nausea, vomiting, and elevation of liver enzymes and bilirubin were the other toxicities encountered. Peak toxicity occurred 2 weeks after drug administration with median recovery by day 24. All but 4 patients with solid tumors had prior anthracyclines. Mild cardiac function changes without clinical symptoms were observed in 17 of 35 patients measured by serial cardiac evaluations. In addition, there were 4 patients with congestive heart failure. On postmortem examination, 4 patients had changes consistent with anthracycline cardiomyopathy at a prior median total anthracycline dose of 175 mg/m². The maximum tolerated dose for patients with solid tumors was 15 mg/m²/course in 3 divided doses. Patients with leukemia tolerated 30 mg/m²/course. Six of 15 evaluable patients with acute lymphoblastic leukemia who received ≥30 mg/m² idarubicin achieved a remission (M, marrow status). The plasma clearance of idarubicin fits a 3-compartment model with a harmonic mean half-life of 2.4 min, 0.6 h, and 11.3 h for α, β, and γ phases, respectively. Idarubicinol was the only metabolite detected in the plasma and it accumulated during the 3 days of therapy. Idarubicin is similar to daunorubicin in pharmacology and toxicity. While the cardiotoxic dose still must be delineated, the complete remissions achieved in multiple relapsed patients with acute lymphoblastic leukemia indicate promising activity in at least that disease.

INTRODUCTION

The anthracycline antibiotics are effective antineoplastic agents (1). DNR is widely used in the treatment of acute leukemia (2, 3). DX, in addition, has activity against a variety of solid human neoplasms (4–7). Both of these drugs produce reversible dose-dependent and single course-limiting marrow and gastrointestinal toxicity. Their long-term administration is limited by cumulative cardiotoxicity (8–14). IDR was synthesized by Arcamone et al. (15) as part of an extended program seeking analogues with an enhanced therapeutic index and reduced cardiotoxicity. It differs from DNR by the absence of the methoxy group in position 4 of the aglycone (15). In preclinical studies, IDR was more potent than the parent compound in murine leukemia and animal tumor models (15–17). Unlike DNR or DX, IDR was active when administered p.o. to mice bearing L1210 leukemia, Gross leukemia, or Sarcoma 180 (18). Chronic toxicity tests in rats, dogs, and rabbits showed that IDR had an improved cardiotoxic index when given i.v. (19, 20). Little or no cardiac damage was seen after p.o. administration. Here we present the results of a dose-finding, phase I and pharmacokinetic study of i.v. IDR in children with advanced cancer.

MATERIALS AND METHODS

After informed consent was obtained, 46 patients with advanced cancer were entered into this study. All had histological proof of malignancy; in each, the disease was refractory to conventional therapy. Eligibility requirements included: (a) recovery from the toxic effects of prior therapy; (b) for patients with no marrow involvement, a WBC ≥3,000/µl, with an absolute neutrophil count ≥1,500/µl and a platelet count ≥100,000/µl; and (c) adequate hepatic function (bilirubin ≤2.0 mg/dl) and renal function (creatinine ≤1.5 mg/dl). Evaluation during study included: (a) daily blood counts until a pattern of biological effect was apparent and weekly thereafter; (b) hepatic and renal function tests three times weekly during the initial phases of inpatient treatment and weekly thereafter; (c) repeat echocardiogram and/or gated cardiac pool scan after two courses of therapy; and (d) bone marrow aspiration and biopsy on day 14 and/or before each course of therapy in patients with marrow involvement.

Drug Preparation, Administration, and Treatment. Idarubicin hydrochloride was provided by Farmitalia Carlo Erba, Milan, Italy. The i.v. preparation was supplied in sterile vials containing 5 mg of IDR. This was reconstituted in 5 ml of sterile water (U.S.P.) and administered by slow i.v. infusion over 5 to 15 min. The initial dose was 10 mg/m²/course, each course consisting of three equal daily doses given on three consecutive days (21, 22). The treatment course was to be repeated every 14 to 24 days depending on recovery from prior toxicity. In the absence of toxicity, doses could be escalated to 12.5, 15, and 20 mg/m²/course in the same patient. Children with leukemia had further dose escalations to levels of 30 and 40 mg/m²/course.

Criteria of Toxicity and Response. Toxicity was graded according to the method of Miller et al. (23) with minor modifications for pediatric patients. The toxicity of each single course was evaluated. In patients with leukemia, a decrease in marrow cellularity or peripheral blood counts was not considered toxicity.

The antileukemic effect of IDR was evaluated according to the composition of bone marrow aspirates and cellularity on the marrow biopsy specimens. The biopsies were graded: (a) aplastic (very hypocellular specimen, <5% immature cells, with only a few histiocytes, plasma cells, and lymphocytes remaining); (b) hypoplastic (decreased marrow cellularity with ≥50% reduction in leukemic infiltrate but residual disease clearly evident); and (c) no effect (minor or no reduction in the degree of leukemic infiltration). The therapeutic response was quantified as M₁, remission when ≥5% blasts were present in the aspirate of a normocellular marrow, and M₂ remission when 6–24% blasts remained. Patients with no response were given alternate therapy. Four patients, after achieving complete remission, were placed on multigent maintenance regimens in an effort to prolong the duration of leukemic control.

Clinical Pharmacological Studies. The pharmacokinetic behavior of IDR was examined using a HPLC method adapted from that of Peng

Received 5/5/86; revised 2/17/87; accepted 3/6/87.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Supported in part by NIH Grant CA29564 and by grants from Farmitalia Carlo Erba and Adria Laboratories.
2 To whom requests for reprints should be addressed.
3 Present address: American Cyanamid Company, Wayne, NJ.
4 Present address: 177 N. Dean Street, Englewood, NJ.
5 Present address: University of Texas Health Science Center at Dallas, 5323 Harris Hines Boulevard, Dallas, TX.
6 The abbreviations used are: DNR, daunorubicin; DX, doxorubicin; IDR, idarubicin; HPLC, high-performance liquid chromatography; IDR-ol, idarubicinol; AUC, area under the curve; ALL, acute lymphoblastic leukemia; ANLL, acute nonlymphoblastic leukemia; echo, echocardiogram; RNA-C, radinunclide cineangiography; FS, fractional shortening; LVEF, left ventricular ejection fraction; CHF, congestive heart failure.
et al. (24). Seven patients were studied after receiving dosages of 15 mg/m² (1 patient), 20 mg/m² (2 patients), 30 mg/m² (1 patient), and 40 mg/m² (3 patients). The drug was given as a constant rate infusion over 15 min using an Autosyringe.

For each patient studied, 2-5 ml samples of venous blood were drawn into heparinized tubes prior to treatment and at the following times after the conclusion of the infusion: day 1, 0, 2, 5, 7, 10, 15, 30, 45, 60, 120, 240, and 480 min; days 2 and 3, 24 h (immediately prior to infusion), 0, 0.5, 1, 2, 4, and 8 h; days 4–7, 72, 96, 120, and 144 h after the first infusion. Each blood sample was centrifuged immediately and the plasma was transferred to an appropriately labeled tube and frozen at −70 °C until assayed.

Chemicals. Pure samples of IDR, IDR-ol, and DX were supplied by Farmitalia Carlo Erba. Acetonitrile (HPLC grade), methanol (HPLC grade), and ammonium formate were Baker-analyzed reagents. Stock solutions of the drugs and standards were prepared in CH₃CN:0.05 M KH₂PO₄, pH 3.0 (25:75) with 10 µg/ml desipramine to prevent adherence of drug to glass.

High Performance Liquid Chromatography. Analyses were performed with a Waters Associates (Milford, MA) liquid chromatograph. The technique used a reverse phase C₁₆H₁₃O₂N₂ bondapak column (30 mm x 3.9 mm; particle size, 10 µm; Waters Associates). Compounds were detected by fluorescence, using excitation and emission wavelengths of 470 and 585 nm, respectively, with 15-nm slit widths. IDR, IDR-ol, and DX (the internal standard) were separated by gradient elution at 2 ml/min using the following mobile phases: Solution A, CH₃CN:NH₄COOH 0.1%, pH 4.0 (35:65); Solution B, CH₃CN:NH₄COOH 0.1%, pH 4.0 (65:35). The linear gradient was from 100% A to 100% B over 10 min. The retention times of DX, IDR-ol, and IDR were 3.66, 5.03, and 6.18 min, respectively. The lower limit of quantitation was 1 ng/ml for IDR and IDR-ol using 1 of plasma.

Sample Analysis. DX, 50 ng, was added to each patient sample or plasma standard as an internal standard. The volume of plasma used was generally 1 ml; however, in the immediate postinfusion samples with high concentrations of IDR, 1:10 or 1:20 dilutions of plasma were made. The extraction procedure for plasma was described previously (37). Recovery for the standards was >90%.

Quantitation of plasma concentrations of IDR and IDR-ol was performed by linear least-squares regression of the drug internal standard area ratios in plasma concentrations of 1–200 ng/ml. From this standard regression, the respective concentrations of IDR and IDR-ol in patient samples were calculated based on the area ratio in the sample. Coefficients of variation for quadruplicate plasma standards in concentrations of 1–200 ng/ml were 2-18% for same-day extractions.

Pharmacokinetic Analysis. The measured IDR concentration versus time data for each patient were fitted using weighted nonlinear least-squares models in NONLIN84 (Statistical Consultants, Lexington, KY) to a multieponential equation of the form

\[ C_p(t) = \sum_{i=1}^{\infty} C_i(t) \cdot \exp(-\lambda_i t) \]

where \( C_p(t) \) is the concentration in plasma at time \( t \), \( \lambda_i \) is the first order elimination rate constant of \( i \)th term, and \( A_i \) is the coefficient of the \( i \)th term with appropriate correction for the 15-min infusion time (25). From these estimates of the slopes, we derived the half-lives of the a, b, and c phases (26). The data from days 2 and 3 were corrected for the residual amount of drug from the dose of the previous day by the method of reverse superposition (27). The AUC for IDR was derived from weighted nonlinear fitting of the data using NONLIN84 and the

\[ \text{AUC} = \int_0^\infty C_p(t) \, dt \]

where \( C_p(t) \) is the plasma concentration of IDR at the last measured time and \( \lambda \) is the terminal phase rate constant of the 13-hydroxy metabolite estimated on NONLIN84 from the day 3 concentration-time data. Potential correlation between AUC and dose, as well as clearance and dose, were investigated using Spearman’s rank correlation (28).

RESULTS

Patient Characteristics. Forty-six patients were enrolled in the study. Twenty-eight patients had marrow involvement: 16 by ALL; 4 by non-Hodgkin’s lymphoma; and 8 by ANLL. Eighteen had various types of solid tumors (osteogenic sarcoma, 4; embryonal rhabdomyosarcoma, 3; neuroblastoma, 3; Ewing’s sarcoma, 2; and miscellaneous, 6); in 3 of these, there were extrinsic cells in the bone marrow. These 3 patients were excluded from the evaluation of hematological effects.

Of the 46 patients entered into this study, 42 were evaluable for toxicity and response. One patient with non-Hodgkin’s lymphoma refused further therapy after receiving one dose, one patient each with osteogenic sarcoma and neuroblastoma died of progressive disease within 1 week, and one patient with embryonal rhabdomyosarcoma was lost to follow-up.

The age range was 1–19 years; median age for patients with leukemia was 6 years and for patients with solid tumors it was 12 years. The number of prior relapses in patients with leukemia was 1–3 (median, 2). The prior anthracycline dose (DX equivalent = total dose of DX mg/m² plus two-thirds total dose of DNR mg/m²) for patients with leukemia and lymphoma was 20–256 mg/m² (median, 147 mg/m²); for patients with solid tumors, it was 0–465 mg/m² (median, 158 mg/m²); the latter group included the 3 patients who received more than 300 mg/m² total cumulative doses (375, 420, and 465 mg/m²) of anthracycline and in whom the echocardiograms were normal.

Toxicity. The hematological effects of IDR were evaluable in 18 courses in children with solid tumors without bone marrow involvement (Table 1). No significant myelosuppression was seen at the 10- and 12.5-mg/m²/course levels. A dosage of 15 mg/m² resulted in median WBC and platelet nadirs of 1,300/µl and 20,000/µl, with recovery by day 24. At the 20-mg/m²/course dose level, the median WBC and platelet nadirs were 400/µl and 14,000/µl, respectively. The nadirs occurred 10–16 days (median, 14 days) following initiation of treatment, and the median time of recovery was 2 weeks from the nadir.

The nonhematological effects of IDR in children with solid tumors were mild; in a total of 23 courses, 1 had nausea and vomiting at 12.5 mg/m², and 1 had mucositis at 15 mg/m²/course dose levels; reversible elevation of bilirubin and transaminase occurred in 9 courses (in 4 of these, the liver abnormalities were related to disease progression). The nonhematological effects in children with leukemia are

<p>| Table 1 Hematological effects of idarubicin in children with solid tumors |
|-----------------------------|---------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Dosage (mg/m²/course)</th>
<th>No. evaluable Patients</th>
<th>WBC × 10⁹/µl</th>
<th>Platelets × 10⁹/µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>12.5</td>
<td>3</td>
<td>3</td>
<td>2.3</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>5</td>
<td>1.3</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

2991

Downloaded from cancerres.aacrjournals.org on November 8, 2017. © 1987 American Association for Cancer Research.
shown in Table 2. The 26 evaluable patients received a total of 56 courses (range, 1–4 courses; median, 2 courses). Seven patients were treated at 2 different dosage levels; the last course is listed as “subsequent course.” The side effects of their initial and subsequent courses showed very little difference and are evaluated together. Nausea and vomiting and oral ulcers were mild to moderate. Transient drug-induced elevations (2.5–10 times the base line values) of transaminase and bilirubin values were dose related. This was observed about 2 weeks after treatment with recovery within the subsequent 2 weeks.

Alopecia was seen in 5 of 38 evaluable courses. Fever after treatment was observed in 7 of 37 courses in patients with leukemia only. One child had chills and fever within 2 h after each daily dose despite premedication with diphenhydramine. No chills or fever were seen during her second course when she was premedicated with hydrocortisone, diphenhydramine, and acetaminophen.

Cardiac toxicity was assessed in 35 of 42 evaluable patients using serial M Mode echo and/or cardiac scans (RNCA). Children above 5 years of age had echos and RNCA at rest and exercise. Normal values (FS ≥ 30% and LVEF by RNCA ≥ 50–55%) were based on the published studies in children (29–32). Seven of the 42 patients had only base line studies; no subsequent clinical sign of cardiac dysfunction was seen in those 7. Fourteen of the 35 patients who were monitored serially for a median of 3.5 months (range, 0.75–48 months) demonstrated no change in cardiac function tests or clinical symptoms. Twenty-one patients displayed deterioration in cardiac function parameters. In 17 patients the changes were subclinical with only varying degrees of decline from base line values demonstrated. The specific changes in these 17 patients are grouped as follows: (a) 5 patients had no change in RNCA but had a decrease in FS by 12–36% of base line value. Only 2 of these had a persistent decrease of FS to below 30%; (b) 6 patients had no change in FS by echo but had a decrease in RNCA LVEF by 16–33% of base line value. Only 1 decreased to below normal (48%). One other had a decrease to 55%. Both recovered. One other patient had a decrease to 51% with no recovery; (c) 6 patients had decreases in both RNCA LVEF and echo FS to below the lower limits of normal; in 3 the changes were transient with recovery even on continued treatment, 2 patients had decreased to borderline function without complete recovery, and the other had progressive decrease of FS to 24% whereas his RNCA LVEF had shown some improvement.

Four patients had progressive decrease of FS and RNCA LVEF to abnormal values and developed signs of CHF. The detailed data of these 4 children are shown in Table 3. In patient 1 CHF was probably related to hemorrhage; after the first course of IDR, this patient had a rapid recovery and received a further course of IDR without recurrence of cardiac symptoms. He had received 330 mg/m² DNR in addition to 60 mg/m² IDR. Patient 2 had abnormal echo and patient 3 had borderline cardiac studies prior to IDR; both had further deterioration of cardiac function with IDR therapy. In both patients there was
progressive malignant disease and CHF developed in terminal stages 3 months after the course of IDR. Patient 4 had normal base line studies with good response to stress. Her cardiac functions deteriorated 2 months after the second course while in marrow remission. Postmortem changes were consistent with anthracycline-induced changes in patients 1, 3, and 4 and in one additional patient who had received 114 mg/m² DX in addition to 24 mg/m² IDR and did not have cardiac symptoms. The extent of subclinical abnormalities, the incidence of CHF, or the postmortem findings cannot be related clearly to previous anthracycline-induced changes in patients 1, 3, and 4 and in a patient who received 40 mg/m²/course. IDR was extensively converted to IDR-ol, which had a prolonged terminal half-life with a median of 43.7 h (range, 27.8-131 h). The median terminal half-life for the parent drug was 8.5 h (range, 2.7-131 h). The median terminal half-life for the parent drug was 8.5 h (range, 2.7-131 h).

Of those who were treated, the majority went into remissions after the first course. There was no significant difference in the prior anthracycline doses between responders (median dose, 134 mg/m²) and nonresponders (median dose, 160 mg/m²).

Of the 15 children with various solid tumors evaluable for drug activity, only 1 child with neuroblastoma had a transient decrease in the size of a metastatic lymph node. No single disease category had sufficient patient numbers to evaluate drug effect.

Pharmacological Results. Pharmacokinetic data were obtained in 7 patients. In all 7, the disappearance curve of IDR was multiphasic without evidence of drug accumulation on repeated dose administration. In 5 of the 7 patients, the data fit a 3-compartment model on day 1, when detailed pharmacokinetic studies were done. The harmonic mean half-lives on day 1 were 2.4 min, 0.6 h, and 11.3 h for the \( \alpha \), \( \beta \), and \( \gamma \) phases, respectively. The derived pharmacokinetic parameters are presented in Table 5; Fig. 1 illustrates the plasma concentration over time of IDR and the only detectable metabolite, IDR-ol, in a patient who received 40 mg/m²/course. IDR was extensively converted to IDR-ol, which had a prolonged terminal half-life with a median of 43.7 h (range, 27.8-131 h). The median terminal half-life for the parent drug was 8.5 h (range, 3.6-36.4 h). The prolonged half-life of IDR-ol is consistent with its accumulation in plasma on repeated daily administration (Fig. 1).

**DISCUSSION**

IDR is a new anthracycline developed with the hope of a lower cardiotoxic index with maintenance or enhancement of antitumor activity. The drug is being examined in children and adults by the i.v. and p.o. routes. This phase I study of i.v. IDR evaluated the toxicity and pharmacokinetic behavior of the drug in a 3-consecutive-day schedule. The toxicity of IDR was similar.
IDARUBICIN IN CHILDREN WITH ADVANCED CANCER

Fig. 1. Plasma concentration-time graphs of IDR (•) and IDR-ol (•) following an i.v. dose of 13.3 mg/m² daily for 3 days.

to that observed with DNR and DX; myelosuppression and mucositis were the dose-limiting toxicities for short-term drug administration. Nausea, vomiting, and liver function abnormalities were also toxicities encountered. As with the other anthracyclines, the peak of toxicity occurred 2 weeks after drug administration with recovery by day 24. The maximum tolerated dose for patients with solid tumor is 15 mg/m²/course given over 3 days. This dose is similar to that tolerated by adult patients (33–35). Patients with leukemia can tolerate 30 mg/m²/course given in 3 days. We recommend these levels for phase II trials. The 30-mg/m²/course induced marrow hypoplasia in a majority of patients with ALL, but only 1 of 6 with ANLL achieved reduced marrow cellularity. It is possible that ANLL may require a higher dose for efficacy. However, we do not have sufficient data on the safety of this dose level.

The potential cardiotoxicity of IDR is very difficult to evaluate in a phase I study, where by necessity the patients are in relapse, have advancing disease with multiple organ involvement, and have received extensive prior therapy including anthracycline and amsacrine. Frequently, systemic infection and hemorrhage requiring administration of antibiotics, transfusions, and parenteral nutrition complicate the picture. Furthermore, there are few references for normal values of radionuclide cineangiography available in children, and only one in children with cancer. Understandably, exercise capacity varies in these sick children. These factors make the interpretation of test results more difficult. Serial cardiac follow-up in our patients demonstrated changes of cardiac function in 21 of 35 patients (60%). In 17 of these patients, changes were subclinical. Four patients did develop CHF, the first 2 patients within 1 month and the other 2 at 3 and 5 months after the start of study. These patients had many of the complicating factors mentioned. In 2 of them there were preexisting cardiac abnormalities on base line studies. However, 4 patients (3 with CHF, 1 without) did have postmortem changes of vacuolization by light microscopic findings associated with anthracycline-induced cardiomyopathy. Their total cumulative anthracycline exposure, including previous therapy plus the IDR dose, was below 280 mg/m². While there is individual variation in cardiotoxicity, with occasional clinically significant early toxicity at doses much less than usual for chronic cardiomyopathy (36), and while children may be more susceptible than adults (13), it is difficult to state based on our data whether or not i.v. IDR is more cardiotoxic than DNR.

The pharmacokinetic behavior of IDR and IDR-ol in this pediatric population is similar to that observed in adults, both in the overall pattern and in the rate of drug clearance (33, 37). In patients with acute leukemia, there was considerable interpatient variability in the clearance rate (this study, 299–549 ml/min/m²; adult leukemics, 23.2–2033 ml/min/m²) with no consistent differences between the pediatric and the adult population.7

We were unable to find a physiological parameter that predicted a high or low rate of clearance; this is consistent with the fact that all patients enrolled in the study had normal bilirubins and only minimal abnormalities of other liver functions. There was a significant correlation between dose and total AUC of IDR (r = 0.96; P = 0.009, one-sided). Within a dosage level, patient numbers are too small to attempt a meaningful correlation between AUC and the duration of myelosuppression. The issue is further clouded by the need for additional drug administration in most patients because of residual leukemic cells on bone marrow evaluation.

The accumulation of the 13-hydroxy metabolite, which has been described in adults, was observed also in children. This metabolite has antileukemic activity both in vitro and in vivo (38) and may contribute to the response rate noted in children. Although a phase I study is not designed to evaluate antitumor activity, the beneficial effects on acute leukemia were unmistakable. IDR was effective in producing bone marrow remissions in children with refractory or relapsed acute leukemia. Patients with ALL have shown a higher incidence of remissions than ANLL, although the number of ANLL patients studied was small. The duration of remission in general was short. However, the 4 patients who were maintained on multiagent therapy after achieving M₁ marrow remission continued in remission for 3.5, 24, 45+, and 53+ months. In a group of patients who had multiple prior relapses (median, 2 relapses), these results are encouraging. Similarly, IDR has shown significant activity against refractory acute leukemia in adult studies (37, 39–42). Adult i.v. doses varied from 18 to 45 mg/m² given over 2–5 days.

IDR is a new anthracycline analogue with pharmacology and toxicity similar to those of the parent compound DNR. While the cardiotoxic dose still must be delineated, the 40% remission induction rate achieved with it as a single drug in children with ALL after multiple relapse and with prior anthracycline therapy indicates promising activity for IDR against ALL.

ACKNOWLEDGMENTS

The authors thank Dr. Charles Young for his thorough review of the manuscript and Christine Berhle, Lee Roepke, Margaret Harvie, and Nancy Anton for their secretarial assistance.

REFERENCES

2. Tan, C. T. C., Taska, C., Yu, K. K., Murphy, M. L., and Karmofsky, D. A.

7C. Hancock, Y-W. Stevens, and C. W. Young, unpublished results.


This text continues with a list of references.
Phase I and Clinical Pharmacological Study of 4-Demethoxydaunorubicin (Idarubicin) in Children with Advanced Cancer

Charlotte T. C. Tan, Counce Hancock, Peter Steinherz, et al.