Dose-finding and Pharmacologic Study of Chronic Oral Idarubicin Therapy in Metastatic Breast Cancer Patients

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ABSTRACT

Oral idarubicin (IDA) is an active drug in metastatic breast cancer, but its role in the management of this tumor is yet not established completely. To investigate a new modality of IDA administration, a dose-finding study was designed with hyperfractionated doses. The purpose was to determine the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and the pharmacokinetics of this schedule. IDA was administered twice daily as outpatient therapy in cycles of 3 weeks followed by a 1-week rest. Thirty-one patients with progressive metastatic breast cancer and pretreated with chemotherapy (including epirubicin and doxorubicin) were enrolled. DLT was defined as G4 hematological toxicity or any other toxicity G3 or higher (Bloom and Richardson grading). Inter- and intrapatient dose increases were studied. Pharmacokinetics of IDA and its metabolite idarubicinol (IDOL) were evaluated. IDA dose was increased from 2 mg/day to 10 mg/day, by steps of 1 mg/day, with the larger dose given in the evening. MTD was reached at 10 mg/day. Overall, the therapy cycles were 69 (median/patient, 2; range, 1–6). DLTs were G4 neutropenia associated with leukopenia and thrombocytopenia in one patient and G3 diarrhea in another of the 5 patients in the 10 mg/day cohort. The two patients developing DLT at the daily dose of 10 mg received a dose normalized for body surface of 6.85 and 5.65 mg/m²/day, respectively. We considered 5.5 mg/m²/day to be the MTD. Other toxicities were nausea, vomiting, neutropenia, and diarrhea, grades G1 to G2. By univariate analysis, significant correlations were observed between absolute neutrophil count at nadir and IDA area under the curve \((P = 0.022; r = -0.33)\), IDA \(C_{\text{max}}\) \((P = 0.0067; r = -0.38)\), IDOL area under the curve \((P = 0.0009; r = -0.43)\), and IDOL \(C_{\text{max}}\) \((P = 0.0016; r = -0.41)\), respectively. By multivariate analysis, IDA \(C_{\text{max}}\) was the strongest determinant for neutropenia \((R^2 = 0.14; P = 0.01)\). Among the 21 patients evaluable for response, 3 (14.3%) had partial response (lasting 3, 6, and 8 months, respectively), and 6 (28.6%) had a complete arrest of disease progression (lasting 2–6 months). In conclusion, the MTD of this schedule is 10 mg/day and the DLTs are neutropenia and diarrhea. Tolerance was good, and the treatment is feasible as home therapy. Some objective measurable responses were documented in this group of anthracycline-pretreated patients. IDOL could have a role for the pharmacological effect. Further evaluation of this schedule is warranted to assess the activity and toxicity of prolonged oral IDA administration.

INTRODUCTION

IDA\(^3\) is a DAU analogue that has achieved a clinical role in the treatment of some hematological malignancies (1–7). Recently, IDA has been also proposed in the management of adult solid tumors (8–13). IDA is endowed with greater biological activity and lower cardiotoxicity than DAU (2). Our and other in vitro studies have indicated that IDA is more effective than DAU in tumor cell lines displaying the multidrug-resistant phenotype, thus suggesting that IDA could be useful in circumventing multidrug resistance (3, 14).

IDA therapy generally is well tolerated. The main IDA adverse effect is myelosuppression. Gastrointestinal toxicity is also common. This includes nausea, vomiting, and stomatitis of different WHO grades, according to the IDA dose schedule used. G1–G2 diarrhea occurs in \(
\approx 10\%\) of patients after a single i.v. dose (10–15 mg/m²) and in \(10–30\%\) of patients after oral administration (40–45 mg/m²; Ref. 9).

The pharmacokinetics of IDA have been evaluated in cancer patients after i.v. or oral administration (10, 15). IDA has a large volume of distribution, which probably indicates extensive tissue accumulation. IDA is metabolized, mainly in the liver after oral administration, to IDOL (10). IDOL retains good cytotoxic activity in vitro (15). Variability in oral absorption has been reported both between patients and within the same patient (10).

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3 The abbreviations used are: IDA, idarubicin; DAU, daunorubicin; IDOL, idarubicinol (4-demethoxy-13-dihydrodaunorubicin); AUC, area under the curve; \(t_{1/2}\), half-life; MTD, maximum tolerated dose; FEC, fluorouracil-epirubicin- cyclophosphamide; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; DLT, dose-limiting toxicity; \(C_{\text{max}}\), maximum plasma concentration; CL, clearance; \(V_{\text{d}}\), volume of distribution; P-gp, P-glycoprotein.
IDA is the first anthracycline that can be given both p.o. and i.v. Oral IDA has been used in advanced breast cancer (11, 16). However, the role of oral IDA in this tumor needs to be better clarified. The oral route is useful in palliative treatment of patients with poor venous access and may be particularly appropriate for older patients (17). Oral IDA in solid tumors was administered over 1, 3, or 5 days (9). However, as demonstrated previously for other antineoplastic drugs (18, 19), the effectiveness of IDA might improve by low-dose continuous exposure. Although IDA is not a typical cell cycle phase-specific drug, it exerts some antitopoisomerase II activity (1). It has been demonstrated that the commitment to cell killing by antitopoisomerase II agents predominantly occurs in S-phase cells (20). Therefore, prolonged treatments with this drug increase the number of cells exposed to the drug during the most chemosensitive phase of the cell cycle. The increased ratio of IDOL/IDA AUC after oral compared with i.v. administration represents another advantage of prolonged low-dose treatments because IDA and its metabolite can cooperate in determining cytotoxic effects. Finally, the long plasmatic t1/2 of IDA and the longer t1/2 of IDOL (10) are pharmacological characteristics extremely favorable in protracted oral drug administration. In fact, they reduce the fluctuations in the plasmatic concentrations of the drug, allowing cells to be exposed to steadier drug concentrations, as with continuous i.v. infusion therapy.

To investigate a simple modality of IDA administration instead of the cumbersome and costly continuous i.v. infusion, a dose escalation of oral IDA was devised. The drug was given p.o. in hyperfractionated doses over a long period of time with the purpose of determining the MTD, toxicity profile, and pharmacokinetics of IDA this schedule.

PATIENTS AND METHODS

Patients. Thirty-one patients, ages 39–73 years, with histologically confirmed, measurable, and evaluable metastatic breast cancer were eligible for the study. All patients had been pretreated with chemotherapy, including anthracyclines. Pretreatment was adjuvant in seven patients: fluorouracil (600 mg/m²), epirubicin (75 mg/m²), and cyclophosphamide (600 mg/m²; FEC) in three patients; FEC and cyclophosphamide (600 mg/m²), methotrexate (40 mg/m²), and 5-fluorouracil (600 mg/m²) in two patients; and epirubicin (75 mg/m²) and cyclophosphamide (500 mg/m²) in two patients. Median time to recurrence from the end of chemotherapy in these patients was 8 months (range, 1–35 months). Chemotherapy for advanced breast cancer had been performed in 24 patients: FEC in 13 patients; fluorouracil (500 mg/m²), doxorubicin (60 mg/m²) and cyclophosphamide (500 mg/m²) in 1 patient; epirubicin and cyclophosphamide in 6 patients; doxorubicin (50 mg/m²) and cyclophosphamide (500 mg/m²) in 1 patient; doxorubicin (50 mg/m²) and cyclophosphamide (500 mg/m²) and Taxotere (100 mg/m²) in 1 patient; and cyclophosphamide-methotrexate-5-fluorouracil in 2 patients. All of the patients had relapsed after adjuvant treatment or had disease progression during chemotherapy. Overall, 28 patients were pretreated with anthracyclines. The median doses of epirubicin and doxorubicin received in previous treatments were 440 mg/m² (range, 155–765 mg/m²) and 180 mg/m² (range, 140–317 mg/m²), respectively.

The patients should not have received chemotherapy and/or radiation within 4 weeks before IDA treatment and were not receiving concurrent hormonal therapy. Patients with a history of cardiac disease were excluded. Other inclusion/exclusion criteria were: normal baseline (≥50%) LVEF; life expectancy of at least 8 weeks; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; WBC count ≥4,000/μl; platelet count ≥150,000/μl; ANC ≥2,000/μl; bilirubin level ≤1.5 mg/dl; aspartate aminotransferase level two times normal or lower, serum creatinine level ≤1.5 mg/dl, and creatinine clearance ≥60 ml/min. Written informed consent was obtained before study entry and the protocol was approved by the local Ethical Committee.

Pretreatment and Treatment Evaluation. Pretreatment evaluation included history and physical examination, chest X-ray, liver ultrasound, electrocardiogram, determination of resting baseline LVEF by echocardiography and computed tomography, total body Tc⁹⁹ bone scan when clinically indicated, full blood cell count, electrolytes, blood urea nitrogen, creatinine clearance (24-h urinary collection), liver function tests, prothrombin time-international normalized ratio (PT-INR), and partial thromboplastin time (PTT). Laboratory tests were performed on a weekly base. Toxicities were graded using the WHO criteria. The compliance to therapy was assessed through weekly pill counts in addition to a patient diary and evaluation was according to the criteria of Miller et al. (21).

Treatment Plan. IDA was provided by Pharmacia Upjohn (Milan, Italy) in powder oral capsules of 1 and 5 mg. Each therapy course was administered for 21 days every 28 days. The starting dose of 1 mg was taken around either 8.30 a.m. or 8.30 p.m. In the subsequent cycles, the dose was increased by 1 mg/day (with the larger dose given in the evening) until disease progression, refusal, or DLT. The 1-mg capsule to be added was given alternatively in the morning or in the evening. Patients had a standard meal 20 min before intake of IDA. Supportive care was administered when necessary. DLT was defined as G4 hematological toxicity or any other toxicity of G3 or higher, and MTD was the dose level at which two DLT events occurred. Antiemetics were used in the presence of vomiting of G2 or higher, whereas hematological growth factors were administered in the presence of G4 hematological toxicity.

To achieve a safe treatment, the protocol was planned to start with a very low dosage but permitting dose escalation within the individual patient to better evaluate cumulative toxicity of IDA and duration of response. We planned to enroll cohorts of five patients at each dose level. The dose was escalated by 1 mg/day only if G2 toxicity was not exceeded. If patients had G3 hematological toxicity, they were re-treated at the same dose level. If a patient experienced DLT, the next 5-patient cohort started at the same dose level (for a total of 10 patients), and the patient who had developed DLT was re-treated at 50% of the dose level. If two patients of a cohort of at least five patients experienced DLT, no additional cohort was enrolled and MTD was established.

Patients who needed 2 weeks instead of 1 to recover from toxicity were re-treated at the same dose level. If patients did not recover from toxicity after 2 weeks, they were dismissed from...
the study. Patients were also dismissed from the study if during
the 21 days of IDA intake they had a neutrophil count
$\leq 1,000/$l and/or platelet count $\leq 50,000/$l for $>1$ week, or
cardiac events (congestive heart failure, reduction of LVEF
$\geq 20\%$). In those cases, patients were replaced with new patients
entered at the same dose level. Patients with progressive disease
at the end of a specific dose level were taken off the study and
replaced with new patients. Assessment of toxicity included all
patients, whereas only those patients who received at least one
28-day course of IDA were assessable for response.

**Drug Assay and Pharmacokinetic Analysis.** Blood
samples for drug assay were taken on day 21 at 0 (immediately
before drug intake), 1, 2, 3, 4, 6, 12, 24, 48, and 72 h after the
last oral IDA dose. Blood samples were also collected at 0, 1, 2,
3, and 4 h on day 1, and at 0 h on days 8 and 15. Blood samples
were picked up in lithium heparinate tubes and centrifuged
immediately; the plasma was stored at $-20^\circ$C until analysis.

IDA and its metabolite IDOL were measured using a
reversed-phase high-performance liquid chromatography
method with fluorescence detection, as reported by Zanette
et al. (22) with slight modifications. Plasma IDA and IDOL concen-
trations were quantified using the internal standard method and
a calibration curve ranging between 0.10 and 10 ng/ml. The
limit of quantification was 0.10 ng/ml. Doxorubicin was used as the
internal standard within this range of concentrations. The within-
and between-day precision was $<10\%$ (as the coeffi-
cient of variation) for both IDA and IDOL.

Pharmacokinetic parameters were calculated using a non-
compartmental model. Estimates of pharmacokinetic parameters
and the numerical validation of the model were obtained by the
PCNONLIN 4.0, a nonlinear regression program. The $C_{\text{max}}$
and corresponding time to maximum concentration were determined
from the experimental data. AUC was calculated by the trape-
zoidal rule from time 0 to 12 h ($\text{AUC}_{0-12}$ h). $\text{AUC}_{0-24}$ h was
obtained by multiplying $\text{AUC}_{0-12}$ h by 2. The apparent CL
($\text{CL}_{\text{app}}$, in liters/h) was calculated as the ratio of daily IDA dose
(in micrograms), and $\text{AUC}_{0-24}$ h by 2. $\text{CL}_{\text{app}}$ and $\text{V}_d$
for IDOL were obtained with the same dose used for IDA
calculations. An approximation would be introduced depending
on the proportion of absorbed IDA that was not converted to
IDOL and on the rate at which the parent drug was converted to
its metabolite.

Statistical analysis was performed with software SAS sys-
tion between kinetic and dynamic parameters was performed by
the linear regression analysis. Regression analysis of multiple
parameters against a single variable, to determine independently
predictive parameters, was performed using a stepwise regres-
sion analysis. The Wilcoxon test was used for statistical eval-
uation of paired data when two groups of parameters were com-
pared. The significance of the coefficients of the correlation
found was determined as reported elsewhere (23).

**RESULTS**

**Toxicity and Response Data.** A total of 69 cycles of
treatment with IDA were administered (mean, 2.1 ± 1.4; me-
dian, 2; range, 1–6; Table 1). Three patients did not complete
even a single 21-day therapy cycle. One of them refused to
continue therapy after 5 days at 5 mg/day because of psycho-
logical problems. The other two patients had neutrophils count
$<1000/$l for $>7$ days at the dose level of 7 mg/day and were
taken off study on day 17 of therapy. In both patients, neutro-
phils ($\geq 2000/$l) spontaneously recovered in 1 week.

The toxicities are listed in Tables 2, 3, and 4. Overall, IDA
was well tolerated. Hematological toxicity was the most com-
mon. Generally, the ANC nadir decreased with the increase in
IDA dose with a statistically significant correlation ($P = 0.00019$; $r = -0.44$). At the highest dose level of IDA (10
mg/day), the median ANC was 850/$l (min, $<100$/l; max,
1500/$l; mean, 870 ± 430/$l). However, a single patient ex-
gperienced G4 neutropenia at a dose level of 3 mg/day. Such a
toxicity occurred when the dose was escalated from 2 to 3
mg/day; to further explore treatment safety, we treated two
additional patients at 2 mg/day. Thus, 5 patients had the dose
escalated from 2 to 3 mg/day and a total of 10 patients were treated
with 3 mg/day. No DLT was observed in these 10 patients.

The mean time to neutrophil nadir was 23.0 ± 4.5 days
(median, 21 days; range, 7–58 days). Twenty-two patients had
an adequate neutrophil count for recycle (i.e., $\geq 2000/$l) within
7 days from the end of IDA administration. Seven patients
recovered within 2 weeks and thus were re-treated with the same
dose: three, one, one, and two patients were re-treated at the
dose levels of 6, 7, 9, and 10 mg/day, respectively. Among these
patients, two had three cycles (one patient at 6 mg/day and one
patient at 10 mg/day, respectively; Table 1). Only two patients
did not recover adequate neutrophil counts within 14 days and
were dismissed from the study. One of these patients had an
ANC nadir of 1000/$l at 7 mg/day and completely recovered
from toxicity in 29 days. The other patient had an ANC nadir of
1555/$l at 3 mg/day and recovered in 35 days. Both these
patients had been pretreated with chemotherapy (FEC).

**Table 1.** Dose escalation and number of courses

<table>
<thead>
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<th>Total dose/day (mg/day)</th>
<th>No. of courses</th>
<th>No. of patients</th>
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<td>9</td>
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<td>3</td>
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<tr>
<td>10</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>29</td>
</tr>
</tbody>
</table>

$^{a}$No. of cycles experienced by the patients as first dose levels. $^{b}$No. of cycles experienced by the patients after intrapatient dose escalation. $^{c}$No. of cycles repeated in the same patient at the same dose level. $^{d}$No. of patients treated at a specific dose level.
One patient developed a G4 hematological toxicity (DLT) at 10 mg/day. The ANC nadir was 10,000/μl, platelets were 10,000/μl, erythrocytes were 2.07 × 10^6 /μl, and hemoglobin was 6.2 g/dl. Erythrocyte and platelet transfusion, together with granulocyte colony-stimulating factor rescue, was performed. The toxicity resolved completely in 21 days. It must be considered that in this patient’s ANC was 4400/μl on day 14.

Analysis of the neutrophil nadir over multiple courses of IDA showed no evidence of cumulative hematological toxicity.

Concerning nonhematological toxicity, diarrhea occurred in few patients and at doses $\geq 9$ mg/day. (Table 3). G1-G2 diarrhea was observed in four different patients. One patient had G3 diarrhea (DLT) when treated at 10 mg/day. Diarrhea started on day 17 of IDA intake and was maximum on day 21; it needed 1 week for resolution.

Two patients experienced DLT (G4 hematological toxicity and G3 diarrhea) at 10 mg/day, and MTD was defined at this dose level. The median dose intensity at 10 mg/day, as defined by the amount of drug delivered per week, was 44.7 mg (range, 35–52.5 mg; mean, 44.9 ± 7.5 mg).

One patient had a LVEF fall of ~30%, with bradycardia and hypotension, during the second cycle with IDA at 7 mg/day. However, it should be considered that this patient was concomitantly treated with radiotherapy in the mediastinum (5000 rads). Despite the previous, large doses of anthracyclines, no additional patient had cardiovascular toxicity. The median LVEF was 62.5% (range, 40–67%; mean, 61 ± 7.1%) with no significant ($P$ not significant by Wilcoxon test) difference with the basal value.

An attempt to calculate toxicities versus IDA dose expressed in mg/m^2/day instead of mg/day was made. The results are shown in Table 4. The two patients that experienced DLT at the dose of 10 mg/day received an IDA dose $\geq 5.5$ mg/m^2/day. The G4 hematological toxicity occurred in a patient treated with 6.85 mg/m^2/day IDA, and the G3 diarrhea was observed in a patient treated with 5.65 mg/m^2/day IDA. Overall, in our study, four patients (for a total of five courses) had an IDA dose of $\geq 5.5$ mg/m^2/day. All of these patients were in the cohort of five patients treated with 10 mg/day IDA.

The response evaluation was performed in 21 patients. A partial response was observed in three patients (14.3%) treated with doses 2 to 6 mg/day, from 7 to 9 mg/day, and from 8 to 10 mg/day, respectively. The response duration was 3–8 months, and the number of therapy cycles was four to six. These three patients previously had received anthracyclines as post-operative adjuvant treatment and had relapsed 11, 29, and 35 months, respectively, from the end of adjuvant chemotherapy. Six patients (28.6%) had stabilization of disease for 2–6 months (median, 4.0 months). Among these, five patients (83%) had progressed previously with an i.v. epirubicin-containing chem-

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### Table 2 Hematological toxicity of IDA

<table>
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<tr>
<th>Dose (mg/day)</th>
<th>No. of patients</th>
<th>No. of courses</th>
<th>Neutropenia grade</th>
<th>Leukopenia grade</th>
<th>Anemia or thrombocytopenia grade</th>
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<td>11    17  8  1</td>
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*Hb, anemia; T, thrombocytopenia.

### Table 3 Nonhematological toxicity of IDA

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<th>Dose (mg/day)</th>
<th>No. of patients</th>
<th>No. of courses</th>
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<th>Mucositis or diarrhea grade</th>
<th>Alopecia or Cardiac grade</th>
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*N, nausea; M, mucositis; C, cardiac; D, diarrhea; A, alopecia; V, vomiting.
Finally, 10 patients were not evaluable for response (Table 5). Among these latter, five had early disease progression after the first course of therapy and were dismissed from the study. Twelve patients (57%) had disease progression after undergoing other treatments.

Pharmacokinetic Analysis. The pharmacokinetics of IDA and its metabolite IDOL were evaluated in 29 patients during 56 courses of therapy. Analysis was not performed in the patient who refused to continue therapy after 5 days of treatment. Both IDA and IDOL exhibited linear pharmacokinetics over the dose range studied and remained at steady-state levels throughout the course of drug administration (Fig. 1). The concentrations of IDOL in plasma exceeded those of IDA immediately after the start of treatment and remained higher over the 21 days of treatment (Fig. 1 and Table 7). By univariate analysis, significant associations were observed between ANC at nadir and IDA AUC (P < 0.0009; r = 0.38), IDA Cmax (P = 0.0067; r = 0.33), and IDOL Cmax (P = 0.0009; r = 0.42). By stepwise linear regression multivariate analysis, significant associations were observed between several clinical parameters and plasma IDA and IDOL levels. The schedule adopted in this study was such to approach an i.v. continuous infusion. With regard to this aspect, intraday fluctuations ([Cmax - Cmin]/Cmean x 100) between IDA concentrations immediately before the last capsule of IDA (Cmean), when drug plasma concentrations were at the lowest level, and after the last capsule (Cmax), i.e., at the peak, were 41.0 ± 15.3%, (median, 44.0%; range, 15.8–62.0%; Fig. 2). Intraday variations of IDOL were 19.3 ± 9.4% (median, 18.0%; range, 9.9–40.9%). Sampling performed on days 8, 15, and 21 indicated that both IDA and IDOL maintained a relatively constant steady-state levels throughout the course of drug administration (Table 7).

Systemic clearance remained constant over the dose range investigated. The IDA/IDOL AUC ratio was not dose-dependent, suggesting that the formation of IDOL is not a relating step of IDA elimination (Table 6). A highly significant correlation was observed between IDA AUC and IDOL AUC (P < 0.000001; r = 0.83). No evidence of accumulation of plasma IDA and IDOL and no significant differences in IDA and IDOL AUC occurred during subsequent cycles with the same dose level in the six patients investigated. In a single patient treated with 2 and 3 mg/day, the plasma level of IDOL was ~6-fold higher than the median value. The IDOL AUC was 152.2 and 201.7 µg/h/liter at the doses of 2 and 3 mg/day, respectively, whereas the IDA AUC was within the range observed in the other patients treated with the same doses. This patient had severe G4 neutropenia at the dose of 3 mg/day and was dismissed from the study because of disease progression. She was receiving, in addition to IDA, quinidine, paracetamol, codeine, and diclofenac.

A relationship between plasma IDA and IDOL and toxicity was investigated. By univariate analysis, significant associations (Fig. 3) were observed between ANC at nadir and IDA AUC (P = 0.022; r = −0.33), IDA Cmax (P = 0.0067; r = −0.38), and IDOL AUC (P = 0.0009; r = −0.43), and IDOL Cmax (P = 0.0016; r = −0.41). By stepwise linear regression multivariate analysis, significant associations were observed between toxicity and IDA AUC (P = 0.0003; r = −0.56) and IDOL AUC (P = 0.001; r = −0.51). The schedule adopted in this study was such to approach an i.v. continuous infusion. With regard to this aspect, intraday fluctuations ([Cmax - Cmin]/Cmean x 100) between IDA concentrations immediately before the last capsule of IDA (Cmean), when drug plasma concentrations were at the lowest level, and after the last capsule (Cmax), i.e., at the peak, were 41.0 ± 15.3%, (median, 44.0%; range, 15.8–62.0%; Fig. 2). Intraday variations of IDOL were 19.3 ± 9.4% (median, 18.0%; range, 9.9–40.9%). Sampling performed on days 8, 15, and 21 indicated that both IDA and IDOL maintained a relatively constant steady-state levels throughout the course of drug administration (Table 7).
analysis that included the IDA AUC, IDOL AUC, IDA C_{max}, and IDOL C_{max} in the model, the strongest and only significant determinant of ANC was IDA C_{max}. However, it accounted for only \sim 14\% of ANC variance ($P = 0.01; R^2 = 0.14$). By univariate analysis, significant associations between ANC at nadir and IDA CL_{app} ($P = 0.0018; r = 0.48$) were also observed.

Finally, The AUC for IDA or IDOL showed no correlation with creatinine, bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, and \gamma-glutamyltransferase, respectively, or with performance status and patient age.

**DISCUSSION**

In this dose escalation study of chronic oral drug administration, IDA was generally well tolerated. Neutropenia was the predominant toxicity. Generally, myelosuppression became more severe as the dose was escalated, and significant associations were observed between ANC at nadir and dose level. Neutropenia was most prominent as patients approached day 21 of therapy, and the treatment was discontinued in two patients on day 17 because of an ANC <1000/\mu L. However, ANC abnormalities were not related solely to the dose, as indicated by the G4 neutropenia toxicity observed in a single patient treated.
with 3 mg/day. Therefore, the possibility of an individual’s predisposition to develop toxicity with this administration schedule should be considered.

The predominant nonhematological toxicity was diarrhea. However, it was generally mild, in agreement with a previous study (4) in which IDA produced severe or moderate diarrhea only in ~5% of patients. Diarrhea was strictly dose dependent and was observed only at a dose ≥ 9 mg/day in 3 of 10 patients.

We determined the MTD of IDA in this schedule to be 10 mg/day. Neutropenia and diarrhea were the DLTs. The two patients that experienced DLT at the dose level of 10 mg/day received an IDA dose > 5.5 mg/m²/day. This represents a 2–3-fold enhancement of dose intensity compared with the standard schedule of oral IDA administration (30–45 mg/m² every 3 weeks). The clinical toxicity/dose relationship for this schedule appears to be steep, and dramatic increases in toxicity were observed when passing from 9 to 10 mg/day or when using IDA doses > 5.5 mg/m²/day, although the percentage of difference between these dosages is little. Therefore, caution has to be observed when doses approximate the total dose/day MTD or between these dosages is little. Therefore, caution has to be observed when doses approximate the total dose/day MTD or between these dosages is little.

In our study, hospitalization was required only for the patients who developed DLTs; with these exceptions, no hematological growth factors or antiemetics were required. Generally, patients recovered adequate neutrophil counts (> 2000/µl) for recycle within 1 week, and only two patients were dismissed from the study for inadequate neutrophil count for > 2 weeks. Concerning cardiac adverse events, chronic IDA administration was safe. This was probably due to the lower cardiotoxicity of IDA compared with other anthracycline analogues (12) and to the prolonged continuous administration (24). Concerning the reduction of ~20% in LVEF observed in one patient, this must be ascribed to an extenuating circumstance (concomitant salvage-radiotherapy with 5000 rads in the mediastinum).

In the clinical practice, drug dose is calculated as a function of body-surface area, but recently this method has been questioned (25). Moreover, because of the standard commercial formulation of oral antineoplastic drugs, it is difficult to adapt the precise dosage to the body surface area. In the present study, we used the IDA dose per day instead of dose/m²/day because previously reported data on oral IDA suggested a great variability in the bioavailability (10) and such variations in bioavailability could be greater than interpatient variations in body surface. However, we also investigated the relationship between toxicity and daily dose adjusted to the body surface area. In particular, the finding that MTD occurred in patients treated with an IDA dose > 5.5 mg/m²/day strongly suggests that this dose/m²/day represents the limit for MTD.

The intrapatient dose escalation adopted in this study does not allow definitive conclusions about cumulative toxicity for a specific dose level. However, cumulative IDA exposure does not appear to be a predisposing factor to myelosuppression because toxicity was not related to the number of cycles administered to each patient. No patient re-treated with the same dose level developed cumulative toxicity, and in addition, the two DLTs were observed during the first course of IDA.

The pharmacokinetic parameters of IDA and IDOL (t½, CL, and Vd) were consistent with those described previously (26), assuming a bioavailability of ~ 10–30% for IDA and a metabolized amount of ~ 80% for IDOL (27). The plasma levels of IDOL rapidly exceeded those of the parental compound and remained higher throughout the treatment, indicating a substantial first-pass conversion of IDA to IDOL during absorption from the gastrointestinal tract. The ratio IDOL/IDA AUC was stable across the dose range, suggesting that reduction of IDA to IDOL by aldoketoreductase was not saturated with the schedule used in this study.

The AUCs for IDA and IDOL showed interpatient variations at selected dose levels. However, the IDA and IDOL
AUCs generally showed a good correlation. We think that this could reflect interpatient variations in IDA absorption rather than IDA metabolism, as also suggested by Schleyer et al. (27). On the contrary, individual abnormalities in IDA metabolism should be considered a very rare event with chronic oral IDA administration because only one patient had an IDOL/IDA ratio ~6-fold higher than that observed in the remaining patients. The abnormal IDOL plasma level in this patient was associated with increased IDOL $t_{1/2}$ and reduced IDOL CL_{app}. The liver function test and creatininemia for this patient were within the normal range, and at present, we cannot conclude that some drugs taken by this patient (i.e., quinidine) during IDA therapy may have influenced the elimination pathway of IDOL. Quinidine is a substrate for P-gp and could compete with IDOL. P-gp is expressed in the liver at the luminal surfaces of bile canaliculi (28) and probably facilitates the biliary excretion of IDOL more than IDA, whose transport is less affected by P-gp activity (15).

At present, few data are available regarding the relationship between oral IDA pharmacokinetics and toxicity (5, 13, 29). We found that the nadir granulocyte count correlated, by univariate analysis, with the IDA AUC, IDOL AUC, IDA C_{max}, and IDOL C_{max}. This strict association could suggest that even the interpatient variability observed in the plasma drug level at selected dose levels is of clinical interest. Multivariate regression analysis identified IDA C_{max} as the strongest determinant of ANC at nadir and the most significantly predictive variable independent from IDOL C_{max}, IDA C_{max}, IDOL AUC, and IDA AUC, which were entered into the stepwise regression equation. However, IDA C_{max} accounted for only ~14% of variance of ANC, and this does not allow definitive conclusions on the identification of the best variable for the prediction of IDA myelosuppression. Nevertheless, the pharmacodynamic correlations indicate that hyperfractionated oral IDA, by reducing the plasma IDA C_{max}, could contribute to reduced hematological toxicity.

This study was not intended to demonstrate an effectiveness of hyperfractionated oral IDA in breast cancer. However, 3 of the 21 patients (14.3%) evaluable for response did have objective responses, and 6 patients (28.6%) showed stable disease. These results could be promising for further phase II studies. The limited sample size precluded conclusions regarding a relationship between response and dose.

In conclusion, chronic oral administration of IDA is easily

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**Fig. 3** Scatter diagram of ANC at nadir in relation to AUC (bottom panels) and C_{max} (top panels) of both IDA (left panels) and IDOL (right panels).
administered and well tolerated by outpatients. This schedule allows greater dose intensity compared with conventional schedules, and IDOL appears to have some pharmacological effects. Whether chronic oral IDA administration offers advantages over a conventional schedule will require formal phase II studies. However, the activity and toxicity profiles of IDA observed with this schedule may be promising.

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Dose-finding and Pharmacologic Study of Chronic Oral Idarubicin Therapy in Metastatic Breast Cancer Patients

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