Phase I Clinical and Pharmacokinetic Study of Carzelesin (U-80244) Given Daily for Five Consecutive Days

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ABSTRACT

Carzelesin (U-80244), one of the synthetic DNA minor groove binding cyclopropylpyrroloindole analogues, was selected for clinical development because of its high potency, promising antitumor activity in murine solid tumors and leukemia, and significant therapeutic efficacy against colon and rhabdomyosarcoma xenografts. In this Phase I study, carzelesin was given daily for 5 consecutive days to (a) determine the maximum tolerable dose (MTD) and the pattern of toxicity of this schedule; (b) define the pharmacokinetic profile of the parent, as was done for the intermediate compound U-76073 and the DNA-reactive agent U-76074; and (c) document any antitumor activity observed. Carzelesin was given as a 10-min infusion with a constant-rate infusion pump. Treatment was repeated every 4 weeks or when blood counts had recovered to normal values. The starting dose of 12 μg/m²/day was escalated by 20–30% increments until the MTD (defined as the dose leading to grade 4 hematological or grade 3 nonhematological toxicity in at least two of six patients) was reached. Pharmacokinetic studies were planned on days 1 and 5 of the first cycle in at least two patients per dose level. Plasma levels of carzelesin, U-76073, and U-76074 were determined by high-performance liquid chromatography with UV detection and a detection limit of 0.5 ng/ml. Twenty-five patients were entered in the study, and 56 cycles were evaluable for hematological toxicity. Subsequent dose levels evaluated were 24, 30, 35, and 40 μg/m². Both neutropenia and thrombocytopenia were dose limiting and cumulative, with a high interpatient variability. Neutropenia occurred earlier (median time to neutrophil nadir and recovery, 15 and 29 days, respectively) than thrombocytopenia (median time to platelet nadir and recovery, 25 and ≥26 days, respectively); there were delays of treatment because of persisting thrombocytopenia in all patients treated at the MTD. At the MTD, the peak plasma concentrations of carzelesin were achieved at the end of the infusion and were higher than those found cytotoxic in vitro against tumor cell lines. Carzelesin was detectable up to a maximum of 1 h after the infusion. Smaller amounts of U-76073 were detectable for a maximum of 30 min only at the MTD, whereas U-76074 was never found. An 8-month partial remission was reported in one previously untreated patient with hepatocellular carcinoma at 40 μg/m². The MTD was fixed at 40 μg/m² daily; 35 and 30 μg/m² are the daily doses recommended for Phase II studies in good- and poor-risk patients. The daily regimen for 5 days seems to offer no advantage over the single intermittent schedule that has been selected for the Phase II program in Europe.

INTRODUCTION

CC-1065 and related CPI² analogues are DNA minor groove binding alkylating agents that, through the cyclopropyl group, covalently bind with a high sequence specificity to N³-adenine of A-T-rich regions (1, 2). The most significant preclinical features of CC-1065 are its unique mechanism of action, high potency, antitumor activity, and also the occurrence of delayed toxicity, which prompted synthetic efforts in the preparation of CPI analogues. Preclinical studies indicated that adozelesin (U-73975), bizelesin (U-77779), and carzelesin (U-80244; Fig. 1) are much less toxic than CC-1065 and retained good antitumor activity. Therefore adozelesin, of which Phase I evaluations have already been completed (3, 4), and carzelesin were selected for clinical development because they retained the favorable characteristics of the parent compound along with desirable pharmaceutical properties. Carzelesin, which acts through the activation of U-76073 and the cyclopropane-containing DNA-reactive agent U-76074, proved to be more effective than adozelesin against solid tumors, such as mouse pancreatic ductal O₂ adenocarcinoma and L1210 leukemia. Carzelesin also produced more long-term survivors and complete remissions than adozelesin (5) and showed significant activity against colon tumors and pediatric rhabdomyosarcoma xenografts, but only at toxic doses, suggesting a narrow therapeutic range, at least in mice (6).

In preclinical studies with carzelesin in mice and rats, bone marrow and kidney were the target organs for toxicity with early neutropenia and late tubular damage (7). Rats were more sensitive than mice to the toxic effects of carzelesin, with LD₁₀ values of 240 and 840 μg/m², respectively, for single-dose treatment and 240 μg/m² in mice for multiple-

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² The abbreviations used are: CPI, cyclopropylpyrroloindole; MTD, maximum tolerable dose; pts, patients.
dose treatment. Because neither antitumor activity nor toxicity were schedule-dependent, Phase I evaluations of carzelesin were performed on a single intermittent schedule and a daily schedule for 5 days. In the latter study, which is reported here, the main aims were to determine the MTD of carzelesin and its pattern of toxicity, antitumor activity, and pharmacokinetic profile.

**PATIENTS AND METHODS**

**Eligibility.** Patients with a histological diagnosis of solid tumor no longer amenable to established forms of treatment entered this study. Eligibility criteria also included WHO performance status ≤2, life expectancy >3 months, age 18–75 years, and adequate bone marrow (WBC count ≥4.0 × 10^3/μl and platelets ≥100 × 10^3/μl) and liver (serum transaminases ≤2 × normal levels and total bilirubin <2 mg/dl unless related to liver metastases), renal (creatinine ≤1.4 mg/dl, normal creatinine clearance, and urinalysis including electrolytes), and pulmonary functions without abnormalities due to prior treatment. Written informed patient consent was required. Because of the pulmonary toxicity reported for adozelesin, prior treatment with bleomycin was a criterion of exclusion. Patients with clinical involvement of the central nervous system, active infections, or any other medical, social, or psychological condition that could prevent adequate follow-up were ineligible.

**Drug Formulation and Administration.** Carzelesin was supplied by Upjohn Company (Kalamazoo, MI) through the European Organization for Research and Treatment of Cancer's New Drug Development Office (EORTC-NDDO; Amsterdam, the Netherlands) in 2-ml vials containing a drug concentrate of 250 μg/ml in a nonaqueous vehicle consisting of 60% polyethylene glycol 400, 30% ethanol, and 10% Tween 80 (8). This pharmaceutical preparation was kept frozen at −30°C and protected against light. For use, each carzelesin vial was diluted to 1/10 its original strength using the special vehicle up to a concentration of 25 μg/ml. The requested amount of drug was then mixed with 5% dextrose water to a final total volume of 20 ml. Treatment was given over 10 min with a constant-rate infusion pump at 2 ml/min into a 5% dextrose flowing line. Treatment was repeated every 4 weeks or when WBCs and platelets had recovered to 4.0 × 10^3/μl and 100 × 10^3/μl, respectively.

**Study Design.** The starting dose was 12 μg/m²/day, corresponding to 1/20 of the mouse equivalent LD₅₀. In the absence of significant toxicity, the dose could be escalated by 100% increments and by 20–30% increments in instances of toxicity of grade 2 or higher. At least three patients and four complete
cycles per dose level had to be evaluable before dose escalation. The MTD was defined as the dose leading to reversible, tolerable, and manageable grade 3 toxicity, or grade 4 in case of hematological toxic effects, in at least two of six patients. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria. Neutrophil and platelet recovery was defined as a neutrophil count of $\geq 2 \times 10^9/\mu l$ and a platelet count of $\geq 100 \times 10^9/\mu l$. Complete blood cell counts with differential were repeated weekly or twice a week in patients with grade 2 hematological toxicity. Chemistry analysis (including electrolytes, GGT/GPT, bilirubin, total protein, albumin, urea nitrogen, and creatinine) and urinalysis were performed weekly. In addition, analysis of creatinine clearance and urinary osmolarity were repeated before each cycle.

Sample Collection and Drug Assay. Pharmacokinetic studies were planned during the initial course on days 1 and 5 in at least two patients per dose level. Blood samples were collected in NaF-citrate-containing tubes from the arm contralateral to that receiving the infusion, 5 min after start and at the end of infusion, as well as 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 min after cessation of the infusion. Samples were protected against light and placed in ice water until cold centrifugation at $-4^\circ C$. Urinary samples were taken before and up to 48 h after the end of infusion. Plasma and urinary samples were immediately frozen at $-20^\circ C$ for subsequent analysis. The plasma levels of carzelesin, U-76073, and U-76074 were determined by high-performance liquid chromatography with UV detection and a detection limit of 0.5 ng/ml, as already reported (9).

RESULTS

Twenty-five adults were entered into this study from June 1993 to February 1995 (Table 1). Three patients died within 2 weeks of the first cycle. Two patients, one treated at 12 and one...
at 35 μg/m², died of tumor progression without signs of drug-related side effects and were not evaluable for toxicity. One patient, treated at 30 μg/m², died of tumor-related hemoptysis while platelet count was 29 × 10³/μl. Four patients received only one cycle of treatment, three of them because of early tumor progression and the fourth, who had already achieved a partial response after the first cycle (see below), because of the occurrence of severe infection. Eleven patients received two cycles, and 5 received three cycles; 4, 5, and 10 cycles were given to 1 patient each.

The dose was escalated by a 25% increment, from 24 to 30 μg/m², because of the occurrence of grade 4 neutropenia and thrombocytopenia and by 30%, from 30 μg/m² to 40 μg/m² (Tables 2 and 3). An intermediate dose of 35 μg/m² was then evaluated in five patients. Two of these patients were previously untreated, and three had a prior treatment that did not include mitomycin-C, nitrosourea, or carboplatin because of the observation of grade 4 thrombocytopenia and grade 3 neutropenia in the first cycle at 40 μg/m² in one patient pretreated with 5FU and leucovorin. Two previously untreated patients were then entered at 40 μg/m².

Hematological Toxicity. Fifty-six of 63 cycles were evaluable for hematological toxicity. Reasons for inevaluability were tumor-related early death in three cycles and retreatment at a lower dose in four (from 24 to 12 μg/m² in one cycle and from 40 to 30 μg/m² in three). Both neutropenia and thrombocytopenia were dose limiting, showing a high interpatient variability at all dose levels except the MTD, at which all patients suffered severe myelosuppression (grade 4 in two cases, grade 3 in one) complicated by one episode of pneumonitis requiring i.v. antibiotics and one episode of bleeding requiring platelet transfusions. Grade 4 neutropenia lasted 20 days in one patient and 3 days in the other. The median time to neutrophil nadir at 35 μg/m² was 15 days (range, 5–38 days), with a median time to recovery of 29 days (range, 18–44 days). At 30 and 35 μg/m², neutropenia was not significantly different between the patients with and without a previous chemotherapy, and it appeared to be cumulative, occurring after 3 of 12 initial cycles but after 8 of the 15 subsequent ones.

Platelet nadir occurred later (median, 25 days; range, 4–30) and recovery was delayed (median, ≥26 days; range, 8–36), so treatment had to be postponed because of persisting thrombocytopenia in one patient at 35 μg/m² and in all three patients at 40 μg/m². Thrombocytopenia also seemed to be cumulative; at 30 and 35 μg/m², thrombocytopenia was reported in 5 of the 12 initial cycles and in 7 of the 15 subsequent ones; grade 3–4 thrombocytopenia was observed only after repeated administrations in 4 cases.

Nonhematological Toxicity. Treatment with carzolesin was generally well tolerated, and nonhematological toxicities were rare. One patient presented a grade 3 allergic reaction during administration of the second and third cycles, with flushing, nausea, bronchospasm, and tachycardia. The symptoms appeared within 3 min after the start of therapy and subsided quickly after discontinuation of the infusion and i.v. administration of 4 mg of the antihistamine dimethindene. After that, such reactions were averted by premedication with corticosteroids in this patient. All other toxicities were of grades 1 or 2. Nausea or vomiting were reported in 30 and 18% of cycles, respectively. Neither symptom was dose-related, and a causal relationship could not be established. Mucositis, primarily of grade 1, was reported in 25% of cycles. No patients with previously normal liver function developed pathological values. Grades 1 and 2 proteinuria was seen in 55 and 9% of cycles, respectively. Reversible proteinuria of grade 2 was observed in all three patients treated at the highest dose level, where it occurred at least 4 weeks after therapy. A reversible increase of serum creatinine of grade 1 was seen in five cycles and of grade 2 in one cycle. No patient treated at the two higher dose levels developed this toxicity. Creatinine clearance did not change significantly after repeated cycles. Alopecia was never seen.

Pharmacokinetic Results. Table 4 reports the pharmacokinetic parameters (± SE) of carzolesin for individual patients. Cmax was achieved at the end of the infusion and increased linearly with the dose. The values reported after the first and the fifth infusions were comparable. The pharmacokinetic profiles could be adequately described with a one open-compartment model. Carzolesin disappeared rapidly from the plasma compartment with a T½ of approximately 16 min and was detectable up to a maximum of 1 h after the end of infusion in the majority of patients receiving doses equal to or greater than 30 μg/m² (Fig. 2). Smaller amounts of U-76073 were detectable only at 40 μg/m², from 10 up to 30 min after the end of the infusion. U-76074 was not detectable in all cases.

Antitumor Efficacy. One partial remission of ≥8 months' duration was observed in one patient who received one cycle of carzolesin at 40 μg/m² as first-line treatment for a well-differentiated hepatocellular carcinoma with cytologically verified lung metastases. Treatment could not be repeated because of the occurrence of grade 4 thrombo- and neutropenia with life-threatening pneumonia and renal insufficiency, the latter not related to carzolesin. The elevated α-fetoprotein level, which was initially 48.6 ng/ml for a normal value of <7 ng/ml, decreased progressively to normal (up to 12.5 ng/ml after 4 weeks and up to 3.7 ng/ml after 10 weeks), the pulmonary

### Table 1 Characteristics of patients

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<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
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<td>Entered (male/female)</td>
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<td>8</td>
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<td>NSCLC</td>
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*ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.
*One patient each, esophagus, kidney, and parotid gland.

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Clinical Cancer Research 1721

### Table 2  Neutropenia: median nadir counts and median time to nadir/recovery

<table>
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<tr>
<th>Dose (µg/m²/day)</th>
<th>No. of cycles</th>
<th>Median nadir count, ×10³/µL</th>
<th>Median time (days)</th>
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<td>No. of evaluable pts/cycles</td>
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<td>Grade 4</td>
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<td>2.7 (1.5–14.6)</td>
<td>16 (1–25)</td>
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<td>24</td>
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<td>3.4 (0.01–4.92)</td>
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<td>7/17</td>
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<td>14 (1–39)</td>
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<td>5/10</td>
<td>1.8 (0.6–3.5)</td>
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<td>40</td>
<td>3/3</td>
<td>0.1, 0.4, 0.9</td>
<td>24, 39, 45</td>
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</table>

* Range.

### Table 3  Thrombocytopenia: median nadir counts and median time to nadir/recovery

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<th>Dose (µg/m²/day)</th>
<th>No. of cycles</th>
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<th>Median time (days)</th>
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<td>12</td>
<td>3/16</td>
<td>191 (97–308)</td>
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<td>29 (8–29)</td>
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<td>7/17</td>
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<td>24 (5–31)</td>
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<td>35</td>
<td>5/10</td>
<td>140 (7.0–241)</td>
<td>25 (4–30)</td>
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<td>10, 19, 64</td>
<td>18, 28, 31</td>
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* Range.

### Table 4  Pharmacokinetics of carzelesin, U-76073, and U-76074

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<th>Cmax (ng/ml)</th>
<th>T½ (min)</th>
<th>AUC (ng/ml · min)b</th>
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<th>U-76073</th>
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<td>123</td>
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</table>

* Peak concentration.

From a theoretical point of view, knowledge of the specific binding sequences and their correlation to the biological effects of the different compounds would have some relevance; however, for the time being, identification of the DNA minor groove

metastases cleared entirely, and the size of the primary tumor was seen by ultrasound to have been reduced by 50%. No other remissions were seen.

**DISCUSSION**

DNA minor groove alkylators represent a new class of anticancer agents, characterized by a lack of cross-resistance with conventional alkylating agents and a high sequence specificity of DNA alkylation at the N3-adenine of A-T-rich regions (10). Preclinical features common to all DNA minor groove alkylating agents, such as CPI analogues and tallimustine derivatives (11), were high potency, a broad spectrum of antitumor activity against murine solid tumors and leukemia, and a lack of schedule dependency and dose-limiting myelotoxicity.

From a theoretical point of view, knowledge of the specific binding sequences and their correlation to the biological effects of the different compounds would have some relevance; however, for the time being, identification of the DNA minor groove
1722 Phase I Clinical and Pharmacokinetic Study of Carzelesin

The MID was fixed at 40 i.g/m², and 35 and 30 p.g/m² (daily)
influenced by previous treatments, provided that those treat-
ments had not included drugs known to affect megakaryocytes.
The MTD was fixed at 40 µg/m², and 35 and 30 µg/m² (daily 
for 5 consecutive days every 4–5 weeks) were the recom-
dended doses for Phase II studies in good- and poor-risk pa-
In this study, carzelesin was given as a short infusion for 5 
consecutive days. Myelotoxicity appeared to be almost the only
toxicity, with both neutropenia and thrombocytopenia dose-
limiting, occurring 2 and 3 weeks after treatment, respectively, 
and subsiding within 4 or sometimes 5 weeks after treatment. 
Both neutropenia and thrombocytopenia seemed to be cumula-
tive with a very steep dose-response curve between the MID and the recommended dose, 
dose-limiting thrombocytopenia, and the tendency to cumula-
tion suggest that carzelesin might have a low therapeutic index 
and that caution should be used in future studies.

The daily for 5 days regimen seems to offer no advantage 
over the single intermittent schedule of the other European 
Phase I trial (13). In that study, the MTD for the first cycle has 
now been reached at 300 µg/m², whereas the recommended 
dose for the planned Phase II program, the one associated with 
the highest dose intensity, is 150 µg/m². Carzelesin showed a 
pattern of myelotoxicity comparable to that of adozelesin, the 
other CPI analogue that completed Phase I evaluations. A dose 
of 150 µg/m², given as a short i.v. infusion, has been recom-
manded for Phase II. In contrast to carzelesin, however, the 
pharmacokinetics of adozelesin was not studied in Phase I and 
antitumor activity was not reported.

At the same time that CPI compounds have been studied in 
Phase I, the distamycin analogue tallimustine, also a DNA 
minor groove binder, has been undergoing clinical evaluation. 
In contrast to the carzelesin results, tallimustine showed a more 
favorable pattern of myelotoxicity. In the completed European 
Phase I study of tallimustine given on a single intermittent 
schedule, neutropenia was dose-limiting but also selective and 
short-lasting, so that treatment could be repeated every 4 weeks 
(14). At the two highest dose levels, plasma drug concentrations 
of tallimustine between 100 and 400 ng/ml could be achieved 
and maintained for the first hour following administration. 
These concentrations were higher than the mean ID₇₀ of 
165.3 ± 49 ng/ml of tallimustine reported in the comparative in 
vitro study, in which carzelesin and other minor-groove alkyla-
tors were also tested. 

The different hematotoxic effects of distamycin derivatives 
and CPI analogues suggest that these groups of compounds 
produce different types of bone marrow damage, the former at 
the level of late committed progenitors and the latter at the level 
of early progenitors and stem cells. A clonogenic assay of 
hematopoietic cells derived from human umbilical cord blood 
has recently been implemented, and the therapeutic index of 
different minor-groove alkylators as compared to melphalan has 
been determined (15). Studies on long-term cell cultures to 
evaluate damage to hematopoietic cells more primitive than gran-
ulocyte macrophage colony-stimulating factor are also in 
progress.

The promising preclinical data suggested that DNA minor 
groove alkylators could represent a new class of active anticanc-
er agents. Although the data on antitumor activity are still 
limited to Phase I studies, the clinical results thus far achieved 
have not been very promising. It is therefore important that the 
many pieces of information deriving from comparative studies 
with molecular pharmacology (identification of DNA sequence of binding and 
correlation to biological effects) to preclinical toxicology (new in 
vitro systems of hematopoietic cells) and to pharmacokinet-

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**Fig. 2** Plasma concentration-time curves of carzelesin ( ), U-76073 ( ), and U-76074 ( ) of a patient receiving 40 µg/m² of the drug as a 10-min i.v. infusion.

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ics/pharmacodynamics (intermediate metabolism) be integrated for a more rational and successful clinical development.

REFERENCES


Phase I clinical and pharmacokinetic study of carzelesin (U-80244) given daily for five consecutive days.

I Wolff, K Bench, J H Beijnen, et al.


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