Phase I Trial of Recombinant Interleukin 3 before and after Carboplatin/Etoposide Chemotherapy in Patients with Solid Tumors: A Southwest Oncology Group Study

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ABSTRACT

Recombinant human interleukin 3 (rhIL-3, expressed in Escherichia coli) is a hematopoietic growth factor with protein biological effects on bone marrow in animal models, including enhanced granulocyte and platelet production and the capacity to ameliorate chemotherapy-induced bone marrow toxicity. We, therefore, undertook a Phase I trial in patients with advanced solid tumors and normal bone marrow function. Cohorts of four to six patients each received daily s.c. doses of rhIL-3 (SDZ-ILE-964; Sandoz) at dose levels of 1.0, 2.5, 5.0, and 10.0 μg/kg according to the following schedule: cycle 1, rhIL-3 days 1–14; cycle 2, carboplatin (350 mg/m²) on day 1 and etoposide (100 mg/m²) on days 1–3; and cycle 3, carboplatin (350 mg/m²) on day 1, etoposide (100 mg/m²) on days 1–3, and rhIL-3 on days 4–17. Each cycle was a total of 28 days. An analysis of 20 patients entered into all four escalating dose levels revealed that, during cycle 1, absolute neutrophil count (ANC) increased from a median baseline of 6,643/mm³ to a median of 12,692/mm³, and platelets increased from a median baseline of 314,000/mm³ to a median of 465,000/mm³. When cycle 2 was compared with cycle 3, the median ANC nadir increased from 12/2/mm³ to 988/mm³, and the mean ANC nadir increased from 458/mm³ to 1,297/mm³. Median platelet count nadirs increased from 29,000/mm³ to 84,000/mm³, and the mean nadir platelet counts increased from 72,000/mm³ to 129,000/mm³. Total days on which platelets were <50,000/mm³ was 52 for cycle 2 and 19 for cycle 3. The maximum tolerated dose of rhIL-3 was 5.0 μg/kg/day; dose-limiting toxicities included fatigue, chills, fever, and headache. These data suggest a clear but variable biological activity observed with IL-3, as measured by the reduction in the depth and duration of thrombocytopenia and/or neutropenia when cycle 2 was compared with cycle 3. rhIL-3 is a promising cytokine that may help to ameliorate the bone marrow toxicity observed with the use of chemotherapeutic agents.

INTRODUCTION

rhIL-3 expressed in Escherichia coli is a cytokine with multiple biological effects. Numerous in vitro studies have shown that rhIL-3 induces both the growth of multipotential hematopoietic progenitors and the differentiation of more mature hematopoietic elements (1–12). Moreover, the administration of rhIL-3 to nonhuman primates resulted in increases in bone marrow cellularity and WBC and platelet counts. After intensive myelosuppressive therapy in nonhuman primates, rhIL-3 enhanced myeloid and platelet recovery and abrogated the predicted period of severe neutropenia (13).

Several Phase I clinical studies of rhIL-3 administered either after nonmarrow ablative chemotherapy for neoplastic disease or alone for myeloproliferative disorders suggested enhanced production of both neutrophils and platelets without serious adverse effects (14–20). We conducted a multicenter clinical trial to evaluate the safety, tolerability, and biological activity of rhIL-3 given both before and after a chemotherapeutic regimen of carboplatin and etoposide in patients with metastatic or locally advanced solid tumors. In addition, we evaluated the hematological effects and determined the MTD or rhIL-3 administered to cancer patients receiving carboplatin and etoposide.

PATIENTS AND METHODS

Study Design

In this Phase I open-label, nonrandomized trial, 20 patients were enrolled on an outpatient basis in three participating centers from the Southwest Oncology Group.

In cycle 1, enrolled patients were given a single dose of rhIL-3 by s.c. injection once daily for 14 days at designated dose levels followed by a 14-day washout period (Fig. 1). After completion of the initial phase of rhIL-3 treatment (cycle 1), patients received carboplatin (350 mg/m²/day, day 1) and etoposide (100 mg/m²/day, days 1–3) i.v. followed by a 25-day washout period (cycle 2). In cycle 3, patients received carboplatin (day 1) and etoposide chemotherapy i.v. for 3 days (days 1–3) followed by rhIL-3 s.c. for 14 days (days 4–17). Dose

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3 The abbreviations used are: rhIL-3, recombinant human interleukin 3; MTD, maximum tolerated dose; ANC, absolute neutrophil counts.
Phase I Trial of rIL-3

Days of Study

<table>
<thead>
<tr>
<th>Cycle 1</th>
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<th>Cycle 3</th>
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<tr>
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<tr>
<td>Carboplatin</td>
<td>Etoposide</td>
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Fig. 1  Study schema. Carboplatin was administered i.v. at 350 mg/m²; etoposide was administered i.v. at 100 mg/m²; and rhIL-3 was administered at 1.0, 2.5, 5.0, or 10.0 μg/kg s.c.

reduction was not permitted between cycles 2 and 3, and patients requiring dose reduction because of hematopoietic toxicity were not eligible for administration of rhIL-3 in cycle 3. Patients who demonstrated a clinical response were eligible for administration of carboplatin and etoposide followed by rhIL-3 at their assigned dosage level for up to six additional cycles.

Four dose levels of rhIL-3 were evaluated, starting with 1.0 μg/kg/day (n = 4) in the initial cohort of patients and escalating to 2.5 (n = 4), 5.0 (n = 6), and 10.0 μg/kg/day (n = 6) in subsequent cohorts. rhIL-3 dose was assigned at study entry and intrapatient dose escalation was not permitted. Subsequent cohorts were added after patients in a preceding cohort had completed cycle 1 without experiencing any grade III or IV toxicities attributed to rhIL-3. If any of the four patients experienced a grade III or IV toxicity attributable to rhIL-3, two additional patients were added to that dosage cohort, and those patients experiencing the toxicity were removed from the study. If more than one half of the patients at any dose level developed grade 3 or 4 toxicity, the next lower dose was considered to be the MTD. Southwest Oncology Group criteria were used in grading toxicity (grading system, 0–5). A provision was included to withhold the study drug for a maximum of 5 days if, after two consecutive determinations, any of the following occurred: WBC >45,000/mm³, ANC >20,000/mm³, platelet counts >750,000/mm³, and hemoglobin >15.0 g/dl without transfusion.

Medications

rhIL-3. E. coli-derived, nonglycosylated rhIL-3 was provided by the Cytokine Development Unit of Sandoz Pharmaceuticals Corporation (SDZ-ILE-964; Sandoz, East Hanover, NJ). Vials containing 150, 300, or 750 μg SDZ-ILE-964 were reconstituted with 1 ml sterile water and administered by s.c. injection immediately after reconstitution. The initial two doses were followed by a 2-h observation period.

Chemotherapy. Carboplatin and etoposide were obtained from commercial sources. Carboplatin was given first on day 1 of chemotherapy, and both drugs were administered over 1 h.

Evaluations

An assessment of vital signs, including blood pressure, heart rate, and temperature, and a physical examination, including body weight and Karnofsky performance status, were performed every 2 weeks. Complete blood counts, including WBC, differential, platelet, and reticulocyte counts, were performed at baseline and then three times each week (Monday, Wednesday, and Friday). A coagulation profile, urinalysis, and serum chemistries were obtained at baseline and then weekly.

Patient Eligibility

Patients with histologically proven cancer, classified as locally advanced or distant metastatic disease, for which carboplatin and etoposide were considered to be the most appropriate chemotherapy regimen or for which no more efficacious therapy existed, were eligible for enrollment. Additional requirements for enrollment were as follows: age 18 years or older; female patients who were postmenopausal, surgically sterile, or practicing a medically approved method of birth control and having a negative serum β-human chorionic gonadotropin pregnancy test at baseline; a performance status of >70% on the Karnofsky scale; no known or suspected brain or bone marrow metastases; and no previous chemotherapy treatment with carboplatin, etoposide, or cisplatin. Requirements at study entry were as follows: adequate bone marrow function (hemoglobin >10.0 g/dl, WBC count >4000/mm³, granulocyte count >1500/mm³, and platelet count ≥100,000 cells/mm³); renal function (creatinine ≤2.0 mg/dl); hepatic function (bilirubin ≤2.0 mg/dl; aspartate aminotransferase ≤2.0 times the upper limits of normal); and coagulation parameters (prothrombin time and partial thromboplastin time, <125% control). Baseline X-rays, a bone marrow evaluation, and scans for tumor measurement were required within 2 weeks of study onset.

Patients with pulmonary or cardiac disease; a history of dementia or altered mental status; allergies, such as asthma; and/or a history of anaphylaxis were excluded, as were those with active infections requiring antibiotics; a positive HIV test; or any form of active viral hepatitis. Patients also were ineligible if they required treatment with corticosteroids or had received any cytotoxic chemotherapy, radiation therapy, or biological response modifiers, including other hematopoietic growth factors, hormonal therapy, or investigational agents, within 4 weeks of study entry or any nitrosoureas or mitomycin within 6 weeks of study entry.
The incidence and severity of adverse events increased with higher doses of rhIL-3 (Table 3), i.e., zero of four patients at the 1.0 μg/kg/day dose level compared with four of six patients at the 10.0 μg/kg/day dose level experienced grade 3 toxicities related to rhIL-3 treatment.

Dose-limiting (Grades 3 and 4) Toxicities. Of the 20 patients, 13 completed the three cycles of treatment, and 7 were removed from the study before completion of three cycles. One patient at the 2.5-μg/kg/day dose level was removed from the study during cycle 2 because of the development of deep venous thrombosis and attendant fever, which was possibly attributable to rhIL-3 in cycle 1 (grade 3 toxicity). Two of the six patients treated at the 5.0-μg/kg/day dose level discontinued prematurely; one patient experienced a cardiac arrhythmia (grade 3 toxicity) during cycle 1, which was considered by the investigator to be related to rhIL-3 treatment. The other patient at the 5.0-μg/kg/day dose level was withdrawn because of hematologic toxicity during cycle 2 and initiation of another growth factor. Five of the six patients in the 10.0-μg/kg/day dose cohort withdrew from the study during either cycle 1 (three patients) or rhIL-3 administration in cycle 3 (two patients). The grade 3 toxicities reported in the four patients requiring termination of rhIL-3 treatment at the 10-μg/kg/day dose were fatigue, myalgias, anorexia, and malaise. One of these patients developed transient urticaria as well. One patient discontinued rhIL-3 treatment because of subjective (grade 2) intolerance consisting of similar flu-like symptoms. Therefore, rhIL-3 was not well tolerated at the 10.0-μg/kg/day dose level, and the MTD of rhIL-3 was determined to be 5.0 μg/kg/day.

Hematological Effects. During cycle 1, all 20 patients who received rhIL-3 alone for 14 days showed modest (1.2-
1.8-fold) increases in platelet counts, which were maximal by days 14–16. Higher doses were not necessarily associated with greater increases in platelet numbers (Fig. 2).

Thirteen patients at the four dose levels were evaluable for a comparison of the depth and duration of thrombocytopenia during cycle 2 (chemotherapy alone) versus cycle 3 (chemotherapy followed by rhIL-3). Four of the nine patients with platelet count nadirs of less than 50,000/mm³ in cycle 2 (chemotherapy alone) had platelet responses (platelet counts of 50,000/mm³) during cycle 3 (chemotherapy followed by rhIL-3). The duration of thrombocytopenia was reduced by 3 days for six of nine patients who were thrombocytopenic during cycle 2. The duration of thrombocytopenia was not changed or increased for the three remaining patients. Table 4 summarizes and compares the effect of rhIL-3, at each dose level, on recovery of platelet counts after chemotherapy in cycles 2 and 3. Compared with cycle 2, an improvement in median platelet nadir in cycle 3 was seen at doses of 2.5, 5.0, and 10.0 μg/kg/day. Likewise, improvement was noted in the mean duration of thrombocytopenia in cycle 3 compared with cycle 2 at doses of >1.0 μg/kg/day. Although the patient numbers are small, there did not appear to be a dose-related improvement in either the depth or duration of thrombocytopenia as the dose of rhIL-3 was increased from 2.5 to 10.0 μg/kg/day.

Table 5 provides platelet transfusion requirements during cycles 2 and 3. Seven patients required platelet transfusions during cycle 2 (chemotherapy alone); however, only two patients required transfusions during cycle 3 when rhIL-3 was administered after chemotherapy. Three of the five patients who became transfusion free were treated at the 5.0-μg/kg/day rhIL-3 dose level, and one patient was treated at the 10.0-μg/kg/day dose level. The remaining patient, who did not require platelet transfusions during cycle 3, had a chemotherapy dose reduction in violation of the protocol.

Treatment with rhIL-3 for 14 days increased the ANC in cycle 1 (1.3–3.4-fold) (Fig. 3). Maximum ANC were generally observed on days 14–16. Among the 13 patients evaluable for hematological response after chemotherapy, a comparison of ANC indicates improvement in the neutrophil nadir in 12 patients during cycle 3 compared with cycle 2 (Table 6). Although 3 of 13 patients did not have neutrophil nadir counts <500/mm³ in either cycle, 4 of the 10 patients who did have neutrophil nadir counts <500/mm³ in cycle 2 had a clinically significant neutrophil response (nadir >500/mm³) in cycle 3.

Of the 13 patients evaluable for a comparison of the duration of neutropenia in cycles 2 and 3, 2 patients did not expe-
Sandoz, unpublished data.

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11 patients all had a reduction of 1–8 days in the duration of
neutropenia in cycle 3 compared with cycle 2. Table 6 compares
the effect of rhIL-3 on median nadir counts and the mean
count of days that the ANC was <500/mm3 for both cycles 2
and 3 for each dose level. For all dose levels, the median
eutrophil nadir was higher in cycle 3 than in cycle 2, and the
mean duration <500/mm3 was 2–4 days fewer during cycle 3
than cycle 2 at all dose levels. Although only small numbers of
patients were studied in each dose group, it did not appear that
greater hematological effects were achieved with increased
doses of rhIL-3. No effect of rhIL-3 was observed on reticulo-
cyte counts or hematocrit.

**DISCUSSION**

This study was designed to evaluate the safety, tolerability,
and biological activity of rhIL-3 in patients with metastatic solid
tumors undergoing chemotherapy with carboplatin and etopo-
side. In vivo, pharmacological studies of the s.c. administration
of SDZ-ILE-964 to normal healthy primates (dose range, 1–100
µg/kg/day) have shown a modest leukocytosis secondary to
increases in neutrophils, basophils, and eosinophils. Adminis-
tration of rhIL-3 to myelosuppressed primates at a dose of 20
µg/kg/day enhanced neutrophil recovery with prevention of
prolonged periods of neutropenia and possible prevention of
diminution in the degree of thrombocytopenia (13).

In our study, the s.c. administration of rhIL-3 at doses of
1.0, 2.5, and 5.0 µg/kg/day was reasonably well tolerated: only
2 of 14 patients at these dose levels developed grade 3 toxicities
attributable to rhIL-3. Because five of the six patients treated at
the 10.0-µg/kg/day dose level were withdrawn from the study as
a result of adverse events or subjective intolerance to rhIL-3
therapy, the MTD of rhIL-3 was determined to be 5.0 µg/kg/
day.

A comparable safety profile has been observed in other
studies of s.c. administration of rhIL-3 in cancer patients receiv-
ing chemotherapy; flu-like symptoms and headaches are re-
ported as the most consistent and intolerable adverse events.
Likewise, we found fatigue, chills, fever, and headache to be
dose limiting. In a study of rhIL-3 administered s.c. after car-
boplatin chemotherapy in the treatment of patients with recur-
current ovarian carcinoma, dose-limiting adverse effects included
persistent flu-like symptoms and headaches (18). In a similar
study of s.c. rhIL-3 administration after carboplatin and cyclo-
phosphamide chemotherapy in patients with advanced ovarian
cancer, fever, flu-like symptoms, chills, and nausea were
reported (19). Comparable clinical effects were noted in patients
with small cell lung cancer treated with rhIL-3 after combina-
tion chemotherapy consisting of either cyclophosphamide,
doxorubicin, and etoposide or vincristine, ifosfamide, mesna,
and carboplatin. However, fever and flu-like symptoms were
reported as being more pronounced during the first days of
rhIL-3 therapy and tending to diminish during subsequent ad-
ministration (17).

During cycle 1, rhIL-3 administered alone for 14 days
resulted in modest increases in WBC, absolute neutrophil, and
platelet counts in all patients at all dose levels. In a similar Phase
I study, the hematological effects of rhIL-3 administered before
chemotherapy were evaluated in previously untreated patients
with small cell lung cancer and normal bone marrow function.
Patients received a continuous infusion of rhIL-3 at doses that
 ranged from 0.25 to 10.0 µg/kg/day for a 7-day period before
the administration of the first cycle of chemotherapy. During
the prechemotherapy treatment cycle, there were dose-dependent
platelet and neutrophil rises in the rhIL-3-treated group com-
pared with the control group ($r = 0.736, P < 0.001$ and $r =
0.512, P = 0.012$, respectively; Ref. 17). Although similar
increases in platelet and neutrophil counts were observed in our
study during cycle 1 (treatment with rhIL-3 alone), the hema-
topoietic effects were not necessarily dose dependent.

When hematological parameters in cycle 2 (chemotherapy
alone) were compared with those in cycle 3 (chemotherapy
followed by rhIL-3), improvements in the median platelet nadir
were observed in the 2.5-, 5.0-, and 10.0-µg/kg/day dose co-
horts. Likewise, improvement was noted in the duration of
thrombocytopenia between cycle 2 and cycle 3 as well. It is
clear that there was a faster platelet recovery when rhIL-3
therapy was followed by rhIL-3 therapy. However, the effect on
the depth or duration of thrombocytopenia was variable, and higher
doses of rhIL-3 were not always associated with greater in-
creases in platelet counts.

A comparison of the depth and duration of neutropenia
experienced by patients during cycles 2 and 3 indicated that the
administration of rhIL-3 seemed to accelerate neutrophil recov-
er after chemotherapy. A 3–4-fold increase in the median ANC
nadirs was apparent in the 1.0-, 2.5-, and 5.0-µg/kg/day dosing
cohorts as was a shortening of the duration of neutropenia by
several days at all dose levels.

Similar findings have been reported in several Phase I/II
clinical studies of rhIL-3 administered after chemotherapy in

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Table 6 Depth and duration of neutropenia

<table>
<thead>
<tr>
<th>Dose cohort (µg/kg)</th>
<th>Median ANC nadir</th>
<th>Mean no. of days ANC &lt;500 cells/mm³</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Cycle 2</td>
</tr>
<tr>
<td>1.0</td>
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<td>300</td>
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<tr>
<td>2.5</td>
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<td>5.0</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>10.0</td>
<td>3</td>
<td>306</td>
</tr>
</tbody>
</table>

*Includes only those patients with data for both cycles 2 and 3.

*Duration could not be calculated for one patient because ANC ≥500 cells/mm³ were not achieved during the observation period.

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4 Sandoz, unpublished data.
patients with initially normal bone marrow function. D’Hondt et al. (20) found that patients treated with rhIL-3 after chemotherapy had a faster neutrophil recovery and platelet recovery compared with those observed in a previous cycle of chemotherapy alone. In addition, these differences in neutrophil and platelet recovery noted between each chemotherapy cycle were not observed in placebo-treated patients (20).

rhIL-3 was safely administered s.c. to patients after chemotherapy with carboplatin and etoposide in doses up to 5.0 μg/kg/day for 14 days. The MTD of rhIL-3 was determined to be 5.0 μg/kg/day because rhIL-3 was poorly tolerated at the 10.0-μg/kg/day dose level. Clear but variable biological activity was observed with rhIL-3 therapy, as measured by reduction in the depth and duration of thrombocytopenia and neutropenia after carboplatin and etoposide chemotherapy. A relationship between the dose of rhIL-3 administered and its hematological effects was not observed; however, the number of patients in each dose cohort was small.

REFERENCES


Phase I trial of recombinant interleukin 3 before and after carboplatin/etoposide chemotherapy in patients with solid tumors: a southwest oncology group study.


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