A Phase II Study of Carboplatin as a Treatment for Children with Acute Leukemia Recurring in Bone Marrow

A Report of the Children's Cancer Group

Lawrence J. Ettinger, M.D.[1]
Percy Ivy, M.D.[2]
Paul S. Gaynon, M.D.[3]
Alice G. Ettinger, R.N., M.S.N.[1]
Wen Liu-Mares, M.S.[4]
Mark D. Krailo, Ph.D.[4,5]

[1] Department of Pediatrics, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick, New Jersey; The Cancer Institute of New Jersey, New Brunswick, New Jersey.

[2] Department of Hematology-Oncology, Children's National Medical Center, Washington, DC.

[3] Department of Pediatrics, University of Wisconsin Medical Center, Madison, Wisconsin.

[4] Children's Cancer Group, Arcadia, California.

[5] Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, California.

BACKGROUND. Carboplatin is an analogue of cisplatin with less nonhematologic toxicity and a similar spectrum of antineoplastic activity. Although cisplatin has not been found to be an active agent against leukemia, carboplatin-induced complete remissions have been observed in adults with acute myelogenous leukemia (AML), and antileukemic activity has been observed in a Phase I trial involving children with acute lymphoblastic leukemia (ALL) and AML. Therefore, a pediatric Phase II study was undertaken to determine the degree of activity of carboplatin in childhood ALL and AML.

METHODS. Between October 1991 and November 1994, the Children's Cancer Group conducted a Phase II study of carboplatin given by 5-day continuous intravenous infusion to children with acute leukemia recurring in bone marrow.

RESULTS. Minimal antileukemic activity was demonstrated in patients with ALL and AML. One of 21 eligible patients with ALL achieved a partial response. Of 23 eligible patients with AML, including 1 patient with chronic myelogenous leukemia in blast crisis, 1 had hypocellular M1 bone marrow with a platelet count of 15,000/mm^3, and 2 achieved partial responses. Nonhematologic toxicities, which were infrequent, included mild hepatic and renal dysfunction.

CONCLUSIONS. In this pediatric Phase II trial of carboplatin as a treatment for acute leukemia, minimal activity was demonstrated in patients with ALL and AML recurring in bone marrow. Further evaluation of carboplatin as a treatment for childhood leukemia, using the dose schedule of 216 mg/m^2/day given by 5-day continuous intravenous infusion, does not appear warranted. ***Cancer* 1997;80:311–6.**

KEYWORDS: carboplatin, leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, acute nonlymphoblastic leukemia.

Supported by grants from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services.

Principal Children's Cancer Group participants (with their National Cancer Institute grants in parentheses): W. Archie Bleyer, M.D., Anita Khayat, Ph.D., Harland Sather, Ph.D., Mark Krailo, Ph.D., Jonathan Buckley, M.B.B.S., Ph.D., Daniel Stram, Ph.D., and Richard Sposto, Ph.D., Group Operations Center, Arcadia, California (CA 13539); Raymond Hutchinson, M.D., University of Michigan Medical Center, Ann Arbor, Michigan (CA 02971); Katherine Matthay, M.D., University of California Medical Center, San Francisco, California (CA 17829); Susan Shurin, M.D., Rainbow Babies & Children's Hospital, Cleveland, Ohio (CA 20320); Gregory Reaman, M.D., Children's National Medical Center, Washington, DC (CA 03888); Jorge Ortega, M.D., Childrens Hospital of Los Angeles, Los Angeles, California (CA 02649); Frederick Ruymann, M.D., Children's Hospital of Columbus, Columbus, Ohio (CA 03750); Sergio Piomelli, M.D., College of Physicians & Surgeons of Columbia University, Columbia-Presybyterian Medical Center, New York, New York (CA 03526); Joseph Mirro, M.D., Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania (CA 36015); John Lukens, M.D., Vanderbilt University School of Medicine, Nashville, Tennessee (CA 26270); Lawrence Wolff, M.D., Doernbecher Memorial Hospital for Children, Portland, Oregon (CA 26044); William Woods, M.D., University of Minnesota Health Sciences Center, Minneapolis, Minnesota (CA 07306); Anna Meadows, M.D., Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (CA 11796); Christopher Fryer, M.D., University of British Columbia, Vancouver, Canada (CA 29013); Robert Wells, M.D., Children's Hospital Medical Center, Cincinnati, Ohio (CA 26126); Jerry Finklestein, M.D., Harbor/UCLA and Miller Children's Medical Center, Torrance/Long Beach, California (CA 14560); Stephen Feig, M.D., University of California Medical Center (UCLA), Los Angeles, California (CA 27678); Gerald Gilchrist, M.D., Mayo Clinic and Mayo Foundation, Rochester, Minnesota (CA 28882); Milton Donaldson, M.D., University of Medicine and Dentistry of New Jersey, Camden, New Jersey; and Mitchell Cairo, M.D., Children's Hospital of Orange County, Orange, California.

Address for reprints: Lawrence J. Ettinger, M.D., Children's Cancer Group, P.O. Box 60012, Arcadia, CA 91066-6012.

Received December 11, 1996; revision received March 12, 1997; accepted March 12, 1997.

Carboplatin (CBDCA [platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0′]-, (SP-4-2)], National Service Center [NSC]-241240) is an analogue of cisplatin that was developed to have less nonhematologic toxicity than its parent compound and a similar spectrum of antineoplastic activity. It is less emetogenic, nephrotoxic, and ototoxic than cisplatin; however, its dose-limiting toxicity is myelosuppression.[1–11] In previous clinical trials, single-agent activity has been documented for carboplatin in a spectrum of solid tumors in children.[4–6,8–10]

Cisplatin has not been found to be an active agent against leukemia. However, when carboplatin was studied in adult patients with acute leukemia in relapse, complete remission was achieved in patients with acute myelogenous leukemia (AML) on a 5-day continuous intravenous infusion schedule.[12,13] This response was not achieved with rapid intravenous infusion daily for 5 consecutive days.[14]

A Phase I study[11] of carboplatin given by 5-day continuous intravenous infusion to children with acute leukemia in relapse demonstrated activity in both acute lymphoblastic leukemia (ALL) and AML. The recommended Phase II dose of carboplatin was 216 mg/m^2/day. Glomerular and tubular nephrotoxicity was considered dose-limiting. At the two higher doses studied, i.e., 336 mg/m^2/day and 270 mg/m^2/day, mild nephrotoxicity was seen in the majority of patients. The etiology for this toxicity was not clearly determined in this high risk group of patients, although carboplatin and nephrotoxic antibiotics (vancomycin, an aminoglycoside, or amphotericin B) were implicated. Furthermore, the decision to administer carboplatin at a dose of 216 mg/m^2/day was also based on the outcomes of two patients who received doses of 270 mg/m^2/day, one of whom died of acute hepatic necrosis and hepatic encephalopathy, and the other of whom developed presumed hemorrhagic cystitis secondary to carboplatin.

MATERIALS AND METHODS

Eligibility Criteria

Patients ages 1–21 years with cytologically verified leukemia recurring in bone marrow (>25% leukemic blasts) were eligible for CCG-0916, a 5-day continuous infusion of carboplatin. Patients could not have received carboplatin previously or any chemotherapy in the 2 weeks prior to study entry. Other entry criteria included an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and a life expectancy of at least 8 weeks, as estimated by the attending physician. Adequate renal and hepatic function were required at study entry and were defined as serum creatinine less than or equal to 1.5 times normal, total bilirubin less than 1.5 times normal, and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) less than 2.5 times normal. Patients with active central nervous system (CNS) leukemia were eligible for study. Signed, informed consent, with an understanding of the investigational nature of this study, was obtained in accordance with federal and institutional guidelines.

Treatment Plan

Patients received carboplatin at a dose of 216 mg/m^2/day by 5-day continuous intravenous infusion. This was followed by a 23-day period during which no chemotherapy was given. Twenty-eight days after the start of treatment, the patient was evaluated for response. Patients were considered evaluable for response if they received 1 complete 5-day course of carboplatin and if they had either persistent circulating leukemic blasts or an evaluable bone marrow examination performed between Days 14 and 28 (see ''Definition of Response'').

The 28-day cycles of carboplatin were to be continued for a total of 2 years of therapy unless the patient (1) demonstrated progressive disease, including extramedullary disease or rapidly increasing peripheral blast count; (2) experienced Grade 4 organ toxicities, excluding hematologic toxicities, related to chemotherapy; or (3) terminated protocol-mandated therapy. If other chemotherapeutic agents or immunomodulating agents, including steroids or intrathecal chemotherapy, were utilized during the first 28-day cycle, the patient was removed from the study and considered inevaluable. If patients achieved M_1 bone marrow (<5% leukemic blasts) during the first course of carboplatin but the absolute neutrophil count (ANC) and platelet count did not recover to ≥1,000/mm^3 and ≥100,000/mm^3, respectively, the next cycle of therapy was to be delayed for up to 2 weeks to permit the counts to recover. If on Day 28 of the first course of carboplatin the patient had M_2 bone marrow (5–25% leukemic blasts), therapy was continued regardless of the ANC and platelet count until M_1 bone marrow was obtained or progressive disease or unacceptable toxicity was detected.

The dose of carboplatin was to be decreased to 160 mg/m^2/day if the patient demonstrated objective evidence of response and the treatment was delayed beyond Day 42 from the prior course of therapy. There was no dose escalation in this study. Subsequent 28-day cycles were to be repeated with the same infusion schedule as long as the patient did not have progressive disease or unacceptable toxicity. Patients who demonstrated unacceptable toxicity or progressive disease were removed from protocol therapy.

Hydration, alkalinization, and allopurinol for prevention of hyperuricemia were recommended. Hypocalcemia and hypomagnesemia noted prior to car-

boplatin infusion were to be corrected with supplementation prior to administration of carboplatin. Investigators were instructed to avoid the use of aminoglycoside antibiotics, except where clinically indicated, in order to reduce the risk of nephrotoxicity and ototoxicity. The use of colony-stimulating factors (G-CSF or GM-CSF) was neither prescribed nor prohibited by this protocol.

Definition of Toxicity

Toxicity was graded on a scale of 1–4, with Grade 4 defined as life-threatening. The specific limits were those designated as the National Cancer Institute Common Toxicity Criteria. Patients who received at least 1 day of the 5-day carboplatin infusion and were followed to at least Day 14 without the administration of other anticancer therapy were considered evaluable for the occurrence of toxicity. In addition, any patient whose therapy was terminated because of toxicity at any time after the start of the infusion was considered evaluable for toxicity. The definition of significant toxicity was (1) Grade 3 nonhematologic toxicity not returning to Grade 2 levels prior to the initiation of the next cycle of therapy, (2) Grade 4 toxicity occurring at any time, or (3) Grade 2 nonhematologic toxicity persisting for more than 6 weeks. Ototoxicity was graded according to criteria modified from that of Khan et al.[15]

Definition of Response

Patients who received at least 1 day of the 5-day carboplatin infusion were followed to at least Day 14 without the administration of other anticancer therapy, and had disease status evaluated prior to Day 28 after the start of treatment were considered evaluable for response to therapy. Patients who died prior to Day 28 of therapy and before evaluation of response were considered nonresponders.

Response was evaluated at the end of each 28-day cycle. The following definitions were used to define response: A complete response (CR) required $\leq$5% leukemic blasts in a normocellular or slightly hypocellular bone marrow and recovery of peripheral blood counts to an ANC of $\geq$1,000/mm^3 and a platelet count of $\geq$100,000/mm^3 within 1 week of bone marrow response. A partial response (PR) required a bone marrow leukemic blast percentage of 6–25% and recovery of peripheral blood counts to an ANC of $\geq$1,000/mm^3 and a platelet count of $\geq$100,000/mm^3. An increase of at least 25% in the absolute number of circulating leukemic cells or the development of extramedullary disease was considered progressive disease. Evaluable patients who did not demonstrate a CR or PR during therapy were considered to be nonresponders. Responses were determined at the local institution without central review.

Monitoring of Patients during the Study

On Days 7 and 14 of each 28-day treatment cycle, electrolytes, calcium, magnesium, creatinine, AST or ALT, and total bilirubin were to be measured. On Day 28, in addition to these measures, a complete blood count (CBC) with platelet count and white blood cell differential, a bone marrow examination, an audiogram, and a lumbar puncture were to be obtained.

STATISTICAL ANALYSIS

Study Design

Within each diagnosis category (ALL and AML), a two-stage design was employed. Ten patients were to be enrolled in the first stage. If no patient demonstrated a response (CR or PR), the trial was to be terminated for that disease category and carboplatin declared ineffective. If two or more patients demonstrated a response, the trial was to be terminated for that disease category and carboplatin declared effective. If 1 patient demonstrated a response, an additional 10 patients were enrolled.

Calculation of Response Rates

The response rate was calculated as the number of patients who achieved CR plus the number of patients who achieved PR divided by the number of patients evaluable for response. Confidence intervals were constructed according to the method of Chaing and O'Brien.[16]

RESULTS

Patient Characteristics

Forty-four patients were entered on the study: 21 with ALL, 22 with AML, and 1 with chronic myelogenous leukemia (CML) in blast crisis (Table 1). No patient had CNS leukemia at study entry. One patient received only 1 day of the infusion and was removed from protocol therapy because of severe nausea and emesis. The patient was not evaluated for response and was included only in the analysis of toxicity. One patient received 3 days of the 5-day infusion before protocol therapy was terminated because of azotemia. This patient demonstrated a rising blast count on Day 14 after the start of therapy and was included for evaluation of response and toxicity. Ten patients received two courses of carboplatin, one patient received three courses, and one patient received four courses.

Nonhematologic Toxicity

Twenty-two episodes of Grade 3 or 4 nonhematologic toxicities were observed among 13 patients (Table 2).

TABLE 1
Demographic Characteristics and Response to Therapy of 44 Eligible Children Entered on CCG-0916

Age at diagnosis (yrs)	
Median (range)	6 (0–19)
Age at study entry (yrs)	
Median (range)	9 (0–20)
Best response[a]	
Acute lymphoblastic leukemia	
Complete response	0
Partial response	1
No response	20
Response rate	4.8%
95% confidence interval	0.12–24%
Acute myelogenous leukemia (including CML)	
Not evaluable	1
Complete response	0
Partial response	3
No response	19
Response rate	14%
95% confidence interval	2.9–35%
Histologic diagnosis[a]	
Acute lymphoblastic leukemia	21 (47.7%)
Acute granulocytic leukemia	2 (4.6%)
Acute myelogenous leukemia–FAB M1	6 (13.6%)
Acute myelogenous leukemia–FAB M2	7 (15.9%)
Chronic myelogenous leukemia	1 (2.3%)
Acute myelomonocytic leukemia	3 (6.8%)
Acute megakaryoblastic leukemia	3 (6.8%)
Acute mixed lineage leukemia	1 (2.3%)
Gender[a]	
Male	23 (52.3%)
Female	21 (47.7%)
Race[a]	
White	22 (50.0%)
Hispanic	11 (25.0%)
Black	8 (18.2%)
Filipino	1 (2.3%)
Other	2 (4.5%)

CCG: Children's Cancer Group; CML: chronic myelogenous leukemia; FAB: French–American–British (leukemia classification system).
[a] No. (%) of patients.

The most frequent toxicity was blood urea nitrogen $\geq$60 mg/dL. The next most frequent toxicity was creatinine elevation. Other serious nonhematologic toxicities occurred two or fewer times.

One patient developed life-threatening acute renal failure while concurrently receiving other nephrotoxic agents, including flucytosine and amphotericin B. Therapy with carboplatin was discontinued after the third day. Another patient requested discontinuation of carboplatin after the first day of therapy due to severe emesis.

Hematologic Toxicity

In the 56 administered courses of carboplatin, red blood cell transfusions were administered during 46 courses and platelet transfusions during 51 courses, intravenous antibiotics were given during 37 courses, and intravenous antifungal agents were given during 13 courses.

One patient developed severe thrombocytopenia refractory to platelet transfusions and died after an intracranial hemorrhage.

The most significant complications were infectious events. *Pseudomonas aeruginosa, Bacillus* species, *Staphylococcus aureus, Staphylococcus epidermidis,* and *Enterobacter cloacae* sepsis were seen. *Pneumocystis carinii* and *Aspergillus* pneumonia were seen in one patient each. Dermatomal herpes zoster, pneumonitis, sinusitis, warts, and otitis media were reported.

Therapeutic Activity

Of the 21 patients with ALL entered onto the study, one had M2 bone marrow (12% blasts) after Course 1 but M3 bone marrow (50% blasts) after Course 2. Of the 22 patients with AML, responses were seen in 3. One patient had hypocellular M1 bone marrow after Course 1. A bone marrow biopsy was not performed. Course 2 was started when the absolute neutrophil count recovered to 6636/mm^3, although the platelet count was only 56,000/mm^3. The patient died on Day 14 of Course 2 of carboplatin. Another patient achieved M2 bone marrow (9% blasts) after Course 1; this response was sustained after Course 2. However, after Course 3, circulating blasts were present. A third patient had M2 bone marrow (9% blasts) after Course 1. After Course 2, circulating blasts were noted. The only patient with CML in blast crisis did not respond.

DISCUSSION

Cisplatin is one of the most active agents against a spectrum of childhood malignancies, including neuroblastoma, osteogenic sarcoma, Wilms' tumor, germ cell tumors, hepatoblastoma, and medulloblastoma.[15,17–22] However, it has never been shown to be active against childhood leukemia. Its utility has been limited by significant gastrointestinal, renal, neurologic, and otologic toxicities. Carboplatin is an analogue of cisplatin that was developed to provide a better therapeutic index. Prior pediatric Phase I and II studies have confirmed that carboplatin is associated with significantly less nonhematologic toxicity and that it has a spectrum of activity similar to that of cisplatin.[1–11]

Prior experience would suggest that carboplatin has activity in adults with AML, although cisplatin is inactive. In a Phase I study[12] of 28 patients with AML treated on a 5-day continuous intravenous infusion schedule, complete remissions were achieved in 6 patients and partial remissions in 2 patients, for a re-

TABLE 2
Grade 3 or 4 Nonhematologic Toxicities Related to Carboplatin

	Course 1 (n = 44)		Course 2 (n = 10)		At any time during therapy (n = 44)	
Toxicity type	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
SGOT ≥5.1 × N	1	43	0	10	1	43
SGPT ≥5.1 × N	1	43	0	10	1	43
Total bilirubin ≥1.5 × N	1	43	1	9	2	42
Glucose (≤39 or ≥251 mg/dL)	1	43	1	9	2	42
BUN (≥60 mg/dL)[a]	2	42	2	8	3	41
Creatinine ≥3.1 × N	1	43	2	8	3	41
Systolic blood pressure (≥1.3 × N or ≤0.7 × N)	1	43	0	10	1	43
O_2 required or assisted ventilation	1	43	0	10	1	43
Mild or severe CHF responding to Rx	1	43	0	10	1	43
Generalized eruption of the skin requiring Rx	2	42	0	10	2	42
Serum potassium (≤2.5 or ≥6.5 mEq/L)	1	43	1	9	2	42
Serum calcium (≤6.9 or ≥12.6 mg/L)	1	43	0	10	1	43
Serum magnesium (≤0.8 mEq/L)	0	44	1	9	1	43

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; N: Normal; n: number of patients; CHF: congestive heart failure; Rx: therapy; BUN: blood urea nitrogen.
[a] One patient had BUN ≥60 mg/dL during Course 1 and Course 2.

sponse rate of 28.6%. The suggested Phase II dose of carboplatin was 300 mg/m^2/day. Except for prolonged myelosuppression, no other dose-limiting toxicity was reported.

In a Phase II study[13] performed in adults with AML, carboplatin was given at a dose of 300 mg/m^2/day for 5 days by continuous intravenous infusion. Of 27 patients treated, 8 achieved a CR and four a PR, for a response rate of 44%. Significant nonhematologic toxicity was not observed.

As the preceding pediatric Phase I study demonstrated,[11] and as has been confirmed in this study, the major toxicity of the dose schedule utilized in these studies is profound myelosuppression with or without documented sepsis. Nephrotoxicity and hepatotoxicity were also observed. At the initial dose level in the pediatric Phase I study, renal tubular and glomerular toxicities in the majority of patients resulted in the first dose reduction. Although the causal relationship of these effects was not absolute, carboplatin was implicated in these toxicities. These toxicities were assessed further in this Phase II study and were considered to be acceptable in this group of heavily pretreated patients with bone marrow relapse when treated with carboplatin at a dose of 216 mg/m^2/day.

Hematuria was not observed in the current study. In the Phase I trial, gross hematuria was observed in a single patient during each of two courses of therapy, although the platelet count was normal during the second course.[11] The pathogenesis of this toxicity is not known.

Although 2 patients developed Grade 4 hyperbilirubinemia and 1 patient had Grade 3 transaminase elevation in this study, these toxicities were not considered to be life-threatening. Hepatic necrosis was not observed, in contrast to the single patient on the Phase I study who died on Day 14 of acute liver failure and hepatic encephalopathy.[11] At autopsy, micronodular cirrhosis with marked centrilobular necrosis and hemorrhage was present. There appeared to be a direct association between carboplatin and liver failure in this patient.[23]

The current study has demonstrated that carboplatin given on a 5-day continuous infusion schedule at a dose of 216 mg/m^2/day has only minimal antileukemic effect in children with ALL and AML. Although the studies discussed did not address the reason for the differences in dose-limiting toxicity and maximum tolerated dose between the adult and pediatric trials, it is likely that the patients enrolled on the pediatric trial were more heavily pretreated than those on the adult trials and were more likely to have received or required nephrotoxic antibiotics. Therefore, the difference in therapeutic outcome between this study and prior adult studies may be due to the 28% lower dose of carboplatin given in this study as compared with the doses given in the adult trials cited above. Therefore, at the dose and schedule adminis-

tered in this study, carboplatin does not have sufficient activity to warrant further evaluation in children with ALL and AML.

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