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Short communication

Phase I trial of a new nitrosourea, CGP 6809, given every 2 weeks

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Summary. A phase I study was carried out on a new water-soluble nitrosourea, 6-deoxy-3,5 di-O-methyl 6-(3 methyl-3-nitrosoureido)-alpha-D-glucofuranoside (EDMN, CGP 6809), given every 2 weeks. A total of 18 patients received doses of 1, 2, 3, and 3.75 g/m^2 as a 2- to 5-h infusion. Toxicity principally involved nausea and vomiting, hepatotoxicity, and abdominal pain. There was no evidence of cumulative toxicity. The dose of 3.75 g/m^2 was not exceeded because in a previous phase I study, 4.5 g/m^2 every 6 weeks was not tolerated; the recommended dose for phase II studies is 3.75 g/m^2 every 2 weeks.

Introduction

Ethyl 6-deoxy-3,5 di-O-methyl-6-(3 methyl-3-nitrosoureido)-alpha-D-glucofuranoside (EDMN, CGP 6809), is a novel water-soluble nitrosourea developed by Ciba-Geigy Ltd. (Basel, Switzerland) that is active against a variety of solid tumors, including a human melanoma cell line implanted in nude mice [2]. Because it is a nitrosourea and delayed myelosuppression was expected, it underwent an initial phase I study on a q 6 week schedule. The maximal dose evaluated, 4.5 g/m^2, was not tolerated, and 3.75 g/m^2 q 6 weeks was considered to be the maximum tolerated dose (MTD). However, it demonstrated a lack of myelosuppression and an absence of delayed toxicity [1]. The dose-limiting toxicity was acute hepatotoxicity that was maximal on day 2 or 3 but resolved by day 8 [1]. Accordingly, we investigated tolerance to a q 2 week schedule of the drug to determine (a) whether more drug could be given over a 6 week period if the dose were given every 2 weeks, and (b) whether evidence of cumulative hepatotoxicity would occur if the drug were given on this schedule.

Materials and methods

Patients with advanced cancer nonamenable to other treatments or for whom other treatments had proven ineffective were entered in the study after they had given written informed consent. The requirements for entry were: an expected survival of at least 2 months; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; an interval of least 2 weeks since the last dose of potentially myelosuppressive therapy (6 weeks for nitrosourea and mitomycin-C) and recovery from reversible toxicity; an interval of 3 weeks since last receiving radiotherapy or surgery (except minor procedures); and the absence of acute intercurrent complications, pregnancy, or a history of cardiac arrhythmia. The minimal hematologic parameters required were a white blood cell count (WBC) of at least 4,000/mm^3 and a platelet count of at least 100,000/mm^3; the minimal biochemical parameters required were serum glutamic oxaloacetic transaminase (SGOT) levels of 100 IU/l or less and a serum creatinine of 1.5 mg/dl or less. Patients were not allowed to have radiation (except small-port radiation) during the course of the study. Before treatment and on day 2 and then weekly following each course of treatment, the following measurements were done: a complete blood count (CBC) and serum Na^+, K^+, CA^{2+}, and PO_4^{3-}, creatinine, uric acid, total protein, albumin bilirubin, alkaline phosphatase, lactic dehydrogenase (LDH), SGOT and blood urea nitrogen (BUN). The drug was supplied by the Pharmaceutical Research Department at Ciba-Geigy Ltd. (Basel, Switzerland) in ampules containing 500 or 1500 mg; it was reconstituted in 5% dextrose in water and given i.v. as an infusion over 2–5 h, depending on the infusion volume, which varied from 100 to 800 ml.

Results

Of the 18 patients entered in this study, 13 were men and 5, women. The mean age was 56 years (range, 18–75 years). In all, 15 (83%) had had prior chemotherapy and 8 (44%), prior radiotherapy. Five patients (28%) had an ECOG performance status of 0; eight (44%), a status of 1; and five (28%), a status of 2. A total of 53 courses of drug were given. The starting dose was 1 g/m^2 (three patients), with escalation to 2.0 (six patients), 3.0 (four patients), and 3.75 g/m^2 (seven patients). The doses of two patients who received 2.0 g/m^2 were subsequently escalated to 3.0 g/m^2; no other doses were escalated. Three patients received one dose, four were given two, seven received three, and four were given between four and six doses. The drug was stopped before the administration of three doses due to disease progression (six patients) and drug toxicity (one case).

Toxicity

Nausea and vomiting (N & V) was nearly universal in spite of pretreatment with antiemetics generally given in combi-

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nation. N & V was seen in 3/3 patients at 1 g/m^2, in 5/6 at 2 g/m^2, in 3/4 at 3 g/m^2, and in 6/7 at 3.75 g/m^2. At these doses grade 3 N & V was seen, respectively, in 2, 4, 2, and 2 cases. Abdominal pain was reported by four patients treated at 3.75 g/m^2 (grade 1, 1; grade 2, 2; grade 3, 1). Dyspnea (grade 1, 1) and noncardiac chest pain (grade 3, 1) were also seen at this dose. Grade 2 diarrhea was seen in 1 patient at 2.0 g/m^2.

Laboratory changes

Hematology. Four patients showed a decrease in hemoglobin (Hb) of >2 g/dl, which was not dose-related and was probably due to disease. Only one WBC of $<4{,}000/mm^3$ ($3{,}900/mm^3$ at 3.75 g/m^2) and only two platelet counts of $<100{,}000/mm^3$ ($44{,}000/mm^3$ at 2 g/m^2 and $64{,}000/mm^3$ at 3.0 g/m^2) were recorded. The drug does not appear to be significantly myelotoxic.

Hepatic function abnormalities. Changes in hepatic function were modest: at a dose of 3.75 g/m^2, 2/7 patients showed bilirubin levels of >2.5 mg/dl and SGOT measurements of >100 IU/l. Values promptly returned to baseline levels.

Renal function. No significant drug-related rise in serum creatinine or BUN was seen.

Cumulative toxicity. There was no evidence that repeated doses of EDMN caused cumulative toxicity. Two patients (one at 3.75 g/m^2) received six doses of drug without progressive change in any parameters measured. In the two patients showing a bilirubin level of >2.5 g/dl, the values were 2.5 and 3.8 mg/dl after dose 2 and 1.0 and 1.2 mg/dl after dose 3, respectively.

Antitumor activity. There were no complete or partial responses. Four pts were continued on EDMN beyond dose 3 (6 weeks of therapy) due to the stabilization of their disease.

Discussion and conclusion

In a phase I study of EDMN given q 6 weeks, a dose of 4.5 g/m^2 was not tolerated because of hepatotoxicity, N & V, and abdominal pain; thus, a dose of 3.75 g/m^2 was recommended for phase II studies [1]. The present study was carried out to determine the feasibility of giving this dose every 2 weeks. The data indicate that this is feasible. As in the study of the 6-week schedule, the major toxicities were N & V, hepatotoxicity that is mild, rapidly reversible, and noncumulative, and abdominal pain. Our current dose recommendation for phase II studies is 3.75 g/m^2 q 2 weeks.

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