Phase I Trial of Homoharringtonine Administered by Prolonged Continuous Infusion

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ABSTRACT

Cephalotaxine alkaloids have been extensively used in the Peoples Republic of China for treatment of acute leukemias and solid tumors (Yu-hua, L., Shu-fen, G., Fu-ying, Z., Shu-zhi, X., and Hui-lin, Z. Chin. Med. J., 96: 303–305, 1983). Several Phase I trials of homoharringtonine have been completed in the United States using either bolus administration or continuous infusion over a 5-day period. The major toxicities have been hypotension following rapid administration and myelosuppression when lower doses are infused over 5 to 7 days. None of these studies, however, reproduce the schedule used in China which is i.v. infusion of approximately 1 mg/day over 4-8 h for a period of 14–28 days or more, followed by a rest period of approximately 7–14 days. This study more closely reproduces that schedule and using a continuous infusion schedule to allow escalation of total days of treatment. Forty-eight patients entered the study. The final recommended dose of homoharringtonine is 1 mg/m²/day for 30 days followed by a 2-week rest period. The dose limiting toxicity of myelosuppression was severe and prolonged in some patients. Nonhematological toxicities were minimal and generally well tolerated. Patients should be followed with at least weekly blood counts and treatment interrupted pending full marrow recovery if the granulocyte count falls below 1,000/mm³ or the platelet count falls below 100,000/mm³.

INTRODUCTION

The cephalotaxine esters are isolated from several species of evergreens indigenous to mainland China and have long been used in traditional Chinese medicine. Harringtonine or homoharringtonine have been incorporated into frontline combination chemotherapy for acute leukemia in China since 1977. Powell et al. (1) reported the structures of several of these alkaloids in 1970 and their in vitro antitumor effect was confirmed several years later (2). Phase I trials in this country primarily used bolus infusion (3) or continuous infusion over a period of 5–10 days (4, 5). The bolus schedule was not recommended for Phase II trials due to hypotension seen at a dose of 6.4 mg/m²/day (3). A dose of 3.25 mg/m² over 5 days was tolerated well and was recommended for Phase II trials by Cooney et al. (4). Neither of these regimens, however, are similar to the regimen used by the Chinese who administered a dose of approximately 0.05 to 0.1 mg/kg/day by 4 to 8-h infusion administered for 28 consecutive days or more (6). We attempted to more closely reproduce this schedule in a Phase I trial. The present study was instituted to determine a safe dose of homoharringtonine administered by continuous infusion over approximately a 30-day period.

MATERIALS AND METHODS

Patient Eligibility and Monitoring. Patients with histologically proven advanced solid tumors refractory to standard therapy were entered. Patients with leukemia were eligible but were evaluated only for nonhematological toxicity. A Zubrod performance status of 2 or better or a life expectancy of at least 12 weeks was required (7). Baseline hepatic enzymes were less than 2-fold normal and serum creatinine was less than 2 mg/100 ml in all patients. WBC were 3,000/mm³ and more and platelet counts were greater than 100,000/mm³ at initiation of treatment. Patients were required to have a 4-week rest period after any previous chemotherapy and must have recovered from all prior toxicities. All patients signed an informed consent and were screened and registered by a protocol research nurse prior to initiation of therapy. The initial dose level was 4 mg/m²/day by continuous infusion over 5 days. A grade 1 or greater toxicity was noted at each level. The daily dose was decreased by 20–30% and the days of administration increased by 20–30% for the next entry level. Cycles were initially repeated every 21 days and dose escalation was allowed in individual patients. The protocol was later amended to allow continuous treatment for an indefinite period of time to toxicity, followed by a 7-day rest period and reinstatement of treatment after complete recovery from side effects. The drug was administered on an outpatient basis, using a Comed pump in patients not otherwise requiring hospitalization. A Hickman catheter was used for venous access. Patients were seen at least every 21 days, although blood counts were phoned in weekly. A complete blood count including hemoglobin, WBC, platelet count and differential, as well as an aspartate aminotransferase, alanine aminotransferase, and bilirubin were obtained weekly. Creatine phosphokinase, electrolytes, glucose, blood urea nitrogen, creatinine, and urinalysis, as well as history and physical examination, performance status estimate, and measurement of tumors were obtained at least every 21 days. Standard toxicity grading scores were used (8). Grade 1 hypotension was defined as an asymptomatic fall in mean pressure of greater than 20 mm of mercury. Any clinical suspicion of symptomatic hypotension or documented fall of greater than 20 mm of mercury was graded as 2 if it required no interruption of therapy, and 3 if it resulted in interruption of treatment. All required data were entered by the research nurse at the time of each clinic visit into an on-line clinical data management system. Homoharringtonine was supplied by the Division of Cancer Treatment, National Cancer Institute. The study was activated on February 1, 1983 and closed on September 15, 1984.

RESULTS

Table 1 presents the patient’s characteristics. Eighty-eight percent of the patients had a performance status of 2 or better. Eleven patients had received no prior therapy. Fifteen patients had adenocarcinoma of the colon, six patients had prostate cancer, five patients had renal cancer, and the remainder had an assortment of different tumor types. The only patient with leukemia

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entered had blastic transformation of chronic myelogenous leukemia. Hematological toxicity is outlined in Table 2. Daily dosage ranged from an initial dose of 4 mg/m²/day through a final dose of 1 mg/m²/day. Treatment durations at the final dose of 1 mg/m²/day ranged from 13-30 days, followed by a 7-day rest period and reinstitution of treatment if recovery had occurred. Table 3 outlines nonhematological toxicities, and Table 4 contains information regarding hypotension. At doses of 2 mg/m²/day and above, nonhematological toxicity and hypotension were sufficient to preclude treatment beyond 13 days. The primary nonhematological toxicities were hypotension, anorexia, and fatigue. Hypotension, although usually mild and infrequent, did induce clinical symptoms in 3 of 18 patients entered at the 2-mg/m²/day level. No patients had irreversible or permanent damage secondary to hypotension. The 1.5-mg/m²/day dose was stopped at 13 days of therapy when dose limiting fatigue and myelosuppression developed. At the 1-mg/m² level, the nadir of WBC and platelets tended to occur about 3 weeks into treatment. At the shorter treatment durations (13-17 days), the myelosuppression did not develop. At the 1-mg/m² level, the nadir of WBC and platelets occurred about 3 weeks into treatment. The degree of myelosuppression was usually not evident until the second or sometimes the third course of therapy. The time required for full marrow recovery was approximately 2 weeks in most patients, but did range up to 30 days in one case and 60 in another at the 1-mg/m²/day dose. Both of these patients developed the myelosuppression midway into the second course and both received more than 30 total days of treatment in two courses. Fig. 1 shows the pattern of myelosuppression in two patients treated at 1 mg/m²/day for 30 days. Marrow suppression tended to affect all three cell lines. The hematocrit decreased by more than 6 in 24 patients during the course of therapy. The average decrease in all patients was 6.5. Nonhematological toxicities at a dose of 1 mg/m²/day were mild and tolerable anorexia, fatigue, nausea, and diarrhea. Hypotension was rare and not clinically significant at a dose of 1 mg/m² for up to 30 days. Most patients in this study had cardiac monitors placed as part of a randomized, prospective, and blinded study of cardiac arrhythmias during Phase I trials. While frequent tachycardia and occasional premature arterial or ventricular contractions were seen, there was no clear-cut increase over a control period of saline infusion.

Four patients had a normal base-line aspartate aminotransferase with subsequent increase by 2-fold or more. This is a possible drug related effect and was not clearly caused by the patient’s disease. Seven patients with normal base-line serum creatinines had a subsequent rise in their serum creatinine by greater than 0.3 mg/100 ml. This was clearly related to disease induced obstructive neuropathy in three patients. The rise was possibly drug related in the other four patients.

One patient with blastic transformation of chronic myelogenous leukemia had clearing of both peripheral blood and marrow but died without recovery of normal marrow or peripheral counts. One patient with rectal adenocarcinoma and a large pelvic mass had over 50% decrease in the size of that mass by computed tomography scan of the abdomen but eventually progressed.

**DISCUSSION**

Homoharringtonine can be administered at a dose of 1 mg/m²/day by continuous i.v. infusion for up to 30 days. Nonhematological toxicities are minimal using this schedule. Some patients will develop significant and prolonged myelosuppression. We recommend a 2-week rest period after each course of therapy before treatment is reinstituted. Patients should be monitored with weekly complete blood counts and treatment should be held for marrow recovery if the platelet count falls below 100,000 and the WBC falls below 2,500. Nonhematological toxicities are modest and well tolerated on this schedule, although an occasional patient may develop substantial anorexia and fatigue. Patients who tolerate the 1-mg/m² dose for 30 days probably could be escalated by 0.5-mg daily increments for the second course of therapy.
The mean time for complete remission in this study was 42 days, with a range of 28-76 days. Warrell et al. (9) treated 28 patients with acute nonlymphocytic leukemia obtained complete remission. Therapy might also be extended at 1-mg/m²/day for 9 days and achieved marrow hypoplasia in 70% of patients who had failed prior therapy. Complete remissions were eventually achieved in seven patients. The mean time for full recovery of peripheral counts was 48 days in those patients who achieved complete remission. Alopecia and hypotension were noted using the higher daily doses.

A strong case for a more prolonged period of administration can also be made on the basis of in vitro studies. Huang in 1975 (10) demonstrated that homoharringtonine inhibits protein biosynthesis. Baske and Heinstein (2) subsequently demonstrated growth inhibition and cytotoxicity of homoharringtonine against KB, HeLa, and L-cells. As expected, protein synthesis was preferentially inhibited in cells in the G, and G phases of the cell cycle. These authors postulated that homoharringtonine might be more active against slow growing tumors with a larger fraction of cells in the G, and G phases of the cell cycle. These authors concluded that the effects of homoharringtonine are more dependent on exposure time than on concentration and recommended that continuous infusion be explored in clinical trials.

Prolonged infusion is well tolerated and can be easily administered with ambulatory infusion pumps. There is reason to believe homoharringtonine exerts maximal effect on nondividing cells and might eventually be a valuable agent for combination regimens designed to kill cells in all phases of the cycle. We believe efficacy trials using this schedule are warranted in leukemia and solid tumors.

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