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Short communication

A phase II trial of continuous-infusion 6-mercaptopurine for childhood leukemia

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Summary. A phase II pediatric trial of a continuous intravenous infusion of 6-mercaptopurine (6MP) in patients with refractory leukemia was performed. The dosing schedule, 50 mg m^{-2} h^{-1} for 48 h, was based on the results of a previous phase I trial of this approach. Among the 40 children treated for acute lymphoblastic leukemia (ALL), all of whom had received prior therapy with oral 6MP, 1 complete and 1 partial response were achieved. No response was observed in 17 patients with refractory acute nonlymphocytic leukemia (ANLL). Reversible hepatotoxicity, the primary dose-limiting toxicity, was observed in approximately 50% of cases. Mucositis was encountered infrequently and was usually not severe. 6MP given on the present continuous intravenous infusion schedule overcomes the limited and variable bioavailability of oral 6MP but shows limited activity as induction agent in children with recurrent ALL.

Introduction

6-Mercaptopurine (6MP) has been in clinical use for over 30 years and is currently a mainstay of maintenance chemotherapy for children with acute lymphoblastic leukemia (ALL). When 6MP is given orally, its bioavailability is limited, resulting in low and variable plasma drug concentrations [6]. As based on in vitro studies using human leukemia cell lines, the optimal cytotoxic concentration range of 6MP is between 1 and 10 μM and is dependent on the duration of exposure, with a minimum of 12 h exposure being required to obtain a greater than 50% decrease in cell survival [2]. In patients monitored following a standard 75-mg/m^2 oral dose of 6MP, however, peak concentrations have exceeded 1 μM in less than half of the patients treated [6].

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To circumvent the shortcomings of oral 6MP therapy, a continuous intravenous dosing schedule was developed. In a phase I trial of this approach, an infusion rate of 50 mg m^{-2} h^{-1} was tolerable for up to 48 h [7]. The mean steady-state plasma concentration of 6MP in that trial was 6.9 ± 0.4 μM. Reversible hepatotoxicity, myelosuppression, and mucositis became dose-limiting when the infusion duration was increased to 60 h.

The present phase II trial evaluated the activity of this continuous intravenous infusion approach in pediatric patients with refractory ALL or acute nonlymphocytic leukemia (ANLL).

Patients and methods

Patients' eligibility. Patients aged less than 25 years who had histologically confirmed recurrent acute leukemia that was refractory to conventional forms of therapy were eligible for this trial. Subjects were required to show adequate hepatic and renal function as manifested by a serum bilirubin level of <1.5 mg/dl, a serum aspartate aminotransferase (AST) value of <80 IU/l, and a creatinine clearance of >60 ml min^{-1} 1.73 m^{-2} or a serum creatinine level of <1.5 mg/dl. Prior to entry in the study, informed consent was obtained from the patients or their parents in accordance with the individual institutional policies.

Study design. 6MP was given as a continuous infusion at a rate of 50 mg m^{-2} h^{-1} for 48 h. Courses of therapy were repeated every 14 days. No other chemotherapeutic agent was permitted in this trial. Patients were monitored by complete blood counts; determinations of levels of electrolytes, creatinine, calcium, phosphorus, and uric acid; liver-function tests; and urinalysis at 48–72 h after the completion of the 6MP infusion and then weekly. Children experiencing moderate or severe mucositis subsequently received a 36- or 24-h infusion, respectively. In cases of moderate, reversible hepatic toxicity (a serum bilirubin level of >2.5 mg/dl or a serum AST value of 300–500 IU/l), the infusion duration was reduced to 24 h, and patients experiencing severe or irreversible hepatotoxicity (a serum bilirubin level of >3.5 mg/dl or a serum AST value of >500 IU/l) were removed from the study.

Responses were graded as follows: complete response (CR), M1 bone marrow (<5% blasts) and no evidence of circulating blasts or extramedullary disease; and partial response (PR), M2 bone marrow (<25% blasts) and no evidence of circulating blasts. Patients who either developed progressive disease after one cycle or failed to achieve a PR or

Table 1. Patient's characteristics

ALL:	
Number of patients entered	40
Number of courses	61
Median age (years)	9.5 (range, 1–20)
Median number of prior reinduction attempts	4 (range, 2–10)
Number of patients with AGC value of <1,000/mm^3 at study entry	15
Number of patients platelet counts of <50,000/mm^3 at study entry	11
ANLL:	
Number of patients entered	17
FAB classification:	
M1 or M2	10
M3	2
M4	3
M5	2
Number of courses	25
Median age (years)	6 (range, 1–19)
Median number of prior reinduction attempts	3 (range, 1–7)
Number of patients with AGC value of <1,000/mm^3 at study entry	8
Number of patients with platelet counts of <50,000/mm^3 at study entry	11

AGC, Absolute granulocyte count

a CR within 14 days of completing their second cycle were removed from the study and considered to represent treatment failures.

Drug formulation and administration. 6MP was supplied by Burroughs Wellcome as a lyophilized powder in sterile vials containing 500 mg 6MP as the sodium salt. The drug was reconstituted with 49.8 ml sterile water (10 mg/ml, pH 10–11) and was further diluted to a concentration of 1 mg/ml using saline or 5% dextrose and saline (final pH, 8.4–8.6). This solution was given intravenously as a 48-h infusion at a rate of 50 mg m^{-2} h^{-1} (total dose, 2,400 mg/m^2).

Results and discussion

In all, 40 patients with ALL and 17 with ANLL were entered in this trial, and all were evaluable for response. Their characteristics are summarized in Table 1. All patients presenting with ALL had undergone prior therapy that included the oral administration of 6MP (50–75 mg m^{-2} day^{-1}) during maintenance therapy; 6 of these subject had also received prior therapy with 6-thioguanine (6TG). Among the children with ANLL, 16 had undergone prior therapy that included 6TG (100–300 mg m^{-2} day^{-1}); 5 subjects had received prior therapy with 6MP given as a 500-mg/m^2 intravenous bolus dose.

Two patients with ALL showed objective responses (one CR of 7 weeks' duration and one PR of 5 weeks' duration), for a response rate of 5% (95% confidence interval, 0.6%–16.9%). None of the children with ANLL responded (95% confidence interval, 0–19.5%).

Table 2. Hepatotoxicity observed in the present study

Median hepatic values	Cycle 1 (51 patients)[a]	Cycle 2 (18 patients)[b]	Cycle 3 (5 patients)
AST (SGPT) (IU/l)	66 (range, 10–1,194)	57 (range, 10–636)	27 (range, 10–354)
ALT (SGOT) (IU/l)	81 (range, 10–1,428)	56 (range, 10–480)	77 (range, 24–588)
Total bilirubin (mg/dl)	1.3 (range, 0.2–15.8)	0.8 (range, 0.1–6.3)	1 (range, 0.6–1.8)

[a] Data not complete for 6 patients
[b] Data not complete for 1 patient

The toxicities encountered were similar to those previously observed using this dose schedule [1, 7]. In all, 28 of the 57 evaluable patients developed grade III or IV hepatotoxicity (an AST or ALT value of >150 IU/l or a bilirubin level of >3.0 mg/dl), showing a median peak values of 81 (AST) and 66 IU/l (ALT; Table 2). No correlation was found between the degree of hepatotoxicity and the patient's age. Hepatotoxicity was frequently cholestatic in nature and was generally rapidly reversible. Minor toxicities included mucositis (seven patients), diarrhea (three subjects), and skin rash (two cases). Among the 19 patients who received more than one cycle of therapy, the infusion duration was shortened to 36 h in 2 cases due to the occurrence of mucositis following the first course. None of these 19 subjects met the requirements for reduction of the infusion duration because of hepatotoxicity.

Patients could not be evaluated for hematologic toxicity due to leukemic involvement of the bone marrow. However, in a phase II trial of continuous-infusion 6MP in patients with solid tumors, dose-limiting myelosuppression occurred in approximately 25% of cases [1]. The approximate 50% incidence of reversible hepatotoxicity in leukemia patients is higher than that observed in patients with solid tumors. Infusions of shorter duration (24–36 h) may prove to be less hepatotoxic and should nevertheless result in cytotoxic drug exposure.

Clinical trials performed during the 1960s in children with ALL determined that the chemotherapeutic agents most effective in maintaining remission were not necessarily those most effective in inducing remission [4, 5]. As a single agent, oral 6MP induced remission in only 27% of newly diagnosed patients, and when given in combination with methotrexate, it caused remission in 45% of cases. This contrasts with the 84% remission-induction rate obtained using vincristine and prednisone. However, 6MP and methotrexate were found to be significantly more effective than vincristine and prednisone in maintaining remission [5]. The performance of a classically designed phase II trial such as the current study may thus not be the most appropriate method of identifying chemotherapeutic agents that are effective during maintenance therapy for ALL.

All patients entered in this trial had undergone prior therapy that included 6MP or 6TG. Based on this observation and given the aforementioned differences between the ability of oral 6MP to induce remission versus maintain

remission, it is perhaps not surprising that 6MP given by continuous infusion demonstrated limited activity as an induction agent in patients with refractory recurrent ALL. However the potential utility and advantage of the present dosing schedule should not be overlooked. This regimen consistently maintains steady-state plasma drug concentrations above the cytotoxic threshold. Furthermore, it enables significant penetration of 6MP into the CNS (CSF: plasma ratio, 0.27) [7], a property that may improve CNS preventive therapy. Continuous-infusion 6MP has recently been successfully incorporated into intensification therapy of newly diagnosed children with ALL [3]. Attention should be given both to its potential to improve overall event-free survival and to the possibility that it plays a beneficial role in CNS preventive therapy. The administration of continuous-infusion 6MP as post-induction therapy to children with ALL merits further evaluation.

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