Cancer Chemother Pharmacol (1990) 26: 343–344

Cancer Chemotherapy and Pharmacology



# A phase II trial of continuous-infusion 6-mercaptopurine for childhood solid tumors

**Peter C. Adamson[1], Solomon Zimm[1], Abdel H. Ragab[2, 3], Seth M. Steinberg[1], Frank Balis[1], Barton A. Kamen[4], Tresa J. Vietti[5], Andrea Gillespie[1], and David G. Poplack[1]**

[1] Pediatric Branch, National Cancer Institute, Bethesda, MD 20892, USA
[2] Division of Pediatric Hematology Oncology, Emory University School of Medicine, Atlanta, GA 30322, USA
[3] Pediatric Oncology Group, Gainesville, Florida 32601, USA
[4] Department of Pediatrics, University of Texas Health Sciences Center, Dallas TX 75235, USA
[5] Department of Hematology-Oncology, St. Louis Children's Hospital, St. Louis, MO 93178, USA

Received 19 January 1990/Accepted 6 April 1990

**Summary.** A phase II pediatric trial of a continuous intravenous infusion of 6-mercaptopurine (6-MP) in patients with refractory solid tumors or lymphoma was performed. The dosing schedule of 50 mg/m$^2$ per hour for 48 h was chosen to produce optimal cytotoxic concentrations of 6-MP. There were no complete or partial responses in the 40 patients entered in the trial. Accrual was sufficient for the conclusion to be drawn that there was >95% probability that the true response rate was no greater than 22% and 26% in osteosarcoma and Ewing's sarcoma, respectively. Dose-limiting toxicity was observed in one-third of the patients and included reversible hepatotoxicity, myelosuppression, and mucositis. The excellent penetration of drug into the cerebrospinal fluid (CSF) suggests that future trials of this intravenous dosing schedule should be conducted on tumors of the CNS.

## Introduction

Although orally dosed 6-mercaptopurine (6-MP) has been effective in the treatment of acute lymphoblastic leukemia (ALL), there is little information regarding the efficacy of this drug against pediatric solid tumors. Studies performed during the 1960s [1, 2] on administration of 6-MP as either a weekly intravenous bolus or a low-dose continuous infusion to adults with solid tumors demonstrated only a small number of responses.

When 6-MP is given orally, its bioavailability is poor, resulting in low and variable plasma drug concentrations [4]. In addition, the plasma 6-MP concentrations that have been achieved are well below those (1–10 μ*M*, sustained for at least 12 h) required for optimal cytotoxicity in vitro [3].

*Offprint requests to:* Peter C. Adamson, Pediatric Branch, National Cancer Institute, Building 10, Room 13N240, 9000 Rockville Pike, Bethesda, MD 20892, USA

To circumvent the shortcomings of oral 6-MP therapy, we have developed a continuous intravenous dosing schedule. In a phase I trial of this approach, an infusion rate of 50 mg/m$^2$ per hour could be tolerated for up to 48 h [5]. The mean steady-state plasma concentration of 6-MP for that trial was 6.9 μ*M*, which is within the in vitro cytotoxic range. The CSF-to-plasma drug ratio was 0.27 ± 0.14, producing cytotoxic CSF concentrations as well. Reversible, dose limiting toxicities, which included hepatotoxicity, myelosuppression, and mucositis, were encountered when the infusion duration was increased to 60 h. The present phase II trial evaluated the utility of this continuous intravenous-infusion approach in pediatric patients with refractory malignant solid tumors or lymphomas.

## Patients and methods

*Patient eligibility.* Patients under 25 years of age with histologically confirmed solid tumors or lymphomas refractory to conventional forms of therapy were eligible for this trial. Prior therapy was limited to no more than two prior phase II trials and no prior phase I therapy.

Patients must have recovered from the toxic affects of prior therapy before receiving 6-MP and were required to have a granulocyte count of >1,500 cells/mm$^3$, a platelet count of >100,000/mm$^3$, serum bilirubin levels of <1.5 mg/dl, serum aspartate aminotransferase (AST) values of <80 units/l, creatinine clearance of >60 ml min$^{-1}$ 1.73 m$^{-2}$, and serum creatinine levels of <1.2 mg/dl. Informed consent was obtained from the patients or their parents prior to entry in the study, in accordance with the individual institutional policies.

*Study design.* The primary objective of this phase II trial was to determine the response rate of 6-MP given as a continuous infusion at 50 mg/m$^2$ per hour for 48 h in children with refractory solid tumors or lymphoma and to define further its toxicity. Courses of therapy were repeated every 21 days. No other chemotherapeutic agents were permitted during the trial.

Patients were monitored with complete blood counts, determination of electrolytes, creatinine, calcium, phosphorus, and uric acid, liver function tests, and urinalysis 48–72 h after completion of the 6-MP infusion and then weekly thereafter. Patients who had a granulocyte nadir of <500 cells/mm$^3$, a platelet count nadir of <50,000/mm$^3$, serum bilirubin levels of 2.5–3.5 mg/dl, or serum AST values of 300–500 units/l received a 36-h infusion during subsequent cycles. Patients with hepatic toxicity

manifested by a serum bilirubin level of >3.5 mg/dl or a serum AST value of >500 units/l were removed from the study.

Appropriate radiologic evaluation of malignant lesions was made prior to each cycle. Responses were graded as follows: complete response, the disappearance of all evidence of active tumor as determined by physical examination and appropriate diagnostic imaging scan for a minimum of 4 weeks; partial response, a decrement of ≥ 50% in the sum of the product of the largest diameter of all measurable lesions, without an increase in the size of any lesion or the appearance of new disease; stable disease, the failure of a patient to qualify as having either an objective response or progressive disease after having received at least two cycles; progressive disease, an increase in the size of any lesion or the appearance of new disease. Individual patients were removed from the study if they experienced unacceptable toxicity or if objective disease progression was noted after one or more courses of 6-MP.

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

## Results and discussion

In this phase II trial, 6-MP was given as a continuous intravenous infusion at a dose rate of 50 mg/m$^2$ per day for 48 h. This continuous-infusion schedule was chosen to provide optimal exposure to cytotoxic concentrations of 6-MP. A total of 40 patients were entered in this trial and all were evaluable. The patient characteristics, including diagnoses, are summarized in Table 1.

**Table 1.** Patient characteristics

| | |
|---|---|
| Number of evaluable patients | 40 |
| Number of courses | 74 |
| Median age (range) | 13 (1–24) years |
| Diagnosis: | |
| Osteosarcoma | 12 |
| Ewing's sarcoma | 10 |
| Rhabdomyosarcoma | 5 |
| PNET | 2 |
| Neuroblastoma | 2 |
| Wilms' tumor | 2 |
| Lymphoma | 2 |
| Hepatoblastoma | 2 |
| Hepatocellular carcinoma | 1 |
| Infantile sarcoma | 1 |
| Fibromatosis | 1 |

### *Toxicity*

The intensity of the continuous-infusion approach is evidenced by the fact that dose-limiting toxicity occurred in approximately one-third of the patients. The primary toxicities were hepatotoxicity (14 patients with AST or ALT values of >150 units/l) and myelosuppression (10 cases with absolute granulocyte counts of <1,000 cells/mm$^3$ and 9 patients with platelet count nadirs of <50,000/mm$^3$); severe mucositis was seen in only 3 subjects. Of 17 patients who received more than one cycle, 6 required a decrease in the duration of their infusion because of toxicity. It is thus unlikely that 6-MP could be given in a more dose-intensive regimen.

### *Responses*

Despite the intensity of the 6-MP regimen, no complete or partial responses were observed. Five patients (two with osteosarcoma, one with rhabdomyosarcoma, one with neuroblastoma, and one with hepatocellular carcinoma) had stable disease lasting 11–20 weeks.

The study was terminated because no responses were seen in the 40 evaluable patients. Accrual was sufficient for the conclusion to be drawn that in patients with osteosarcoma and Ewing's sarcoma the true response rate was likely to be no greater than 22% and 26%, respectively ($P$ <0.05, one-sided confidence interval). The small number of patients with other tumor types who were treated in this study does not enable a definitive statement to be made regarding the possible activity of this intravenous 6-MP regimen against these childhood cancers.

Although the results of the present study are disappointing, we believe that this 6-MP schedule should be further studied in view of the excellent penetration of intravenous 6-MP into the CSF, particularly in the treatment of CNS tumors.

## References


1. Regelson W, Holland JF, Frei E III, Gold GL, Hall TC, Krant M, Miller SO (1964) Comparative clinical toxicity of 6-mercaptopurine (NSC-755) and 6-mercaptopurine ribonucleoside (NSC-4911) administered intravenously to patients with advanced cancer. Cancer Chemother Rep 36: 41–48
2. Regelson W, Holland JF, Gold GL, Lynch J, Olson KB, Horton J, Hall TC, Krant M, Colsky J, Miller SP, Owens A (1967) 6-Mercaptopurine (NSC-755) given at weekly intervals to patients with advanced cancer. Cancer Chemother Rep 51: 277–282
3. Tidd DM, Paterson ARP (1974) A biochemical mechanism for the delayed cytotoxic reaction of 6-mercaptopurine. Cancer Res 34: 738–746
4. Zimm S, Collins JM, Riccardi R, O'Neill D, Narang PK, Chabner B, Poplack DG (1983) Variable bioavailability of oral mercaptopurine. Is maintenance chemotherapy in acute lymphoblastic leukemia being optimally delivered? N Engl J Med 308: 1005–1009
5. Zimm S, Ettinger LJ, Holcenberg JS, Kamen BA, Vitti TJ, Belasco J, Cogliano N, Balis FM, Lavi LE, Collins JM, Poplack DG (1985) Phase I and clinical pharmacological study of 6-mercaptopurine administered as a prolonged intravenous infusion. Cancer Res 45: 1869–1873