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Short Communication

Phase I–II Trial of 14 Day Infusional 6-Mercaptopurine in Advanced Colorectal Cancer

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6-Mercaptopurine (6-MP) is a cycle specific antineoplastic agent with a short serum half-life following bolus administration, providing a rationale for continuous infusional administration of the parenteral formulation. 22 patients received 38 courses of 14 day 6-MP infusion. The maximum tolerated dose (MTD) was 35 mg/m^2/day (total dose per 14 day cycle 490 mg/m^2) with cycles repeated at 28 days. Toxicities included transient hyperbilirubinaemia, leucopenia and thrombocytopenia. 13 evaluable patients with advanced colon cancer resistant to 5-fluorouracil with or without leucovorin received infusional 6-MP at the MTD as part of the phase II study analysis, but no objective responses were observed. Phase II studies in previously untreated patients and longer infusion durations are being evaluated. © **1998 Published by Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

BASED ON pharmacological and toxicological considerations, infusional administration of antineoplastic agents is particularly applicable for cycle specific agents which demonstrate a short serum half-life, limiting tumour cell exposure. 6-Mercaptopurine (6-MP), a cell cycle specific antipurine antimetabolite with a short plasma half-life (50 min) has been administered in a daily dosing scheme using an oral formulation.

The parenteral formulation of 6-MP obviates the problem of bioavailability and, therefore, a phase I–II study of a 14 day intravenous infusion was initiated to establish the optimal dose rate and maximum tolerated dose (MTD) for 6-MP and to identify clinical activity as second line therapy in 5-fluorouracil (5-FU) resistant colon cancer.

PATIENTS AND METHODS

Eligibility criteria included a histological diagnosis of a malignancy that was either resistant to standard therapy or without alternative standard therapies available. Life expectancy had to be at least 8 weeks with a performance status of not greater than 2 by the ECOG score. A total white blood cell count of $\geq$3500/mm^3 and a platelet count of $\geq$100 000/mm^3 were mandatory, in addition to adequate renal and liver function as defined by a normal serum creatinine and a serum bilirubin level of less than 1.5 mg%. A minimum interval of 4 weeks had to elapse from prior chemotherapy or 2 weeks from prior radiation therapy. All patients provided written informed consent.

Patients had central venous access established using either a vascular access device or a standard subclavian catheter. 6-MP (Purinethol®, Glaxo Wellcome Durham, North Carolina, U.S.A.) for injection was provided in 500 mg vials and was reconstituted with 49.8 ml of preservative-free sterile water for injection, resulting in a concentration of 10 mg/ml. The total dose of 6-MP for 7 days was calculated, further diluted with bacteriostatic normal saline (benzyl alcohol preserved) and stored in polyvinyl chloride pump reservoir bags. The resulting concentration of drug was 2–5 mg/ml. The stability at room temperature of the reconstituted solution was established to be at least 7 days [1]. Patients were connected to the ambulatory infusion pump for 14 days with the drug reservoir exchanged at day 7 and discontinued at day 14. Cycles were repeated at 28 day intervals in patients in whom more than one cycle was administered. Dose limiting toxicity (DLT) was defined as grade 3 neutropenia or thrombocytopenia, febrile neutropenia or any grade 3 or greater non-haematological toxicity. The MTD was defined as the highest dose studied with DLT in at least 50% of patients.

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Table 1. *Dose related haematological and hepatic toxicity*

	Dose (mg/m^2/day)		
	25	30	35
n patients	13	7	7
n courses	20	10	8
Toxicity (incidence %)			
Neutropenia			
Grade 2	6 (30)	2 (20)	6 (75)
Grade 3	2 (10)	1 (10)	1 (12.5)
Thrombocytopenia			
Grade 3	4 (20)	0	1 (12.5)
Grade 4	1 (5)	1 (10)	0
Hyperbilirubinaemia	1 (12.5)	2 (20)	4 (50)

RESULTS

22 patients were entered into the trial. 13 patients had advanced colon cancer. The median age was 60 years (range 41–83 years). Performance status was ECOG 0–1 in 17 patients and 2 in 5 patients. All patients had received prior chemotherapy and 7, radiation therapy as well.

Three daily dose rates for infusional 6-MP were evaluated sequentially: 25 mg/m^2/day; 30 mg/m^2/day and 35 mg/m^2/day representing a 40% dose escalation from the starting dose to the MTD. The 22 patients received a total of 38, 14 day cycles; the maximum number of cycles administered was four with a minimum of one cycle; the median number of cycles was two per patient.

No gastrointestinal toxicity was identified. Haematological toxicity in the form of neutropenia and thrombocytopenia was observed at all dose levels and is summarised in Table 1. Hyperbilirubinaemia with bilirubin levels up to 2.8 mg% was dose related and developed in 4 of 8 patients at the highest dose.

All 22 patients had measurable disease. No objective responses were recorded. Within the cohort of patients with advanced colorectal cancer, no patient had an objective response, although 1 patient had a transient decrease in CEA and CA 19-9 levels.

DISCUSSION

6-MP has had limited clinical trials in solid tumours. Older studies of the oral preparation in a spectrum of tumours have shown responses in breast cancer and lymphoma [2], as well as anecdotally in other tumours [3]. These studies from the early days of chemotherapy employed the oral drug for the most part with the attendant problem of bioavailability. The parenteral formulation was evaluated in a 1964 report in which patients received either a continuous infusion of 6-MP for 6–10 days or daily or weekly bolus administration. The MTD, using criteria different from those used in the present study, was a total dose of 240 mg/m^2 [4].

Pinkel used high-dose short-term (24 h) 6-MP infusion and suggested the MTD was 25 mg/kg (675 mg/m^2) [5]. In contrast, for a 48 h infusion, the MTD reported by Zimm and associates was 2400 mg/m^2 [6]. DLTs for these high-dose short-term infusion programmes were mucositis, myelosuppression and hyperbilirubinaemia.

The present phase I study of a 14 day infusion establishes an MTD of 490 mg/m^2 and a recommended dose rate in solid tumours of 30 mg/m^2/day or 420 mg/m^2 cumulative dose per cycle. The toxicity profile is comparable for oral and parenteral infusion, with neutropenia the DLT. Hepatic toxicity, manifesting as hyperbilirubinaemia, appears to be more common with the parenteral infusion.

The phase I study included 13 patients with advanced colon cancer all of whom were previously treated and received infusion 6-MP at either of the highest daily dose rates. No objective responses were observed using stringent response criteria, which is consistent with the fact that, in general, second line therapy for colon cancer is only marginally effective. As infusional 6-MP yielded no responses as second line therapy, it would be reasonable to conclude that infusional 6-MP is unlikely to be active in this tumour using the dose and schedule employed. None the less, the number of patients treated was small and it is possible that infusional 6-MP would be active in previously untreated patients or in schedules utilising longer infusion durations.

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