Phase II study of flavopiridol in patients with advanced colorectal cancer

M. Aklilu1, H. L. Kindler1*, R. C. Donehower2, S. Mani1 & E. E. Vokes1

1Department of Medicine, University of Chicago, Chicago, IL; 2Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, MD, USA

Background: Flavopiridol, a synthetic flavone that inhibits cell cycle progression, has demonstrated activity in colon cancer in xenografts and in a phase I trial. We evaluated flavopiridol in a phase II trial in patients with previously untreated advanced colorectal cancer (ACRC).

Patients and methods: Twenty chemotherapy-naive patients with ACRC received flavopiridol at a dose of 50 mg/m²/day via a 72-h continuous infusion every 14 days. Response was assessed by computed tomography or magnetic resonance imaging every 8 weeks.

Results: Twenty patients were enrolled; 19 were evaluable for toxicity and 18 for response. There were no objective responses. Five patients had stable disease lasting a median of 7 weeks. The median time to progression was 8 weeks. Median survival was 65 weeks. The principal grade 3/4 toxicities were diarrhea, fatigue and hyperglycemia, occurring in 21%, 11% and 11% of patients, respectively. Other common toxicities included anemia, anorexia and nausea/vomiting.

Conclusions: Flavopiridol in this dose and schedule does not have single-agent activity in patients with ACRC. Recent preclinical data suggest that flavopiridol enhances apoptosis when combined with chemotherapy. Trials that evaluate flavopiridol in combination with active cytotoxic drugs should help to define the role of this novel agent in ACRC.

Key words: clinical trial, colorectal cancer, flavopiridol

Introduction

Colorectal cancer is the third leading cause of cancer-related mortality in the USA. It is estimated that 147,500 new cases of colorectal cancer will be diagnosed in 2003, resulting in 57,000 deaths [1].

Since its discovery in the 1950s, 5-fluorouracil (5-FU) has been the cornerstone for the treatment of advanced colorectal cancer (ACRC). Reported response rates rarely exceed 20% [2]. The addition of irinotecan or oxaliplatin to 5-FU results in significantly higher response rates, but only a modest improvement in overall survival has been achieved [3–5]. It is clear that new agents with different mechanisms of action need to be identified.

Movement through the cell cycle is regulated by complex and coordinated kinase and phosphatase reactions [6–9]. A family of potential molecular targets that would explain this phenotype is the cyclin dependent kinase (cdk) family of cell cycle regulatory kinases. cdk1 is an enzyme central to cell cycle progression through G2 into M phase. It interacts with cyclin B and initiates a sequence of phosphorylations and dephosphorylations [10].

Flavopiridol is the first drug considered for clinical development that can disrupt cell cycle regulatory kinases. It is a synthetic flavone that is a potent and direct antagonist of cdk1 activity via competitive inhibition of ATP. This blocks cell cycle progression prior to entry into S or M phase [11]. Flavopiridol alters the normal activity of cdk1, both directly and indirectly, inhibits progression from G2 to M phase and delays progression through S phase [12]. Flavopiridol also directly inhibits cdk2 and cdk4 [13]. Flavopiridol is not cytotoxic to resting cells in vitro, although it reversibly inhibits the growth of dividing tumor cells. Some investigators have observed that flavopiridol can be cytotoxic to some resting cell lines and induce apoptosis in others [14–19].

Antitumor activity has been observed in preclinical colorectal cancer models including Colo-205 xenografts [20]. Antitumor activity is schedule dependent; the greatest activity has been achieved with prolonged exposure. In the initial phase I trial reported by Senderowicz et al. [21], using a 72-h continuous infusion of flavopiridol every 2 weeks, the maximum tolerated dose was 50 mg/m²/day; diarrhea was dose-limiting. One patient with colon cancer had a minor response.

The activity observed in colon cancer xenografts in and in the phase I trial led us to perform a phase II trial of flavopiridol in previously untreated patients with advanced colorectal cancer.
Patients and methods

Patient selection

Eligible patients were required to have histologically or cytologically confirmed unresectable adenocarcinoma of the colon or rectum, bidimensionally measurable disease, no prior chemotherapy for metastatic disease, and adjuvant therapy must have been completed more than 6 months previously. Additional criteria included no radiation to sites of measurable disease; 3 weeks from a major surgical procedure, 4 weeks from wide-field radiotherapy; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; ≥18 years of age; granulocytes >1500/mm³, platelets >100,000/mm³, total bilirubin <1.2 mg/dl, creatinine <1.5 mg/dl and serum aspartate aminotransferase less than three times the upper limit of normal; no unstable pre-existing medical conditions; no history of a second malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of the cervix; using an acceptable form of birth control; willingness to have a central venous catheter placed; and ability to provide written informed consent.

Pretreatment evaluation

On study entry, all patients had a complete screening assessment (history, physical examination and blood tests) within 1 week of beginning treatment. Assessment of measurable disease by computed tomography or magnetic resonance imaging was performed within 2 weeks of entry.

Treatment

Flavopiridol was administered at an initial dose of 50 mg/m²/day over 72 h every 2 weeks as three 24-h infusions via a central venous catheter. Patients returned to clinic daily during the administration period to have the drug cassettes changed. Cycles were given every 2 weeks until disease progression occurred. Tumor measurements were obtained every 4 cycles. Responses required confirmatory scans at 4 weeks.

Patients who developed grade 3 or 4 non-hematological toxicity (with the exception of alopecia, nausea and vomiting, or diarrhea) or grade 4 hematological toxicity lasting more than 3 days were dose reduced to 40 mg/m²/day at the next cycle. Patients who experienced nausea and vomiting or diarrhea could be retreated at the same dose with appropriate anti-emetic or anti-diarrheal therapy. The next course of therapy was not administered until all toxicities returned to baseline. If this did not occur despite optimal prophylaxis, subsequent cycles were given at a dose of 40 mg/m²/day. Continued toxicity required dose reduction to 30 mg/m²/day. Patients who did not experience grade 3/4 toxicity after the initial two cycles could receive dose escalation to 60 mg/m²/day, and if this was well tolerated, to 75 mg/m²/day, at the discretion of the treating physician and the principal investigator.

Response and toxicity criteria

The ECOG criteria for tumor response in measurable disease were employed. Complete response (CR) was defined as complete disappearance of all clinically detectable malignant disease for at least 4 weeks. Partial response (PR) was defined as ≥50% decrease in tumor size (product of longer diameter by the perpendicular diameter) for at least 4 weeks, without increase in any area of malignant disease or any new areas. Progressive disease (PD) was defined as >25% increase over initial measurements in the sum of the product of the two largest perpendicular diameters of measurable lesions, ≥50% increase in size of the product of diameters if only one lesion was available, or appearance of any new malignant lesions. Stable disease (SD) was designated for all patients not qualifying for CR, PR or PD. Toxicity was graded according to standard National Cancer Institute Common Toxicity Criteria.

Statistical methods

Accrual proceeded using a standard two-stage design. Twelve patients were to be entered in the first stage. If one or more patients had an objective response or SD lasting 26 months, then 25 additional patients would be accrued for a total of 37 patients. The primary objective of this study was to determine the activity of flavopiridol in ACRC and to define toxicity in this patient population. Activity was calculated as the proportion of patients with responsive disease and the 95% confidence interval (CI) for response. As flavopiridol may be a cytostatic agent and prolonged (≥26 months) stabilization of measurable disease may have clinical benefit, such stabilization was also considered for evaluation. Time to progression was calculated using the method of Kaplan and Meier [22].

Results

Patient characteristics

Between February and December 1998, 20 patients with ACRC were enrolled in this study at five centers. Nineteen patients were evaluable for toxicity, and 18 patients were evaluable for response. One patient developed a small bowel obstruction that resulted in a prolonged hospitalization following only one cycle of chemotherapy. Another patient received <24 h of drug and refused further treatment.

Patient characteristics are summarized in Table 1. The median age was 68 years (range 42–80). The median WHO performance status was 0 (range 0–1). There were 11 men and nine women. Thirteen patients had colon cancer and seven had rectal cancer. Eighty per cent of patients had liver metastases. Most patients were chemotherapy naïve; only 35% had received adjuvant chemotherapy. Six patients had received prior radiotherapy.

Response

A total of 90 courses of flavopiridol were administered. The median number of treatment courses was four (range one to 14). Only one patient underwent dose escalation to 60 mg/m²/day.

There were no objective responses. Five patients (28%) experienced SD lasting a median of 7 weeks (range 7–15) as their best response. The remaining 13 patients had PD. The median time to progression of the evaluable patients was 8 weeks (range 7–30). The median overall survival was 65 weeks (range 4–156). Accrual to the study was terminated early due to lack of efficacy.

Toxicity

Nineteen patients were evaluable for toxicity. The maximal toxicities are listed in Table 2. Hematological toxicity was mild. No grade 3/4 hematological toxicities were observed. Grade 2 thrombocytopenia developed in 21% of patients and grade 2 anemia in 5%.

The most common non-hematological toxicities were diarrhea and fatigue. Although diarrhea developed in 84% of patients, only 21% experienced grade 3 diarrhea; no patient developed grade 4 diarrhea. Similarly, although 84% of patients noted fatigue, grade 3 fatigue developed in only 11% of patients. Other common non-hematological toxicities included nausea and vomiting, anorexia,
and hyperglycemia. One patient died after the first cycle from rapidly progressive disease. One patient developed a grade 4 gastrointestinal bleed. Two patients had small bowel obstructions secondary to their underlying malignancy. Two patients with a history of atrial fibrillation required hospitalization for rate control.

**Discussion**

We administered flavopiridol as a 72-h continuous infusion to 20 patients with previously untreated ACRC. The drug was relatively well-tolerated in this patient population. There was minimal hematological toxicity and only moderate diarrhea and fatigue. Despite the encouraging anti-tumor activity observed in preclinical and phase I studies, we observed no objective responses in this trial, and only 28% of the patients experienced disease stabilization. The observed median survival of 65 weeks is likely a reflection of the second-line therapies administered.

Although flavopiridol in this dose and schedule does not appear to have single-agent activity in patients with colorectal cancer, it may be worthwhile to examine flavopiridol as a chemotherapy-modulating agent in this disease. There is schedule-dependent cytotoxic synergy *in vitro* when 5-FU is administered after flavopiridol [23]. Flavopiridol can potentiate apoptosis induced by mitomycin in gastric cancer cell lines [24]. Of greater interest in colorectal cancer, flavopiridol augments apoptosis induced by irinotecan in resistant colon cancer cell lines. Sequential treatment with irinotecan followed by flavopiridol results in significant tumor regression, including CRs, in a mouse xenograft model [25]. Motwani et al. [25] observed that single-agent irinotecan causes transient cell cycle arrest, while the addition of flavopiridol activates caspase-3, cleaves inhibitors of apoptosis such as p21 and sensitizes cells to undergo cell death. Preliminary evidence of antitumor activity has been observed in a phase I trial of irinotecan followed by flavopiridol [26]. A phase II trial of this combination in patients with advanced colorectal cancer is in development.

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**References**