Phase II study of etoposide and alpha-interferon in patients with advanced measurable colorectal carcinoma

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Summary

Based on encouraging in vitro and in vivo data, 14 consecutive patients with measurable metastatic previously untreated colorectal carcinoma were treated with a combination of intravenous etoposide and subcutaneous alpha-interferon. Etoposide was given at 60 mg/m$^2$ intravenously on days 1–5 and alpha-interferon at 5 million units/m$^2$ subcutaneously on days 1–5; courses were repeated every 21 days. All 14 patients were evaluable for response and toxicity. None of the patients achieved a complete or partial remission. Toxicity of this combination was moderate. Our data suggest that this combination is ineffective against colorectal carcinoma.

Introduction

Colorectal carcinoma remains a serious health hazard in the USA. Approximately 60,000 deaths are anticipated due to advanced colorectal carcinoma in 1992 [1]. Metastatic colorectal carcinoma is an incurable disease. Chemotherapy with 5-fluorouracil and leucovorin has resulted in a modest survival advantage in a randomized trial [2], however, the available chemotherapy options are less than satisfactory due to a low rate of response and only occasional complete response. It is obvious that new effective drugs are urgently needed for patients with metastatic colorectal carcinoma.

We made an attempt to develop a drug combination which did not contain 5-fluorouracil. Etoposide and alpha-interferon (Intron, Scherring corporation) were combined based on encouraging in vitro [3] and in vivo [4] information; although both drugs when given individually are ineffective against advanced colorectal carcinoma.

In the soft agar assay, Von Hoff [3] found that the combination of etoposide and alpha-interferon was synergistic. Among 23 specimens from a variety of human tumors, 10 (43%) demonstrated synergistic cytotoxicity and among these three of nine were colon carcinoma specimens. In this report, agents were simultaneously or singly exposed to the tumor cells for one hour. Interestingly, the etoposide had the highest rate of synergism with interferon compared to all other chemotherapy drugs investigated (doxorubicin, 5-fluorouracil, 4-hydroxycyclophosphamide, and vinblastine) individually with alpha-interferon. In addition, the combination of etoposide and interferon has resulted in a 38% response rate in patients with Kaposi’s sarcoma [4]. The maximum tolerated dose of etoposide in the clinical study was 300 mg/m$^2$/course. Based on these results and particularly in vitro data, we performed a phase II study of etoposide and alpha-interferon in patients with measurable metastatic colorectal carcinoma.

Patients and methods

Patients with histologic proof of measurable, metastatic colon carcinoma were eligible. All patients
were required to have no prior chemotherapy or immunotherapy, Zubrod scale performance status of 2 or less, life expectancy of at least 12 weeks, serum bilirubin level less than or equal to 1.5 mg/dL, serum creatinine level less than or equal to 1.4 mg/dL, and normal peripheral granulocyte and platelet counts. All patients were required to give an informed consent. Patients with active infection or brain metastases were excluded from this study. A response rate of 20% was considered desirable, thus an initial cohort of 14 patients was studied. If one response occurred in the first 14 patients, additional 16 evaluable patients were to be studied to confirm a response rate of 20% with 95% probability (rejection error, 5%). The study was to be terminated if there was no response in the first 14 patients.

All treatments were administered in the outpatient setting. The starting dose of etoposide was 60 mg/m² bolus intravenously once a day for 5 consecutive days; alpha-interferon was given at a dose of 5 million units/m² subcutaneously daily for 5 consecutive days. The dose of etoposide was increased or decreased by 25% based on myelosuppression (dose was increased in the event of grade 2 myelosuppression; decreased for grade 4 myelosuppression; and not changed for grade 3 myelosuppression), however, the dose of alpha-interferon was not altered. Courses were repeated every 5 weeks. An attempt was made to administer at least two courses of chemotherapy prior to response evaluation unless there was evidence of rapidly progressive cancer.

Complete blood counts, differential count, and platelet count were monitored on a weekly basis during therapy. Objective disease parameters such as computerized tomography were repeated every two courses. The response criteria were standard. Toxicity grading was based on the criteria developed at M.D. Anderson Cancer Center [5].

**Results**

A total of 14 patients were accrued; all patients were evaluable for response and toxicity. There were seven men and seven women with a median age of 49 years (range, 37 to 78); and the median performance status was 1 (Zubrod scale; range, 0–1). All patients were previously untreated and had measurable metastatic carcinoma.

A total of 28 chemotherapy courses were administered with a median of 2 courses per patient (range, 1–3). Etoposide dose was decreased by 25% in four patients (inappropriately in one patient) and dose was increased in five patients. In additional two patients, the dose of etoposide could have been increased but was kept the same because of nonhematologic side effects.

There were no complete or partial responses; one patient had no change in the measurable cancer after two courses but clinically progressed after receiving the third course of chemotherapy.

Hematologic toxicity was moderate with the median absolute granulocyte count nadir being 1,200 cells/μL (range, 300 to 4,500 cells/μL). Thrombocytopenia was not a clinical problem (median platelet nadir count was 231,000/μL). Grade 2 and 3 non-hematologic toxicity consisting of myalgias, fever, and fatigue contributed by alpha-interferon prevented dose increment in all 14 patients. Other toxicities were minor and included alopecia (all patients), grade 2 vomiting (3 patients), and one patient who had grade 2 reversible mental disorientation.

**Discussion**

Tantalizing in vitro results documenting synergism between etoposide and alpha-interferon provided the incentive for this clinical trial. The schedule of concomitant administration of both drugs was also chosen based on the in vitro method of simultaneous drug exposure. However, the combination proved ineffective against patients with measurable untreated colorectal carcinoma. The toxicity seen in this study was moderate. It is also conceivable that higher doses could have been administered to some patients, nevertheless, the lack of any biologic effect of this combination in any patient suggests that this combination is ineffective in the treatment of colorectal carcinoma. The current in vitro methodology may not be adequate to accurately predict