Brief communication

Phase II trial of 5-fluorouracil and folinic acid in the treatment of advanced breast cancer

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Summary

Standard combination chemotherapy for metastatic breast cancer produces response rates between 30–60% with limited impact on survival. We undertook a phase II trial to determine the activity of 5 fluorouracil (5FU) and folinic acid (FA) in patients with measurable metastatic or recurrent breast cancer who had received no prior chemotherapy. Patients meeting the eligibility criteria received 5FU 370 mg/m²/day and FA 200 mg/m²/day for 5 days repeated every 28 days, toxicity allowing. Response defined by standard criteria was assessed every 8 weeks and toxicity according to WHO criteria was determined on every course. Thirty-three patients were entered on trial. Thirty-two patients were evaluable for response and 33 for toxicity. The dose limiting toxicity was stomatitis with 7/32, 19/32, and 5/32 patients experiencing grade 1, 2, and 3 toxicity. Grades 1 and 2 diarrhea occurred in 17/32 and 11/32 patients respectively. Myelosuppression was not significant. Two complete and 11 partial responses were observed. The overall response rate was 41% (95% CI, 24–58%). Responses were seen in soft tissue and visceral sites. Patients who had received adjuvant chemotherapy more than 6 months prior to receiving 5FU and FA responded also. Six of 29 patients receiving standard combination chemotherapy as second line treatment responded subsequently. We concluded: 1) 5FU and FA is an active combination in the treatment of breast cancer warranting further evaluation in combination with other drugs; 2) the dose-limiting toxicity of stomatitis is tolerable; 3) patients receiving 5FU and FA as first line therapy can respond to conventional combination chemotherapy as second line treatment.

Introduction

It is estimated that 150,000 new cases of breast cancer will be identified in Canada and the United States in 1993. More than 46,000 deaths are likely to occur as a result of metastatic disease. Although changes in surgical approaches have reduced the morbidity of treatment, a significant alteration in long-term survival has not been seen. Standard combination chemotherapy regimens produce responses in 30–60% [1–3] of patients, of which the majority are partial with response durations rarely exceeding one year and median survivals rarely extending beyond two years. Recognizing these limitations, we and others have explored alternate approaches to the treatment of metastatic breast cancer. Based on our experience using 5-fluorouracil and folinic acid in the treatment of advanced colon cancer [4] and with the background of several small pilot projects utilizing a similar regimen in previ-
ously treated advanced breast cancer, we embarked upon a Phase II trial of this regimen as first-line chemotherapy in the treatment of advanced breast cancer.

**Materials and methods**

Thirty-three patients with measurable recurrent or metastatic carcinoma of the breast were entered on this IRB approved study. Entry criteria included the following: 1) biopsy proven adenocarcinoma; 2) patients who were ambulatory at least part of the day (ECOG 0, 1, or 2); 3) patients with life expectancy ≥ 8 weeks; 4) measurable disease; and 5) written informed consent. All patients were informed that they could receive standard chemotherapy as alternative to the study. Patients who had received radiation or hormonal treatment were eligible for study if they had demonstrated disease progression and had been off treatment for a minimum of 4 weeks. Similarly, those patients who had received adjuvant chemotherapy were eligible if a period of six or more months had elapsed since discontinuation of their therapy.

Patients with prior systemic chemotherapy for relapse and/or metastatic disease, prior adjuvant chemotherapy within the previous six months, a bilirubin of ≥ 35 mmol/L, known cerebral metastases, more than one primary tumor (except basal cell carcinoma or carcinoma of the cervix with a greater than three year disease-free interval) or patients who were either pregnant or nursing were excluded.

The patients were treated with folinic acid (Leucovorin, Lederle Laboratories, Montreal, Canada) 200 mg/m² i.v. daily for 5 days given as a bolus followed 10–15 minutes later by 5-fluorouracil 370 mg/m² i.v. daily for 5 days. Patients who had received radiation therapy to a significant amount of marrow-containing bone had an initial dose reduction of 5FU to 300 mg/m² day. In addition, patients received a mouthwash of allopurinol (1 mg/ml in methyl cellulose) 10–15 ml which was taken immediately after treatment and then 1, 2, and 3 hours post-therapy. The mouthwash was swished in the mouth, applied to the lips, and then expectorated [5]. Allopurinol was used as a mouthwash to decrease mucositis. This is based on the rationale that Allopurinol anabolism will decrease cellular levels of phosphoribosyl pyrophosphate in normal tissue which is a necessary cosubstrate for 5FU activation. Courses of chemotherapy were repeated every 28 days. In responding patients therapy was continued until disease progression was documented. In those patients where disease progression occurred, therapy was stopped and subsequent treatment was left to the discretion of the attending physician. Patients who did not achieve a response but had stable disease received a maximum of six cycles of treatment. No growth factor support was included in the treatment protocol. Toxicity was graded using WHO criteria in this study. Dosage modifications were made for hematological toxicity as well as oral and gastrointestinal side effects. The modifications were as follows: 1) the daily dose of 5FU was reduced by 70 mg/m², if the granulocyte nadir was < 750 cells/cu mm and/or platelet nadir < 50,000 cu mm; 2) if grade 2 or 3 gastrointestinal or oral mucosal toxicity developed, a 70 mg/m²/day reduction in 5FU occurred on the following cycle; 3) if on treatment day, granulocyte count was < 2,000 cells/cu mm or platelets < 125,000/cu mm, treatment was delayed at weekly intervals until haematological recovery above this level had occurred; 4) in the event that no significant haematological toxicity occurred and Grade 0 or Grade 1 gastrointestinal and/or oral mucosal toxicity was present, the dose of 5FU was escalated on a subsequent course by 45 mg/m²/day.

Baseline investigations included a complete history and physical examination, weight and height, a complete blood count, bilirubin, creatinine, alkaline phosphatase, serum calcium and SGOT. Tumor hormone receptor data was obtained on all patients, usually from their original surgical specimen. Baseline x-rays, scans, and photographs were obtained to document sites of measurable disease. The blood counts were repeated weekly. The serum biochemistry was determined before each cycle of treatment and radiological studies and photographs were repeated every eight weeks.

Treatment endpoints were defined as response rate, response duration, time to disease progression, survival, and drug-induced toxicity. The latter