Phase II trial of PCNU in breast carcinoma*

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Abstract

The Eastern Cooperative Oncology Group undertook a limited institution phase II study of PCNU in advanced, metastatic breast cancer. The study was limited to patients treated with 1 to 2 prior chemotherapy regimens. Accrual goals were 30 patients but the study was terminated after 10 patients had no response, with a rapid time to progression of 4 weeks, despite considerable hematologic toxicity. Based on this experience and negative results in two prior studies in more heavily pretreated patients, we conclude PCNU is inactive in breast cancer.

Introduction

PCNU (NSC 95466) is a nitrosourea shown to be effective in a wide spectrum of experimental animal tumors [1–3]. The combination of high alkylating activity, low carbamoylating activity and high lipid solubility contribute to its effectiveness in animal tumor systems [4]. Results of phase I studies at M.D. Anderson Hospital suggested clinical activity in melanoma, colon carcinoma, hypernephroma, Hodgkin’s disease, pancreatic and breast carcinoma. Toxicity was largely hematopoietic and dose-related. An ECOG phase II pilot study of PCNU in refractory metastatic breast cancer is the basis for this report.

Materials and methods

Eligibility criteria for study entry included metastatic breast cancer resistant to conventional therapy, a leukocyte count greater than or equal to 4,000/mm³, platelet count greater than or equal to 100,000/mm³, a serum creatinine less than 2.0 dl%, bilirubin less than 1.5 dl%, an ECOG performance status of 0, 1, or 2 and no chemotherapy in the preceding three weeks. A maximum of two prior chemotherapy regimens was allowed, with no prior exposure to nitrosoureas. Measurable or evaluable/non-measurable disease was required according to the usual ECOG criteria. Prior to therapy, all patients underwent a complete history and physical examination, complete blood count, blood chemistries, chest x-ray and nucleide scans where appropriate. Tumor measurements were taken prior to each 6-week cycle and blood counts were done weekly.

PCNU was given as an intravenous solution over 30 minutes at a dose of 100 mg/M² every six weeks. In patients with a history of excessive hematologic toxicity to prior chemotherapy or radiation therapy, the initial dose was 75 mg/M². Subsequent doses were to be escalated by 25% if the nadir WBC was greater than 3000/mm³ and platelet count

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greater than 100,000/mm³, and reduced by 25–50% if the nadir WBC was less than 2000/mm³. All patients receiving 1 course of PCNU were considered to have had an adequate trial of the drug. Response was judged by standard ECOG criteria for complete response, partial response and disease progression.

**Results and discussion**

Ten patients with histologically confirmed breast cancer were entered into the study and all are evaluable for response and toxicity. The median age of the ten patients was 53 years (range 38–71). Eight patients had a performance status of 0–1, and 2 had a performance status of 2. Nine of the patients had exposure to two prior chemotherapeutic regimens; one patient received Adriamycin alone; six had prior endocrine manipulations. Five of the ten (50%) had responded to at least one of the previous treatment regimens. Skin and soft tissue disease only was present in two patients; eight patients had multiple sites of involvement. The most common distant sites of metastasis were bone (five patients) and liver (four).

None of the ten patients had an objective response to treatment with PCNU. All ten patients have died, with an overall median survival from the start of protocol therapy of seven months. The median time from start of treatment to disease progression was four weeks. The mean initial dose of PCNU was 120 mg. (range 100–160 mg.) Only 2 patients were able to receive a second course and both required dose reduction due to hematologic toxicity. Myelosuppression was significant, but was not dose related. Four patients experienced a nadir platelet count of 50,000/mm³ and six patients had a WBC nadir of 3000/mm³. The most severe cytopenias were seen in patients given 75 mg/M² initial dose of PCNU, reflecting a more limited marrow reserve in this group. One patient died as a consequence of thrombocytopenic bleeding (platelet count 13,000/mm³) 30 days after PCNU treatment. This patient had extensive liver metastases, hypercalcemia and mild thrombocytopenia (100,000/mm³) at the onset of treatment. Impaired metabolism of PCNU by the liver and possible bone marrow involvement may have predisposed this patient to excessive hematotoxicity. She developed progressive liver failure and hypercalcemia due to uncontrolled metastatic disease complicating the hematologic toxicity.

Because of the poor results in these ten patients, this study was closed prematurely. The frequently severe hematologic toxicity indicated lack of response was not due to inadequate dosage of drug. Similar disappointing results were recently found at M.D. Anderson Hospital. These authors reported only 1 mixed response in 30 patients treated at a dose range of 60–90 mg/M² [5]. However, their patients were heavily pretreated with 2 to 7 regimens, suffered a low performance score and 14 had brain metastasis. A second study also reported no response in 22 patients who had received at least 2 prior chemotherapy trials [6]. Both of these studies involved heavily pretreated patients, but the ECOG trial allowed only 2 prior chemotherapy regimens and the performance status of our patients was relatively good. We conclude that PCNU has little activity in refractory metastatic breast cancer and may cause considerable myelosuppression in patients with limited bone marrow reserve.

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**References**

3. Clinical Brochure on PCNU (NSC 95466), National Cancer Institute, Dept. of Health, pub. July 1978