Breast Cancer

Gemcitabine Based Combination Regimens for Treatment of Refractory Advanced Breast Cancer

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ABSTRACT

Objective: Anthracycline and taxane are the standard agents in combined chemotherapy of advanced breast cancer. However, when these agents based chemotherapy is failure, the selection of salvage regimen is still of problem. Gemcitabine, an active agent in both lung cancer and pancreas cancer, is demonstrated effective in breast caner. But there have been relatively less data of gemcitabine in anthracycline and/or taxane-resistant breast cancer. Therefore we employe this study to explore the efficacy and safety of gemcitabine based combination regimen in this population. **Methods:** From May 2002 to March 2006, 28 patients with measurable lesion of advanced metastatic breast cancer who were resistant to prior anthracycline and taxane based chemotherapy were enrolled. Patients were treated with gemcitabine based combination chemotherapy with a median cycles of 3 (range 2–6). **Results:** The overall response rate was 28.6% (8/28), with 1 CR (Complete response 3.5%) and 7 PRs (Partial response 25%). Stable disease was seen in 8 patients (28.6%) while disease progressed in 12 patiens (42.8%). The median time to progression was 4.5 m (range, 2–23 m). The main toxicity included bone marrow depression, alopecia, mucositis and peripheral neurotoxicity. The grade 3 to 4 clinical adverse effect was leukopenia in 5 cases (17.9%) and thrombocytopenia in 8 cases (30%). **Conclusion:** Gemcitabine based combination regimens is feasible in anthracycline and taxane-resistant advanced breast cancer. The clinical response and TTP is acceptable with limited toxicity pattern.

Key words: Advanced breast cancer; Gemcitabine; Salvage chemotherapy; Anthracycline; Taxane

Approximately 20%–85% of patients with early breast cancer will later develop recurrent and/or metastatic disease, depending on the initial stage, tumor biology, and treatment strategy used. Despite more than 3 decades of research, metastatic breast cancer (MBC) remains essentially incurable and, after documentation of metastasis, the median survival time is approximately 2 year[1].

Anthracyclines such as doxorubicin and epirubicin can yield response rates of around 20% to 40% in MBC patients when used as single agents, and up to 60% when given as part of combination regimens. However, the efficacy achieved with anthracyclines comes at the cost of high toxicity. In recent years, novel drugs have emerged as important agents in the treatment of MBC patients, because of their safety and efficacy in generating symptom relief, in reducing disease progression and in prolonging survival.

Gemcitabine is a cytidine nucleoside analogue with proven activity in advanced breast cancer[2]. In previously treated MBC patients it has produced response rates ranging from 12% to 29%, and it was tolerated satisfactorily[3]. Gemcitabine has in vitro activity against a broad array of human tumor cell lines and has provided objective responses in a variety of human solid tumors including breast cancer[4, 5]. The drug's mild toxicity profile, activity in solid tumors, and relative non-cross-resistance with other classes of drugs offer opportunity for study.

The aim of the present study was to evaluate

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the antitumor activity and tolerance of gemcitabine based combination regimens in previously untreated patients with ABC as well as in those who had failed from one to five prior palliative chemotherapy regimen. Twenty-eight patients participated in this trial between May 2002 to March 2006, most of whom were evaluable for response.

PATIENTS AND METHODS

Patient selection

Eligibility for the study who suffered from refractory advanced breast cancer required the following: they must have previously received anthracycline or taxane or a combination of both in the adjuvant setting and had metastatic disease within 1 year; or have received an anthracycline or a taxane based treatment in the metastatic setting who was documented progressive disease within 3 m. The following criteria were also required: Age ≥18 years; Karnofsky performance status ≥50; adequate bone marrow reserve (ANC $\geq 2.0\times10^9$/L, PLT $\geq 85.0\times10^9$/L, HB ≥8 g/L); hepatic functions (total bilirubin ≤2 times the upper limit of normal, aspartate transaminase ≤3 times the upper limit of normal, or ≤5 times the upper limit of normal in the cases of liver metastases; and renal functions estimated creatinine clearance and albumin ≤ the upper limit of normal; and expected survival ≥12 w.

Exclusion criteria included: diagnosis of another malignancy within the past 5 y (except basal cell or squamous cell skin cancer and adequately treated non-invasive carcinomas); prior treatment with gemcitabine; uncontrolled infection or any chronic debilitating disease; clinically significant effusions (pericardial, pleural, ascites) unless these could be drained; major surgery or any immunologic, genetic, radiation or chemotherapy <4 w prior to randomization; pregnancy and breast feeding. Written informed consent was obtained according to federal and institutional guidelines.

Therapeutic Protocol

Gemcitabine at a dose of 1000–1250 mg/m^2 in 250 ml NS was given as a 30 min infusion on days 1 and 8 followed by vinorelbine at a dose of 25 mg/m^2 in 100 ml NS or 35 mg/m^2 docetaxel in 250 ml NS or 90 mg/m^2 paclitaxel in 500 ml NS on days 1 and 8. Cycles were repeated every three weeks.

Gemcitabine at a dose of 1000–1250 mg/m^2 in 250 ml NS was given as a 30 min infusion on days 1 and 8 followed by capecitabine at a dose of 2500 mg/m^2, p.o, days from 1 to 14.

There were 5 metastatic spinal cord compression MBC, 3 of whom had P185 Overexpression and received gemcitabine based combination regimens plus trastuzumab (first dose 4 mg/kg, where after 2 mg/kg, weekly up to 5 months). 2 of whom received gemcitabine at a dose of 800–1250 mg/m^2 weekly only until the date of progression or intoleration.

All patients were required to receive at least two cycles of treatment. Responding patients achieving CR, PR, or stabilization of disease continued treatment for six cycles. The treatment was discontinued if patients progressed after two cycles. Patients with stable disease continued the treatment at the discretion of the treating physician.

In case of any grade 4 toxicity the patient was taken off study. Toxicity criteria were those adopted by WHO.

Pretreatment and Follow-Up Evaluation

Pretreatment evaluation included a complete medical history and physical examination with measurement of all tumor-associated lesions. Laboratory evaluation consisted of a complete blood count with platelet count and leukocyte differential count and an 18-function biochemical profile. Imaging procedures included chest X-ray, bone scan, skeletal bone survey, and computed tomographic scan of the abdomen. Complete blood cell counts and differential counts were performed 3 to 5 d, and biochemical profiles were assessed before each treatment cycle. Tumor size was measured every 8 w by computed tomographic scan, X-ray, or any other technique that allows retrospective and independent reassessment.

Standard antiemetic treatment consisted of ondansetron. When the ANC was 1000 to 2000 on the day of planned chemotherapeutic drug administration, to maintain dose intensity, a 3 to 5-day course of the hematopoietic growth factor G-CSF (2.5–5 μg/kg/day given s.c.) was started on the subsequent day. In patients experiencing neutropenia, G-CSF support was not continued routinely during subsequent courses; the decision was always dependent on actual ANCs. To avoid fluid retention and/or anaphylactic reactions, patients who treated with docetaxel were premedicated with 7.5 mg of dexamethasone p.o. taken the night before, morning of, and evening after treatment.