Gemcitabine, Paclitaxel, and Trastuzumab in Metastatic Breast Cancer

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A phase II trial evaluated the effectiveness and toxicity of combination paclitaxel (Taxol), gemcitabine (Gemzar), and trastuzumab (Herceptin) as first-line therapy for patients with newly diagnosed HER2-overexpressing breast cancer.

Introduction

Breast cancer is the most common cancer in women, with nearly 184,200 new cases and over 40,000 deaths predicted for the United States in 2000.[1] With combination chemotherapy, objective response rates vary from 40% to 70%; complete response rates are consistently 10% to 20%.[2] Unfortunately, treatment of patients with metastatic breast cancer is typically palliative, with a small minority of patients achieving a complete response and remaining disease-free for more than 5 years.[3] Though combination chemotherapy results in higher response rates than treatment with single agents, major differences in survival are not apparent.[4] Recent efforts to improve survival have focused on biologically based therapies such as trastuzumab (Herceptin).

Trastuzumab

Trastuzumab is a recombinant humanized monoclonal antibody directed against the extracellular domain of the HER2 protein, a member of the epidermal growth factor receptor family of transmembrane proteins.[5] HER2 protein overexpression is observed in 25% to 30% of primary breast cancers and has been associated with poorer prognosis, decreased responsiveness to standard treatment, and a higher recurrence rate.[6,7] Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity. Preclinical studies have shown that trastuzumab inhibits proliferation and induces apoptosis of human breast cancer cell lines overexpressing the HER2 protein.[8-10]

A randomized phase III trial evaluated the safety and efficacy of adding trastuzumab to first-line chemotherapy with either paclitaxel (Taxol) or the combination of doxorubicin plus cyclophosphamide (Cytoxan, Neosar). Patients randomized to trastuzumab plus chemotherapy experienced a higher response rate (62% vs 36.2%) and a significantly longer duration of response (8.6 vs 5.5 months) compared with those who received chemotherapy alone. Combined treatment was well tolerated, though myocardial dysfunction was more commonly reported with trastuzumab plus doxorubicin/cyclophosphamide than with chemotherapy alone.[11]

Perhaps most importantly, the addition of trastuzumab to chemotherapy increased the overall median survival from 20.9 to 25.4 months, even though 65% of patients treated with chemotherapy alone received trastuzumab at the time of disease progression.[12]

Gemcitabine

Gemcitabine (Gemzar), an analog of cytosine arabinoside, is a pyrimidine antimetabolite that is metabolized to difluorodeoxycytidine diphosphate (dFdCDP) and difluorodeoxycytidine triphosphate (dFdCTP). Incorporation of these nucleotides into DNA results in chain termination. dFdCTP is not readily excised by DNA exonuclease, resulting in intracellular accumulation. In addition, gemcitabine inhibits ribonucleotide reductase, an enzyme that produces deoxynucleotides required for DNA synthesis.[13]
Several phase II studies have confirmed the activity of single-agent gemcitabine in the treatment of metastatic breast cancer. Objective response rates range from 14% to 46%, depending on the extent of previous treatment.[14-17] Hematologic toxicity is mild, with grade 4 neutropenia generally limited to < 10% of treated patients.

**Gemcitabine Plus Paclitaxel**

Several phase I trials of gemcitabine and paclitaxel have been conducted using a variety of doses and schedules.[18,19] Einhorn et al.[20] administered gemcitabine in doses of 1,000 to 1,250 mg/m² on days 1 and 8 of a 21-day treatment cycle with paclitaxel doses escalated from 135 to 175 mg/m² on day 1 only. The combination was well tolerated and further dose escalation was discontinued, although the maximum tolerated dose had not been reached. Toxicity was primarily hematologic; grade 3 and 4 neutropenia were reported in 33% and 38% of patients, respectively. Grade 3 thrombocytopenia was seen in 13% of patients, but only 3% experienced grade 4 thrombocytopenia. Anemia and significant nonhematologic toxicity were rare.

**Triple Combination Phase II Trial**

Both paclitaxel and gemcitabine are active agents in the treatment of breast cancer and can be given in combination at full dose. The addition of trastuzumab to paclitaxel was well tolerated, with a dramatic improvement in response rate, duration of response, and survival. We hypothesized that the triple combination of paclitaxel, gemcitabine, and trastuzumab may further improve clinical outcomes.

**Patients and Methods**

From June 1999 to June 2000, 27 patients were enrolled, with a median age of 54 years (range: 32 to 71 years). Patients with histologically confirmed, locally recurrent or metastatic breast cancer were eligible if either HER2 protein overexpression was documented by immunohistochemistry (2-3+) or HER2 gene amplification was documented by fluorescence in situ hybridization. Patients may not have received prior chemotherapy for advanced disease; adjuvant chemotherapy with paclitaxel or docetaxel (Taxotere) was permitted if completed ≥ 6 months from study entry.

Patients had to have a Karnofsky performance status of 60 or higher with adequate renal, hepatic, hematologic, and cardiac function. The institutional review board approved the protocol; written informed consent was provided prior to treatment.

**Dosing**

Patients were treated with paclitaxel at 175 mg/m² over 3 hours on day 1 plus gemcitabine at 1,200 mg/m² on days 1 and 8 plus trastuzumab at a 4-mg/kg loading dose on day 1 followed by 2 mg/kg weekly. Dexamethasone, diphenhydramine, and cimetidine (or another H₂ blocker) were administered immediately prior to paclitaxel. Treatment cycles were repeated every 21 days for a maximum of six cycles of combination therapy; responding or stable patients were eligible to continue single-agent trastuzumab until disease progression. Response evaluations were completed after every two cycles of combination therapy and at least every 16 weeks during single-agent trastuzumab.

Dose modifications were based on nadir blood counts and interval toxicity. Paclitaxel and gemcitabine were delayed until the absolute neutrophil count (ANC) was > 1,500 cells/mL and platelets were ≥ 100,000 cells/mL on day 1 of any treatment cycle. Paclitaxel and gemcitabine doses were reduced 25% if the previous treatment cycle had been complicated by febrile neutropenia, grade 4 thrombocytopenia, or bleeding associated with thrombocytopenia.

Additional dose modifications were mandated for grade 3 or 4 nonhematologic toxicity. Gemcitabine dose was reduced 25% on day 8 if the ANC was between 500 and 1,000/mL or the platelet count was 50,000 to 75,000/mL; gemcitabine was held on day 8 if the ANC was < 500/mL or platelets were < 50,000/mL. The trastuzumab dose was not adjusted for hematologic toxicity; if paclitaxel and/or
gemcitabine therapy was delayed or held, trastuzumab was administered as scheduled.

The study is designed to test the null hypothesis (H0) that the true response rate of this combination is 40% vs the alternative hypothesis (H1) that the true response rate is 60% with a power of 0.90 and a significance level of 0.10. Up to 46 qualified patients will be enrolled in a two-stage sequential schema.

**Results**

There were 18 qualified patients (of 27) enrolled in the first stage. More than 8 of the initial 18 patients responded to therapy, therefore the study is proceeding. Another 28 qualified patients will be enrolled to more accurately determine the true response rate.

Preliminary toxicity data are available for 23 patients (Table 1). Overall treatment has been well tolerated. Of the 23, 2 patients (9%) experienced grade 4 neutropenia but infectious complications were limited to grade 2 infection in 5 (22%). One patient each experienced grade 4 thrombocytopenia and anemia; three patients reached grade 3 fatigue. Grade 3 pulmonary toxicity was reported in one patient. Neither significant cardiac toxicity nor clinical congestive heart failure has been reported to date.

The majority of enrolled patients continue treatment. Preliminary efficacy analysis is available for 13 patients; it is too early to determine response in 14 patients. A partial remission was obtained in 12 patients (52%), including 1 patient with a 90% decrease in cumulative tumor volume. Only one patient had progressive disease. Median time to progression and overall survival have not been reached with the limited follow-up available.

**Discussion**

Unfortunately, metastatic breast cancer remains a largely incurable disease with palliation the goal of therapy for most patients. Selecting among the many available treatment options requires balancing the potential benefits with the expected toxicities of therapy. In this sense, the introduction of trastuzumab represents a major advance in the treatment of patients with metastatic, HER2-overexpressing breast cancer. The addition of trastuzumab to paclitaxel increases response rate, median time to progression, and overall survival with minimal increases in cardiac toxicity (0% vs 2%).[11,12] Nonetheless, most patients relapse and eventually succumb to progressive disease; the need to investigate new treatment combinations continues.

One approach is the combination of chemotherapeutic agents other than paclitaxel with trastuzumab. Burstein et al[21] evaluated the combination of vinorelbine (Navelbine) and trastuzumab in patients with HER2-overexpressing breast cancer who had not previously been treated with trastuzumab. Overall response rate was 60% in the first 17 patients who entered the study. Neutropenia was the most common toxicity with febrile neutropenia complicating 6% of treatment cycles. Two patients had an asymptomatic decrease in left ventricular ejection fraction; no clinical congestive heart failure was reported.

We are investigating an alternate approach, namely the addition of a third cytotoxic agent to the trastuzumab/paclitaxel combination. The single-agent activity and limited myelosuppression of gemcitabine led us to initiate this phase II trial of triple combination therapy with paclitaxel, gemcitabine, and trastuzumab.

Preliminary results confirm encouraging clinical activity with acceptable toxicity. The trial will continue to a total accrual of 46 patients to define response and toxicity more accurately.

**References:**


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