Gemcitabine as Single-Agent Therapy in the Management of Advanced Breast Cancer

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Many active cytotoxic agents exist for breast cancer therapy, and numerous combination chemotherapy regimens are derived from them. Creating these combinations is sometimes empirically motivated by non-overlapping toxicities or the expectation of non-cross resistance. Yet, there is usually no absolute division of these aspects among cytotoxic agents, and the median survival for patients with metastatic breast cancer has not been dramatically prolonged by this approach. When the outcome of treatment is palliation rather than cure, it becomes paramount to optimize the dynamic equilibrium between chemotherapy-induced side effects and the benefits attributable to relief of cancer-related symptoms. To this end, several recent clinical trials have evaluated the novel nucleoside analog gemcitabine (Gemzar) as single-agent therapy for advanced breast cancer. This article reviews these trials. [ONCOLOGY 15(Suppl 3):11-14, 2001]

Introduction

The management of estrogen-receptor-poor or hormone-refractory metastatic breast cancer involves the judicious and timely use of chemotherapy.[1] The application of radiotherapy and bisphosphonates can significantly reduce skeletal complications attributable to osteolytic metastases.[2,3] With the notable singular exception of the humanized monoclonal antibody trastuzumab (Herceptin), which is specific for the HER2 oncoprotein, cytotoxic chemotherapy remains standard treatment for advanced breast cancer insensitive to antiestrogen therapy.[4] Within this realm, taxanes and anthracyclines are recognized as the most active single agents in the management of metastatic breast cancer.[5-10] Other commonly used agents in the treatment of advanced breast cancer include cyclophosphamide (Cytoxan, Neosar), methotrexate, fluorouracil (5-FU), capecitabine (Xeloda), and vinorelbine (Navelbine).[11]

Unlike treatment for advanced lymphomas or germ-cell tumors, combinations of cytotoxic chemotherapeutic agents do not consistently offer a survival advantage to women with metastatic breast cancer. There are data from recent clinical trials demonstrating that monotherapy was similar to or even more effective than combination therapy, often with less toxicity.[10,12-15] One recent notable exception is the survival benefit reported by Norton et al with the concomitant use of trastuzumab when administered with chemotherapy (either doxorubicin [Adriamycin] plus cyclophosphamide or single-agent paclitaxel [Taxol]) as first-line therapy for HER2-overexpressing metastatic breast cancer.[16] In the absence of a survival benefit, the dynamic balance between the treatment’s "plus side" (eg, relieving cancer-associated symptomatology) and the "minuses" (toxicities) of chemotherapy must be carefully considered. This balance between benefit and harm can be imagined as the therapeutic index of a specific drug or regimen. An agent or combination of agents may yield a very high response rate, which may[17] (but not always) be associated with relief of cancer-related symptoms. However, it may also be associated with significant toxicity that impairs quality of life (ie, a low...
therapeutic index). On the other hand, a less active agent or regimen may not yield as high a response rate, but may cause meaningfully less toxicity, thereby actually offering the higher therapeutic index. This is the ultimate goal of palliative therapy, and it is through this lens that the following review of gemcitabine (Gemzar) monotherapy for metastatic disease is best viewed.

Chemistry and Mechanism of Action

Gemcitabine possesses a chemical structure related to cytarabine (ara-C), which is an agent not regarded as significantly active in breast cancer. However, gemcitabine differs from cytarabine in several important respects. This nucleoside analog (2',2'-difluoro-deoxycytidine [dFdC]) is progressively phosphorylated intracellularly by deoxycytidine kinase. The di- and tri-phosphate forms possess cytotoxic activity; the diphosphate inhibits ribonucleotide reductase that catalyzes the production of deoxynucleotide triphosphates necessary for normal DNA synthesis. The triphosphate competes with deoxycytidine triphosphate for incorporation into DNA as a fraudulent base.[18] Several mechanisms self-potentiate gemcitabine’s activity, and may partly explain both the greater intracellular concentration of gemcitabine compared to cytarabine and the increased, broader antitumor activity.[19]

Phase I Trials

A phase I trial of gemcitabine administered weekly for 3 of every 4 weeks determined the maximum tolerated dose at 790 mg/m². Cumulative thrombocytopenia and anemia were the dose-limiting toxicities in previously treated patients.[20] Another phase I study evaluated gemcitabine as a continuous 6-hour infusion weekly for 3 weeks, followed by 1 week of rest.[21] Dose escalation started at 200 mg/m² with planned incremental increases of 50 mg/m². In this study, the maximum tolerated dose was 250 mg/m². The dose-limiting toxicities of grade 3 reversible transaminase elevations occurred in two patients; grade 3 skin reactions occurred in one patient. With this schedule, an overall response rate of 15% was reported in 13 evaluable patients. These results—along with gemcitabine’s subsequent demonstration of activity in non-small-cell lung cancer,[22] epithelial ovarian cancer,[23] and advanced pancreatic cancer[24]—motivated the drug’s evaluation for patients with metastatic breast cancer.

Phase II Development

Carmichael et al.[25] conducted a phase II trial evaluating the efficacy and safety of gemcitabine for patients with locally advanced or metastatic breast cancer. Of the 40 patients evaluable for response, 14 were chemo-naive, 7 had received prior adjuvant chemotherapy, and 19 had received prior chemotherapy for metastatic disease; 17 patients had received prior anthracyclines. The median age was 54.5 years (range: 32 to 77 years). The majority of patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 1 (range: 0 to 2), despite a preponderance of visceral disease (50% with hepatic metastases). Gemcitabine was administered as a 30-minute infusion at a starting dose of 800 mg/m every week for 3 weeks, followed by a 1-week rest. Dose reduction for grade 2 hematologic toxicity or dose omission in the event of grade 3 hematologic toxicity resulted in a mean delivered dose intensity of 725 mg/m². Patients completed an average of 2.7 cycles (median: 2.0), and 81.2% of planned doses were administered as assigned. A 25% response rate (95% confidence interval [CI]: 12.7%-41.2%) was observed among the 40 assessable patients, with 3 complete and 7 partial responses. The reported median response duration was 13.5 months (range: 6 to 43+ months). Minimal anemia or thrombocytopenia was noted. Grade 3 and 4 elevation of hepatic transaminase (aspartate amino transferase [AST]) was reported in 7% and 2% of patients, respectively; 18.2% had a grade 3 elevation of amino alanine transferase. Flu-like symptoms were reported in 6.8% of patients, but were mild, transient, and treated with acetominophen. Alopecia was uncommon, as was significant nausea and vomiting. The authors noted that gemcitabine deserves further investigation in the management of breast cancer.

A second study reported by Blackstein et al.[26] confirmed meaningful antitumor activity and good tolerability for gemcitabine as first-line chemotherapy in metastatic breast cancer. Patients in this trial had a median age of 58 (range: 34 to 84 years), and 21 patients had received prior adjuvant therapy. Of 35 evaluable patients, 13 responded (37.1%; 95% CI: 23%-57%), with 4 complete and 10 partial responses observed. Grade 3 neutropenia occurred in 9 patients, thrombocytopenia in 2, and nausea/vomiting in 4. A higher dose (1,200 mg/m²) was administered 3 of every 4 weeks. These patients had less extensive prior therapy than patients in the Carmichael trial, yet the toxicity
profiles were remarkably similar, with severe neutropenia and infection being uncommon. Gemcitabine has also been evaluated as monotherapy in a cohort of patients who received prior anthracycline therapy, as reported by Spielmann et al.[27] This phase II trial involved five centers and enrolled 43 evaluable patients with bidimensionally measurable metastatic breast cancer. They received gemcitabine per protocol at a dose of 1,200 mg/m² as a 30-minute infusion weekly for 3 weeks, followed by 1 week of rest. All patients had received prior anthracycline-containing chemotherapy; 14 patients also received prior adjuvant chemotherapy. The majority had multi-organ system disease, primarily liver (60%), lung (34%), and bone (28%). The median age was 56 years (range: 33 to 75 years).

The overall response proportion was 28%, with 4 complete and 8 partial remissions. The treatment-limiting toxicity in this trial was asthenia, for which four patients discontinued treatment. Hematologic toxicity was mild, with grade 4 neutropenia observed in two patients, and grade 3 thrombocytopenia in 1. A significant cutaneous hypersensitivity reaction was observed in two patients, requiring treatment cessation in one. Radiation-recall-type skin changes occurred in three patients, which necessitated discontinuation of treatment for one person.

Possinger et al.[28] conducted a phase II trial in 42 patients with locally advanced or metastatic breast cancer. All had received up to one prior adjuvant chemotherapy regimen, and 28 patients had visceral metastases. Gemcitabine was administered at a dose of 1,000 mg/m² on days 1, 8, and 15, with the cycle repeated every 28 days; the mean dose delivered was 942.2 mg/m². Grade 3/4 toxicities were nausea and vomiting (n = 5), diarrhea (n = 1), pain (n = 1), alanine transaminase elevation (n = 7), and segmented neutrophils (n = 8). The overall response rate was a modest 14.3% (95% CI: 5.4%-28.5%), and no complete responses were reported; the authors noted 6 partial responses and 24 patients with stable disease. The median overall survival duration was 15.2 months.

A trial by Brodowicz et al.[29] evaluated gemcitabine as second- (n = 6) or third-line (n = 18) therapy for metastatic breast cancer. All 24 women had received prior anthracyclines, and 8 were previously treated with taxanes; all patients had visceral metastases. Gemcitabine was administered at a dose of 1,250 mg/m² on days 1, 8, and 15, with the cycle repeated every 28 days. Grade 3 leukopenia was noted in 4 of 6 patients receiving second-line therapy. Grade 3/4 leukopenia was seen in 4 of 18 patients receiving third-line therapy. Grade 3 thrombocytopenia was observed in 3 patients receiving third-line therapy.

Of the 6 patients receiving gemcitabine as second-line therapy, 2 had partial responses, with a median time to progression of 12 months. Of the 18 patients receiving gemcitabine as third-line therapy, one (6%) had a complete response, with a median time to progression of 3.9 months (range: 1.5 to 8 months).

Currently, Memorial Sloan-Kettering Cancer Center is conducting a phase II evaluation of "3-weeks-on/1-week-off" gemcitabine, using 800 mg/m² in patients with anthracycline- and taxane-refractory metastatic breast cancer. Preliminary results on 16 patients have noted antitumor activity in several patients (V. Currie, personal communication, December 2000).

Conclusions

Gemcitabine is a novel nucleoside analog that possesses meaningful antitumor activity in the treatment of metastatic breast cancer. Indeed, its antitumor activity is relatively unencumbered by severe toxicities in most patients. While there are no randomized prospective data addressing this issue, it seems unlikely that gemcitabine’s single-agent antitumor activity against advanced breast cancer is comparable to that of very active agents, such as taxanes and anthracyclines. Yet, is gemcitabine a useful agent in breast cancer therapy? Given the available data reviewed herein, the answer clearly appears to be yes.

Among the goals of managing metastatic breast cancer, prolonging survival ranks high for both patients and physicians. Higher response rates inspire physicians, whereas patients are more concerned with prolonging the time until disease progression on a given treatment. In considering the systemic care of patients with metastatic breast cancer, the dynamic equilibria of benefit vs harm as well as relief of tumor-associated symptomatology vs treatment-related toxicity seem of paramount importance and relevance.

In this regard, gemcitabine is emerging as a most welcome addition to the growing chemotherapeutic armamentarium against breast cancer. This is particularly apropos of monotherapy, where the sequential use of gemcitabine with other active agents not only has appeal but is the focus of ongoing clinical investigation. Its use in combination with other cytotoxic
agents,[30-44] as discussed by the other authors in this issue, derives in part from the potential for "nonoverlapping" toxicities (particularly in an era where the use of hematopoietic growth factor support is commonplace), a potential lack of complete cross resistance, and the occasional demonstration of promising preclinical results. Still, the relative benefits for the use of gemcitabine combinations vs single agents has not been clarified in the randomized clinical trials conducted thus far. A large, prospective, randomized phase III trial of paclitaxel with or without gemcitabine for metastatic breast cancer is underway. The meaningful, proven augmentation of the activity (reflected by survival) of chemotherapy by the addition of trastuzumab[16] motivates the exploration of gemcitabine trastuzumab-containing regimens for HER2/neu-overexpressing metastatic breast cancer, as well.

References:


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