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Advanced Breast Cancer: Investigational Role of Gemcitabine

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There have been many recent advances in the treatment of advanced breast cancer including the introduction of novel drugs and the development of high-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT). These innovations may offer significant hope for improvement in the treatment of breast cancer in the near future. Gemcitabine is a nucleoside analogue with significant antitumour activity in many human solid tumours. Conflicting results have been observed from studies evaluating gemcitabine in advanced breast cancer. Efficacy data for single-agent gemcitabine range from 25 to 46% depending on starting dose and whether patients have previously received chemotherapy for metastatic disease (as well as adjuvant use). Gemcitabine is extremely well tolerated, even in heavily pre-treated patients, and is easy to administer on an outpatient basis to both chemo-naive and previously treated patients. The most common toxicity is mild myelosuppression. Gemcitabine causes minimal nausea and vomiting, and significant hair loss is extremely uncommon. Combination chemotherapy studies with anthracyclines are underway and significant activity has been observed in combination with both doxorubicin and epirubicin. In view of its modest toxicity profile, and its novel mechanism of action, gemcitabine warrants further evaluation in breast cancer patients, both as a single agent and in combination chemotherapy schedules. © **1997 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

WORLDWIDE, BREAST cancer represents a major health problem, being responsible for 20% of cancer deaths in the Western World. It remains the leading malignant cause of death in young women. Although significant progress has been made in the adjuvant treatment of breast cancer, progress has been slow in advanced breast cancer treatment. Obviously, the ultimate objective of therapy in all stages of this disease is survival, but this remains elusive in metastatic disease. Single-agent response rates in chemotherapy-naive patients range from 25 to 60%, with higher response rates (45–80%) achievable with combination chemotherapy regimens [1]. Many agents have been shown to be active in advanced breast cancer, including anthracyclines and antimetabolites such as 5-FU and methotrexate.

Recent advances include the development of high-dose chemotherapy with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell transplantation (PBSCT). Preliminary data indicate significant activity of high-dose therapy both in terms of objective response rates and time to progression [2–5].

New cytotoxic agents for breast cancer, in addition to antitumour activity, should have an acceptable side-effect profile. Gemcitabine is active *in vitro* and *in vivo* in experimental systems [6]. It is a new nucleoside analogue with potential for use in breast cancer patients. The recommended dose schedule is a 30-min intravenous infusion once a week for 3 weeks followed by 1 week of rest [7]. Phase II trials of gemcitabine show activity in non-small cell lung cancer [8–10], ovarian cancer [11], small-cell lung cancer [12] and pancreatic cancer [13].

Gemcitabine is inactive in its parental form and is progressively phosphorylated intracellularly via deoxycytidine kinase. The active metabolites include the diphosphate, an inhibitor of ribonucleotide reductase; and the triphosphate, which competes with deoxycytidine triphosphate for incorporation into DNA as a fraudulent base [14]. This fraudulent base is masked from excision by proof-reading exonuclease enzymes [15]. Gemcitabine metabolites exert a number of feed-back effects on metabolism resulting in enhanced activity ('self-potentiation'): (1) Increased activity of deoxycytidine kinase [16]; and (2) Decreased activity of dCMP deaminase [17, 18].

These mechanisms may explain why gemcitabine achieves higher intracellular metabolite concentrations resulting in greater activity against solid tumours than ara-C [6].

The initial phase I study of the weekly schedule (once a week for 3 weeks followed by one week of rest) found the MTD (maximum tolerated dose) to be 790 mg/m^2 [7]. This schedule was carried forward into phase II studies at planned starting doses of 800 mg/m^2. However, subsequent evaluation in patients has indicated that higher doses can be administered without undue toxicity. This paper reviews the findings of single-agent

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studies of gemcitabine together with combination studies with doxorubicin and epirubicin.

PHASE I/II STUDIES OF SINGLE-AGENT GEMCITABINE

U.S. study

In the first single-agent breast cancer study, gemcitabine was administered by 30-min intravenous infusion at 800 mg/m^2 in the standard schedule, on days 1, 8 and 15 of each 28 day cycle [19]. All patients had histologically or cytologically confirmed, bidimensionally measurable advanced breast cancer, which was not amenable to curative surgery or radiotherapy. There were 18 evaluable patients all of whom had stage IV disease. Prior therapy included surgery (all 18 patients), radiotherapy (10 patients), chemotherapy (17 patients), and hormonal therapy (11 patients). None of these patients responded to treatment with gemcitabine. In this early study, the mean dose delivered was 577 mg/m^2/injection which was significantly lower than delivered in subsequent studies. In this small study, all but one of the patients received gemcitabine second or third line as palliative chemotherapy for stage IV disease. In this pretreated population, myelosuppression was seen: WHO grade 3 leucopenia in 20% of patients (but no grade 4), and grade 3 and 4 neutropenia in 25 and 20% of patients, respectively.

U.K./German study

In a U.K./German study [20], gemcitabine was given in the standard schedule (on days 1, 8 and 15 of each 28 day cycle) to patients who had received no more than one previous chemotherapy regimen in an adjuvant setting or for metastatic disease. The mean dose delivered in this study was 725 mg/m^2/injection. For the 40 evaluable patients, prior therapies included radiotherapy (62.5% of patients), chemotherapy (65%), and hormonal therapy (70%). In terms of previous chemotherapy, 14 patients were chemotherapy-naive, 7 patients had received adjuvant chemotherapy and 19 had received chemotherapy for metastatic disease (17 of these patients having received anthracyclines).

Objective responses were observed in 10 patients: 3 complete responses and 7 partial responses (overall response rate, 25.0%: 95% confidence interval (CI) 12.7–41.2%). These responses were seen at all sites including soft tissue, liver metastases and pulmonary metastases. 5 of the responders had received previous chemotherapy and 2 had received neither chemotherapy nor hormonal therapy. 5 responders were oestrogen-receptor negative and in 3 responders oestrogen-receptor status was unknown. The median duration of response and survival for the partial responders was 7 months with a median survival time of 18.6 months. Two of the 3 complete responders remain alive, 1 is still in remission after 4 years. The median duration of survival (for all 40 evaluable patients) was 11.5 months with a duration of response ranging from 6 months to more than 43 months (median 13.5 months).

Treatment was well tolerated. Neutropenia grade 3 and 4 was observed in 10 and 3 patients, respectively, and the incidence of infection associated with this level of neutropenia was very low. There was no significant anaemia or thrombocytopenia, with only 2 patients experiencing grade 3/4 thrombocytopenia. Symptomatic toxicities were rare and mild.

German study

A German phase II study has assessed single-agent gemcitabine in patients with progressive advanced disease or metastatic breast cancer (not amenable to surgery or radiotherapy) [21]. Gemcitabine 1000 mg/m^2 was administered in the standard schedule, on days 1, 8 and 15 of each 28 day cycle. A preliminary report shows six partial responses among 33 patients entered (the number of evaluable patients was not reported). Toxicity was generally mild with no grade 4 WHO symptomatic toxicity.

U.S./Canada study

A multicentre study conducted in the U.S./Canada, included stage IV breast cancer patients with disseminated breast cancer who had not received chemotherapy for metastatic disease [22]. Gemcitabine 1200 mg/m^2 was administered by i.v. infusion on days 1, 8 and 15 of a 28 day cycle.

36 patients aged 42–85 years (median age 56 years) were enrolled. 23 patients were oestrogen receptor positive, 9 were negative and 4 had unknown oestrogen receptor status. 31 patients were postmenopausal, 2 were perimenopausal and 3 were premenopausal. 32 of the 36 patients had received prior chemotherapy in an adjuvant setting. In a preliminary analysis of data from 26 evaluable patients (2 patients were not evaluable and for 8 patients it was too early) there were two complete responses and 10 partial responses for an overall response rate of 46%.

Gemcitabine was well tolerated in these patients with no (WHO) grade 3 or 4 platelet toxicity. Grade 4 neutropenia in the absence of infection was observed in only 1 patient, who was discontinued from the study. No patients were hospitalised due to drug-related adverse events.

French study

A French phase II study has been conducted in patients previously treated with anthracycline-containing regimens [23]. Gemcitabine was administered in the standard regimen, i.e. 1200 mg/m^2 on days 1, 8 and 15 of a 28 day cycle. One-third of the patients had received prior adjuvant chemotherapy and two-thirds of the patients had received hormonal therapy for metastatic breast cancer.

Preliminary data from 27 evaluable patients include two complete responses and six partial responses. Haematological toxicity was mild with grade 4 neutropenia in only 2 patients and 1 grade 3 thrombocytopenia with subcutaneous haemorrhage. No patient had infection related to treatment and no patient was hospitalised due to adverse events.

PHASE I/II STUDY OF GEMCITABINE PLUS DOXORUBICIN

The combination of gemcitabine and doxorubicin has been investigated in a Spanish phase I/II study, in metastatic breast cancer patients, who had not received previous chemotherapy except as adjuvant treatment [24]. Gemcitabine was administered on days 1, 8 and 15 of each 28 day cycle, immediately followed by doxorubicin 25 mg/m^2. The dose of gemcitabine administered was 800 mg/m^2 (in the first 6 patients), 1000 mg/m^2 (in the second 6 patients), and, after analysis of toxicity data, reduced to 800 mg/m^2 in subsequent patients.

Preliminary results from 30 patients, 24 of whom were evaluable for response, showed four complete responses and 14 partial responses. There were no reports of grade 3 and 4 nausea and vomiting. Grade 3 and 4 haematological toxicity was as follows: neutropenia (13 and 4%, respectively), leucopenia (11 and 2%, respectively), thrombocytopenia (4 and 0%,

respectively). This study is still ongoing and plans to recruit 45 evaluable patients.

PHASE I STUDY OF GEMCITABINE PLUS EPIRUBICIN

Gemcitabine at a fixed dose of 1000 mg/m^2 in the standard schedule (on days 1, 8, 15 of a 28 day cycle) has been combined with escalating doses of epirubicin (10 mg/m^2/15 min infusion, escalated in subsequent patients in 5 mg/m^2 steps) in a German phase I study [25]. Patients enrolled had metastatic disease and had not received previous chemotherapy except as adjuvant treatment. Previous hormonal therapy was allowed.

The MTD was reached with epirubicin 20 mg/m^2. The dose-limiting toxicity was myelosuppression after three or more cycles (leucopenia and/or thrombocytopenia), although there was no complicating neutropenic fever or signs of bleeding. Non-haematological toxicity was mild. Of 19 patients included in the study, 16 patients are currently evaluable for response and three partial responses have been recorded to date. The recommended dose for a phase II study of the gemcitabine plus epirubicin combination is likely to be gemcitabine 1000 mg/m^2 and epirubicin 15 mg/m^2 on days 1, 8 and 15 of a 28 day cycle.

DISCUSSION

In phase II trials of metastatic or locally advanced breast cancer, there are many single agents with activity of 25% or more. These agents include carboplatin [26], doxorubicin [27], edatrexate [28], high-dose etoposide [29], epirubicin [30, 31], vinorelbine [32] and the taxoids [33, 34]. Many other drugs also have activity including mitomycin C and 5-FU. However, treatment with these cytotoxic drugs, as single agents or in combination, frequently results in multiple side-effects, including myelosuppression, alopecia, nausea and vomiting. Reported objective response rates to chemotherapy in previously treated breast cancer patients tend to be lower than the response rates in a chemo-naive population, although the activity of paclitaxel appears to be maintained in anthracycline-resistant patients [35].

Apart from one small early lower dose study, response rates for single-agent gemcitabine range from 25% in the U.K./German trial at a starting dose of 800 mg/m^2 (including patients treated with chemotherapy for metastatic disease) to 46% in the U.S./Canada study at a starting dose of 1200 mg/m^2 (which included patients treated with chemotherapy in an adjuvant setting, but not for metastatic disease). These studies would appear to confirm that single-agent gemcitabine is active in breast cancer, but the precise level of activity remains to be identified.

In view of the poor overall outcome in many patients with metastatic breast cancer, important roles of chemotherapy remain palliation of symptoms and maintenance of quality of life. Gemcitabine is well tolerated and easy to administer on an outpatient basis to both chemo-naive and previously treated patients. The most common toxicity is mild myelosuppression. Gemcitabine causes minimal nausea and vomiting, and significant hair loss is extremely uncommon.

In view of the novel mode of action, antitumour activity and modest toxicity profile, gemcitabine justifies further evaluation in breast cancer. The optimal dose has not been clearly defined.

In the gemcitabine plus doxorubicin phase I/II study, with 24 patients evaluable to date, there were four complete responders and 14 partial responders [24]. In the gemcitabine plus epirubicin phase I study, 3 partial responses were seen in the 16 patients evaluable to date [25]. Further combination studies are planned or underway in advanced breast cancer patients with gemcitabine and paclitaxel. The results of these studies are awaited with interest.

There are many developments in the systemic chemotherapy of breast cancer. A number of new drugs have recently been identified with reported activity of greater than 25% e.g. paclitaxel [35], docetaxel [36] and vinorelbine [32]. Of particular interest, evaluation of combination of these drugs with anthracylines has identified combination chemotherapy regimens that result in very high objective response rates and prolonged progression-free survival [37]. Similarly, preliminary evidence of improved outcome with high-dose chemotherapy programmes is encouraging [2–5], although the results of larger randomised studies are awaited.

Currently, further research with gemcitabine in breast cancer is necessary to identify its role more precisely. It is an active agent with low toxicity and the lack of alopecia particularly makes it a valuable palliative cytotoxic drug for patients with a poor prognosis. Much more work needs to be done with combination chemotherapy protocols, although the early results with anthracycline combinations are interesting. These data are necessary before using this agent more extensively and earlier in breast cancer management.

In conclusion, antitumour activity has been seen in breast cancer patients with extremely modest toxicity. Gemcitabine, therefore, represents an interesting new drug that warrants further investigation in breast cancer patients both as a single agent and in combination chemotherapy protocols.

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