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Gemcitabine in advanced breast cancer

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The experience with single-agent gemcitabine in advanced or metastatic breast cancer is reviewed. In all studies, gemcitabine was administered as a 30 min intravenous infusion in cycles once a week for 3 weeks followed by 1 week of rest. In the first European study (gemcitabine 800 mg/m²/week), of 40 evaluable patients, 14 were chemo-naive, 7 had received adjuvant chemotherapy, and 19 had received chemotherapy for metastatic disease. There were 3 complete responders and 7 partial responders (all independently validated by an external Oncology Review Board) for an overall response rate of 25.0% (95% CI: 12.7%–41.2%). The median time to declaration of response was 1.9 months and the median duration of survival for all 40 efficacy-evaluable patients was 11.5 months. Haematological and non-haematological toxicities were particularly mild. WHO grade 3 and 4 toxicities included leukopenia (6.8% and 2.3% of patients), neutropenia (23.3% and 7.0%), AST (6.8% and 2.3%), ALT (18.2% and 0%), infection (0% and 2.3%), nausea and vomiting (25.0% and 2.3%), alopecia (2.3% and 0%). There was no grade 3 or 4 creatinine, proteinuria or haematuria. In the smaller US study (18 evaluable patients, all but one having received prior chemotherapy for stage IV disease) there were no responders. However, the mean dose delivered was very low (577 mg/m²/injection). In an ongoing European trial, with a starting dose of 1000 mg/m², a number of partial responders have been seen in soft tissue, lung and liver. Gemcitabine's modest toxicity profile and single-agent activity make it an attractive candidate for trial in combination therapy in advanced breast cancer where treatment is currently given to palliate symptoms and improve quality of life.

Introduction

In patients with metastatic breast cancer, curative therapy is beyond our reach at present. It is therefore essential to balance the possible objective tumour shrinkage and reduction in tumour-associated symptoms with the drug-related toxicity the patient has to cope with. It is important that the type and intensity of a systemic therapy should be adapted to the patient's individual situations. Therefore, in metastatic breast cancer the main treatment objectives are to improve existing or imminently threatening symptoms caused by the tumour growth, to retain or restore physical ability for as long as possible and, if possible, to prolong survival time. Very few drugs combine therapeutic efficacy with low systemic toxicity and good tolerability, and gemcitabine, a novel nucleoside analogue, seems to be one of these agents.

Preclinical studies with gemcitabine have demonstrated extensive activity with efficacy in a wide variety of murine solid tumour and human xenograft models.[1] Such activity in solid tumours is unusual for a nucleoside analogue and is explained by gemcitabine's interesting pharmacology, in which multiple mechanisms potentiate its activity. Gemcitabine undergoes intracellular phosphorylation to its active diphosphate and triphosphate metabolites. The activity of deoxycytidine kinase (the enzyme controlling the rate-limiting step in phosphorylation) is increased by gemcitabine diphosphate,[2] which is also responsible for reducing the activity of dCMP deaminase (the enzyme responsible for much of the cellular elimination of gemcitabine).[3] Elimination of gemcitabine is also directly inhibited by gemcitabine triphosphate.[4] In this way the di- and triphosphates self-potentiate their activity. These mechanisms are responsible for the rapid and high level accumulation of gemcitabine triphosphate in

The European study was conducted by James Carmichael, Philip Phillip, Helen Kerr and Adrian L Harris from the ICRF Clinical Oncology Unit, Churchill Hospital, Oxford, UK; and Kurt Possinger and Maria Beykirch from the Klinikum Grosshadern, Munich, Germany.

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tumour cells, and its subsequent slow elimination, compared with ara-C triphosphate.[4] The active gemcitabine nucleotides exert their cytotoxic actions as follows. Gemcitabine diphosphate inhibits the formation of deoxycytidine triphosphates in general and deoxycytidine triphosphate in particular.[5] In this way gemcitabine triphosphate competes as a substrate for incorporation into the elongating DNA chain and substitutes for deoxycytidine nucleotide. Of interest, the gemcitabine nucleotide allows one more nucleotide to pair before chain elongation is terminated. In this way, the incorporation of gemcitabine is hidden (masked DNA chain termination), and the lesion is less susceptible to detection and repair by proof-reading exonuclease enzymes.[5]

Phase I and phase II studies have suggested that the balance between activity and tolerability is best achieved in a weekly schedule whereby gemcitabine is given once a week for 3 weeks, followed by a week of rest.[6] In the early phase II studies a starting dose of 800 mg/m^2 was chosen. In the breast cancer programme there were two early studies at this low starting dose (now completed), and a third study is ongoing at a starting dose of 1000 mg/m^2.

European study

In the European Study[7] patients were recruited in two centres (ICRF Clinical Oncology Unit, Churchill Hospital, Oxford, UK; Med. Klinik III, Klinikum Grosshadern Universität, München, Germany). Gemcitabine was administered on an out-patient basis at a dose of 800 mg/m^2 given by 30 min i.v. infusion once weekly for 3 weeks followed by 1 week of rest, this constituting 1 course of chemotherapy. Toxicity was scored monthly using WHO criteria, and the clinical response was initially assessed using WHO criteria following 2 courses of chemotherapy. Forty-four patients with advanced breast cancer (loco-regional recurrence or metastatic disease) with measurable disease were admitted to the study. The most common sites of metastatic disease were liver (50% of patients), bone (45%) and lymphadenopathy (37%). Patients were allowed a maximum of one regimen of chemotherapy as adjuvant treatment or for advanced disease. They had to be aged between 18 and 75 years with a WHO performance status of 2, serum creatinine < 150 mmol/l, serum bilirubin less than twice normal, and ALT/AST less than 3 times normal. Patients with endocrine or radiotherapy in the 4 weeks before the start of the study, with symptomatic involvement of the central nervous system, concomitant cytotoxic, hormonal treatment, immunotherapy, corticosteroids (except corticosteroid antiemetics and oral contraceptives) or experimental agents were excluded. The patient characteristics are summarized in Table 1.

Table 1. Patient characteristics

No. patients	44
Age (years)	
Median	54.5
Range	32–77
Performance status	
0	14
1	25
2	5
Menopausal status	
Pre	9
Peri	4
Post	31
Histology	
Ductal	35
Lobular	3
Adeno	5
Mixed	1
Spread	
Loco-regional	4
Metastatic	40

81.2% of doses were given as assigned, 1.1% of doses were omitted (more than half of these because of progressive disease), 15% were reduced and 2.7% were escalated.

For all 40 patients receiving at least 1 course of gemcitabine, overall response rate was 25% (95% CI: 12.7%–41.2%). All responses were confirmed by an independent Oncology Review Board. Responses were seen in soft tissue (breast, lymph nodes) and in 4 patients with liver metastases. Response by tumour histology was as follows: well differentiated 1, moderately differentiated 1, poorly differentiated 3, differentiation unknown 5. Five responders had received previous chemotherapy, 3 had received up to 3 hormonal therapies, and 2 were chemotherapy and hormonal therapy naive. Responses were generally noted early on in treatment (after 8 weeks two-thirds of eventual responders had been declared as such) and times to complete response were 1.9, 1.9 and 2.1 months. The duration of response ranged from 6 to 43+ months. Median overall survival times were 18.6+ months for responders and 8.6+ months for non-responders.

Table 2. Laboratory values: maximum WHO grades experienced during treatment (% of patients)

	WHO grades				
	0	1	2	3	4
Haemoglobin	47.7	45.5	4.5	2.3	0
Leukocytes	18.2	18.2	54.5	6.8	2.3
Segmented neutrophils	25.6	16.3	27.9	23.3	7.0
Platelets	86.4	6.8	2.3	2.3	2.3
Bilirubin	97.7	2.3	0	0	0
AST	25.0	36.4	29.5	6.8	2.3
ALT	45.5	36.4	0	18.2	0
Alkaline phosphatase	65.9	20.5	13.6	0	0
Urea	81.0	19.0	0	0	0
Creatinine	100.0	0	0	0	0
Proteinuria	55.8	34.9	9.3	0	0
Haematuria	62.8	20.9	16.3	0	0

Table 3. Non-haematological toxicity: maximum WHO grades experienced during treatment (% of patients)

	WHO grades				
	0	1	2	3	4
Infection	90.9	4.5	2.3	0	2.3
Fever	70.5	20.5	9.0	0	0
Hair loss	77.2	9.1	11.4	2.3	0
Consciousness	54.5	25.0	18.2	2.3	0
Pulmonary	86.4	6.8	6.8	0	0
Allergic	97.7	0	0	2.3	0
Cutaneous	75.0	18.2	4.5	2.3	0
Peripheral neurotoxicity	97.7	2.3	0	0	0
Nausea/vomiting	38.6	27.3	6.8	25.0	2.3
Oral	88.7	4.5	6.8	0	0
Diarrhoea	86.4	4.5	9.1	0	0
Constipation	93.2	6.8	0	0	0

There were a number of symptomatic benefits, including decreased analgesic consumption (median duration of improvement 11.6 weeks), increased performance status (median duration 4 weeks), and decreased pain score (median duration 18 weeks).

The WHO toxicity grades for laboratory parameters are given in Table 2. Haematological toxicity was generally mild; in particular very little platelet toxicity was observed, 86.4% of patients having no abnormal platelet count. Although the most sensitive indicator of myelosuppression was neutropenia, with WHO toxicity grades 3 and 4 of 23.3% and 7.0% respectively, the incidence of infection associated with this level of neutropenia was very low. Liver and renal toxicity were minimal. Only 1 patient discontinued treatment due to liver toxicity.

The WHO toxicity grades for symptomatic toxicity are given in Table 3. The only WHO grade 4 symptomatic toxicities were infection (2.3%) and nausea and vomiting (2.3%). WHO grade 3 toxicities were few but included nausea and vomiting (25%: this is misleading as a large proportion of patients were receiving prophylactic antiemetics), hair loss (2.3%) and cutaneous symptoms (2.3%).

Flu-like symptoms were reported in 6.8% of patients, although the incidence of fever was low and easily managed. Peripheral oedema and oedema were reported in 9.1% and 4.5% of patients but there was no evidence of any association with cardiac, hepatic or renal failure.

US study

Gemcitabine at a starting dose of 800 mg/m^2/wk was also evaluated in a smaller US study. Patients had to have received no more than one previous chemotherapy regimen for metastatic disease and could have received one course of adjuvant therapy. In this study 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. The mean dose delivered was calculated as 577 mg/m^2/injection, which was considerably lower than that in the European study, 725 mg/m^2/injection. Although the absence of objective responses was disappointing, it should be borne in mind that in this small study all but one of the patients had been given gemcitabine second or third line as palliative chemotherapy for stage IV disease, and the mean dose received by patients was < 600 mg/m^2/injection. There was little platelet toxicity (10% of patients reporting WHO grade 3 with no grade 4) and no patients required platelet transfusions. Myelosuppression was significant in this pretreated population, with WHO grade 3 leukopenia in 20% of patients (no grade 4), and WHO grade 3 and 4 segmented neutrophils in 25% and 20% of patients respectively. Haematological toxicity was the major cause of dose omissions in these pretreated patients who would be expected to have diminished bone marrow reserves compared with chemo-naive patients.

Second European study

The differing results of the first European study and the US study led to a third study in which single-agent gemcitabine was given to a more homogeneous prognostic group. Patients had to be chemo-naive for metastatic breast cancer, and where they had received adjuvant chemotherapy this treatment had to have finished at least 1 year before enrolment in the study. In this multicentre study gemcitabine was administered in doses of 1000 mg/m^2, again given weekly for 3 weeks every 4 weeks.

To date, 23 patients have entered this study and a number of responses have been seen in soft tissue, lung and liver. One patient was withdrawn from the study due to a cutaneous allergic reaction 24 h after the infusion of gemcitabine. In the other patients haematological and non-haematological toxicities were very mild, with a maximum of WHO grade 2.

Discussion

The systemic treatment of patients suffering from advanced breast cancer is still unsatisfactory. Impressive tumour remissions can be achieved with hormonal and cytotoxic drugs, but curative therapy is beyond our reach at present. This emphasizes the importance of the development of drugs combining high therapeutic efficacy with low systemic toxicity and simple administration. The nucleoside analogue gemcitabine promises to be such a drug. Gemcitabine is a pro-drug requiring intracellular phosphorylation to its active nucleotides. Its cytotoxic activity is related to its incorporation into DNA, and the consequent inhibition of further DNA synthesis. An important variable for the therapeutic index of gemcitabine is the duration of infusion. According to pharmacokinetic studies an optimal intracellular level of gemcitabine triphosphate can be achieved at an infusion rate of 10 mg/m^2/min, but most phase I and II studies in patients with solid tumours have been conducted using a weekly schedule of administration with doses between 800 and 1000 mg/m^2 infused over 30 min. It remains to be clarified whether longer perfusion times adapted to the cellular phosphorylation capacity (10 mg/m^2/min) will increase the therapeutic efficacy.

Overall, the toxicity profile of gemcitabine, administered as a 30 min infusion once a week for 3 consecutive weeks followed by a week of rest, is extremely favourable. Dose-limiting toxicity is myelosuppression. Neutropenia is prevalent but not severe (Table 2), and more importantly the incidence of infection is very low. The low incidence and grade of granulocytopenia and neutropenia is in marked contrast to the levels of grade 3 and 4 granulocyte toxicity routinely seen in single-agent therapy with doxorubicin, paclitaxel, docetaxel or ifosfamide. Also in contrast to other cytotoxic drugs, gemcitabine causes very little nausea and vomiting. The incidence of 25% grade 3 toxicity is misleading as it includes prophylactic use of antiemetics in some patients. Hair loss is a major problem with many cytotoxic treatments. With gemcitabine however, WHO grade 3 and 4 hair loss was only 2.3% and 0%, and this is an important benefit in the population with breast cancer. Flu-like symptoms have been reported with gemcitabine: in the European study 3 patients experienced these symptoms, which were mild, transient and easily treated with acetaminophen. There was no WHO grade 3 or 4 fever. Peripheral oedema was reported in 9.1% of patients as being mild, transient, with no evidence of any association with cardiac, hepatic or renal failure. Cumulative haematological or non-haematological toxicity patterns have not been recognized. This toxicity profile suggests that gemcitabine may be easily incorporated into combination chemotherapy regimens without significantly compromising the doses of the other agents. To maintain the favourable toxicity profile of gemcitabine, especially the minor hair loss and nausea and vomiting, combination with mitoxantrone or fractionated weekly administration of 4'-epidoxorubicin would be suitable chemotherapy regimens.

As in all pivotal phase II gemcitabine studies, response rates have undergone rigorous evaluation. A panel of five experienced independent oncologists evaluated the response of each investigator-determined responder to gemcitabine therapy, reviewing the clinical history, signs, symptoms and the appropriate radiological tests. Drugs effective in the treatment of metastatic breast cancer achieve objective responses in up to 50% of previously untreated patients; however many of these agents are associated with unpleasant toxicities.

In conclusion, gemcitabine has been shown to be active in advanced breast cancer. The objective response rate of 25% seen in the European Study was validated by an independent Oncology Review Board, and is in the range of other single agents used in breast cancer. In the European Study two-thirds of the patients had previous chemotherapy. Therefore another study was started enrolling patients who had not received cytotoxic pretreatment. In this ongoing study objective remissions have been seen. Although increased survival re-

mains the ultimate objective of therapy, metastatic breast cancer remains incurable at this time, and most current treatment is given with the expectation of palliating symptoms and improving quality of life. Under these circumstances an acceptable toxicity profile of a drug is of great importance. Gemcitabine is very well tolerated and easy to administer on an out-patient basis. Dose-limiting toxicity is leukopenia. Administered as a 30 min infusion once a week for 3 consecutive weeks followed by a week of rest, leukopenia WHO grade 3 or 4 occurred in fewer than 10% of the patients. WHO grade 3 hair loss was seen in only 2.3% of patients, with no grade 4 alopecia. The incidence and intensity of nausea and vomiting was relatively low and was controlled with simple antiemetics such as metoclopramide. Gemcitabine deserves further evaluation in breast cancer and is a logical candidate for combination chemotherapy. Separate studies are underway in metastatic breast cancer with gemcitabine and 4'-epidoxorubicin and mitoxantrone.

References

1. Hertel LW, Boder GB, Kroin JS, *et al.* Evaluation of the antitumour activity of gemcitabine, (difluoro-2'-deoxycytidine). *Cancer Res* 1990; **50**: 4417–22.
2. Plunkett W, Gandhi V, Chubb S, *et al.* 2',2'-difluorodeoxycytidine metabolism and mechanism of action in human leukaemia cells. *Nucleosides, Nucleotides* 1989; **8**: 775–85.
3. Xu Y-Z, Plunkett W. Modulation of deoxycytidylate deaminase in intact human leukemia cells. Action of 2',2'-difluorodeoxycytidine. *Biochem Pharmacol* 1992; **44**: 1819–27.
4. Heinemann V, Hertel L, Grindey GB, *et al.* Comparison of the cellular pharmacokinetics and toxicity of 2',2'-difluorodeoxycytidine and 1-β-D-Arabinofuranosylcytosine. *Cancer Res* 1988; **48**: 4024–31.
5. Huang P, Chubb S, Hertel L, *et al.* Action of 2',2'-difluorodeoxycytidine on DNA synthesis. *Cancer Res* 1991; **51**: 6110–7.
6. Kaye SB. Gemcitabine: current status of phase I and II trials (Editorial). *J Clin Oncol* 1994; **12**: 1527–31.
7. Carmichael J, Possinger K, Philip P, *et al.* Difluorodeoxycytidine (gemcitabine): a phase II study in patients with advanced breast cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 64 (Abstract 57).