Anti-Cancer Drugs 2001, **12,** pp. 209–212

Clinical report

Unexpected severe myelotoxicity of gemcitabine in pretreated breast cancer patients

Gottfried J Locker,[1] Catharina Wenzel,[1] Manuela Schmidinger,[1] Michael FX Gnant,[2] Christine Marosi,[1] Raimund Jakesz,[2] Christoph C Zielinski[1] and Guenther G Steger[1]
Departments of [1]Internal Medicine I, Division of Oncology and [2]Surgery, University Hospital of Vienna, 1090 Vienna, Austria.

Gemcitabine is a chemotherapeutic agent with proven antitumor effects in pancreatic and non-small cell lung cancer; however, studies establishing the definite significance in other solid tumors are still in progress. We herein present three female patients with advanced breast cancer who received gemcitabine as salvage chemotherapy. Gemcitabine at a dose of 1250 mg/m^2 was scheduled for days 1, 8 and 15 with a subsequent rest for 1 week. However, within 1 week after the very first administration of gemcitabine myelotoxicity WHO grade IV occurred in all patients, leading to discontinuation of therapy. In two patients this gemcitabine-induced hematotoxicity could be overcome by means of vigorous supportive care, but one patient died after cerebral bleeding due to severe thrombocytopenia. We conclude that gemcitabine in heavily pretreated breast cancer patients should only be used with extreme caution with special focus on platelet counts until solid data from clinical studies for doses and schedules are available. [© 2001 Lippincott Williams & Wilkins.]

Key words: Advanced breast cancer, adverse effects, gemcitabine.

Introduction

Within the past 10 years gemcitabine (2′,2′-difluorodeoxycytidine), a deoxycytidine analog with established antitumor activity,[1,2] has been introduced in the treatment of several malignancies.[3,4] While promising results were rapidly achieved in patients suffering from advanced pancreatic, non-small cell lung or bladder cancer,[5–8] clinical investigations proving the value of gemcitabine in the treatment of other solid tumors are still ongoing.[9–12]

Correspondence to GJ Locker, Department of Internal Medicine I, Division of Oncology, University Hospital of Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria.
Tel: (+43) 1 40400 4492; Fax: (+43) 1 40400 4498;
E-mail: gottfried.locker@akh-wien.ac.at

With an increasing number of anticancer drugs against anthracyclin-resistant breast cancer, third- and fourth-line chemotherapy becomes more and more important in patients—especially younger patients—with advanced breast cancer. As a consequence, many studies focus on the value of gemcitabine, either administered as monotherapy or in combination with other cytostatic drugs, in this tumor entity.[9,11,13–15]

When given as a single agent, the commonly recommended dose is 800–1250 mg/m^2 administered weekly for 3 weeks with a subsequent rest of 1–2 weeks.[3,4] Given in combination with other cytostatic drugs such as cisplatin, etoposide or vinorelbine, a dose reduction of gemcitabine seems to be recommended. In general, the side effects of gemcitabine are described to be modest in chemotherapy-naive as well as pretreated patients. On the other hand, in heavily pretreated patients the dose-limiting toxic effect is myelosuppression with both thrombocytopenia and granulocytopenia encountered, whereby these side effects usually occur after several weeks of administration.[3,10]

We herein report on three females suffering from metastasized breast cancer refractory to standard chemotherapy, who received gemcitabine as third-line (two patients) or fifth-line (one patient) palliative therapy. Unexpectedly, these patients experienced grade IV side effects within a few days after the very first application of gemcitabine leading to one therapy-related death.

Case reports

Despite pending regulatory approval of gemcitabine for the therapy of breast cancer in Austria, patients received the drug in accordance with Austrian compassionate use regulations.

Patient 1 was a 53-year-old postmenopausal female (mastectomy for a G_2, hormone receptor-positive, pT_4, pN_1, M_0 tumor in 1991) with cutaneous, osseous and pleural metastases. Adjuvant treatment consisted of four cycles of cyclophosphamide 500 mg/m^2 and adriamycin 30 mg/m^2 on day 1, and methotrexate 30 mg/m^2 and 5-fluorouracil (5-FU) 500 mg/m^2 on day 8 every 4 weeks. Previous therapy for advanced disease was as follows: six cycles of vinorelbine 30 mg/m^2 every 2 weeks, nine cycles of mitomycin C (a total of 20 mg on day 1) and 5-FU 450 mg/m^2 on days 1–5 every 4 weeks and 16 cycles of 5-FU (450 mg/m^2 days 1–4 every 4 weeks) with leucovorin, L-leucovorin or 5-MTHF as modulator. All four treatment regimen induced a partial remission (PR) or stabilization of the disease.

Patient 2 was a 34-year-old premenopausal female (quadrantectomy and axillary lymph node dissection for a G_3, hormone receptor-negative, pT_2, pN_1, M_1 tumor in 1995) with osseous and supraclavicular lymph node metastases, and three episodes of mild paraneoplastic hypercalcemia. Prior palliative treatment consisted of eight cycles of FEC (5-FU 600 mg/m^2, epidoxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) every 3 weeks and six cycles of docetaxel 100 mg/m^2 every 3 weeks. The patient responded with a PR to both treatment regimens.

Patient 3 was a 57-year-old postmenopausal female (mastectomy for a G_3, hormone receptor-negative, pT_2, pN_1, M_0 tumor in 1990) with osseous and hepatic metastases, and bilateral malignant pleural effusions. In this patient, pretreatment consisted of nine cycles of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and 5-FU 600 mg/m^2 on days 1 and 8 every 4 weeks) to which she responded with a PR, and one cycle of EC (epidoxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1 scheduled every 3 weeks), which resulted in prolonged (more than 6 weeks) WHO grade 2 leuko- and thrombocytopenia, and was therefore discontinued.

In all three patients the common laboratory (Table 1) and medical requirements for the application of cytostatic treatment were fully met. Patient 2 was receiving radiotherapy for pain relief to the fourth lumbar vertebra (field size 4×4 cm) when gemcitabine therapy was started.

Gemcitabine at a dose of 1250 mg/m^2 was scheduled for days 1, 8, and 15 with a subsequent rest for 2 weeks in these patients. All three patients tolerated the drug administration itself without any side effects, but in all three severe myelotoxicity with WHO grade IV leuko- and thrombocytopenia occured within 7 days, thus making further drug administration impossible (Table 1). Patient 3 died because of intracerebral bleeding due to thrombocytopenia despite the immediate administration of single-donor platelet concentrates after diagnosis. In patients 1 and 2, repeated administration of platelet concentrates as well as the s.c. application of filgrastim because of febrile episodes due to the neutropenia was necessary. The patients required antibiotics and cristalloid solutions as well as parenteral nutrition. Prolonged reconstitution of the platelet counts and white blood cell counts took place within the following 3–4 weeks, but the patients' deteriorating conditions prohibited further antineoplastic treatment. Both patients died of progressive disease within the following 3 months.

Discussion

While the value of gemcitabine in pancreatic and non-small cell lung cancer seems to be established, the estimation of its role in other tumor entities requires further clinical investigations. Although recent studies report on promising results in advanced breast cancer, only little is known to date about the optimal doses and regimen for this tumor entity. In a small US study, where the delivered dose was very low (577 mg/m^2), no severe side effects but also no clinical remissions were observed.[11] In a European study, with a dose of 800 mg/m^2 administered weekly, the overall response was about 25% with moderate myelotoxicity.[9,11] However, a more recent study of gemcitabine (900 mg/m^2 on days 1 and 8) combined with docetaxel (100 mg/m^2 on day 8) in anthracycline-pretreated metastatic breast cancer patients reported an overall response rate of 54%, accompanied by grade III and IV thrombocytopenia in 21%.[16] Gemcitabine in

Table 1. Complete blood count before (day 1) and 1 week after the administration (day 7) of gemcitabine 1250 mg/m^2 in three breast cancer patients

Patient	Parameter	Day 1	Day 7
1	hemoglobin (mg%)	9.7	12.0
	white blood cells (g/l)	3.86	0.20
	granulocytes (g/l)	3.10	0.15
	platelet count (g/l)	102	6
2	hemoglobin (mg%)	11, 4	8, 9
	white blood cells (g/l)	3, 65	0, 35
	granulocytes (g/l)	2, 98	0, 1
	platelet count (g/l)	122	11
3	hemoglobin (mg%)	11.4	8.7
	white blood cells (g/l)	9.05	2.00
	granulocytes (g/l)	7.97	1.00
	platelet count (g/l)	115	8

Normal ranges: hemoglobin 12.0–17.0 mg%; white blood cells 4.0–10.0 g/l; granulocytes 2.0–7.5 g/l; platelets 150–350 g/l.

combination with epirubicin has been shown to result in grade IV thrombocytopenia in 20%[17] and in combination with cisplatin up to 31%.[18]

Because of rather rare solid data for dose adjustments when given as a single agent in pretreated breast cancer patients, we herein started the drug administration with the commonly recommended dose of 1250 mg/m^2, but abstained from combining with other cytostatic drugs. Despite leukocytes and platelets being within the acceptable range prior to chemotherapy, severe myelotoxicity occured within 1 week in all patients, thus leading to subsequent deterioration of the patients and to one therapy-related death.

In trying to explain these events of unexpected severe myelotoxicity in our three patients one can identify at least one clinical risk factor in each of them. The extended previous cytostatic treatment in Patient 1 might have been responsible for the observed meylotoxicity on its own and we cannot exclude that this severe side effect was at least in part due to a decreased bone marrow reserve. In Patient 2 the concommitant radiotherapy could have been attributed to the severe myelotoxicity, but the size of the field was relatively small. Patient 3 had already experienced prolonged but only moderate myelosuppression after the application of one cycle of the EC regimen preceding gemcitabine application. Finally, all patients had demonstrated osseous metastases with possible bone marrow involvement, which also could serve as an additional reason for these massive side effects. However, since bone marrow biopsies are not routinely performed at our institution in breast cancer patients without abnormalities in the peripheral blood or atypical bone scan results, this remains only speculative.

Whatever reason might have been responsible for the observed toxicities resulting in a therapy-related death and possibly in the preterm death of the two other patients, it has to be recognized that in all three patients severe myelotoxicity appeared shortly after the very first administration of a relatively moderate dose of gemcitabine. Thus, other mechanisms are also possible which might not be linked to the conditions or findings mentioned previously, but could be directly caused by the drug. Since the published literature about gemcitabine in advanced and pretreated breast cancer describes this drug as mild, well tolerated in general and associated with only mild to moderate myelotoxicity,[16–21] physicians worldwide may have currently the deceptive feeling to be on the safe side when recommending or using this drug. At our institution 84 patients with advanced breast cancer have received gemcitabine as second-, third- or fourth-line chemotherapy until to date. Considering the three patients described in this paper in whom one therapy-related death and two possibly therapy-related preterm deaths happened, 3–4% of these patients might be at risk for such events.

Summarizing our observation, further studies with gemcitabine in monotherapy are urgently warranted to clearly assess the value of this potentially beneficial compound in the treatment of advanced and pretreated breast cancer patients. Until these data are available, the use of gemcitabine in pretreated patients, especially with bone metastases and leukocyte and/or platelet counts below normal ranges or other potential risk factors, has to be monitored very carefully since some breast cancer patients might be susceptible to gemcitabine-induced myelotoxicity in particular. We therefore recommend to administer gemcitabine in only moderate starting doses and slowly increase dose regimens in advanced, pretreated breast cancer patients when treated outside clinical studies.

References

1. Hertel LW, Boder GB, Kroin JS, Rinzel SM, Poore GA, Todd GC. Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). *Cancer Res* 1990; **50**: 4417–22.
2. Plunkett W, Huang P, Gandhi V. Preclinical characteristics of gemcitabine. *Anti-Cancer Drugs* 1995; **6**: 7–13.
3. Abbruzzese JL, Grunewald R, Weeks EA, *et al*. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol* 1991; **9**: 491–8.
4. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced or metastatic solid tumors. A clinical phase I study. *Invest New Drugs* 1994; **12**: 111–9.
5. Anderson H, Thatcher N, Walling J, Hansen H. A phase I study of a 24 hour infusion of gemcitabine in previously untreated patients with inoperable non-small-cell lung cancer. *Br J Cancer* 1996; **74**: 460–2.
6. Carmicheal J, Fink U, Russell RC, *et al*. Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer* 1996; **73**: 101–5.
7. Moore M. Activity of gemcitabine in patients with advanced pancreatic carcinoma. A review. *Cancer* 1996; **78**(Suppl 3): 633–8.
8. Moore MJ, Tannock IF, Ernst DS, Huan S, Murray N. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 1997; **15**: 3441–5.
9. Carmichael J, Possinger K, Phillip P, *et al*. Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol* 1995; **13**: 2731–6.
10. Lund B, Hansen OP, Neijt JP, Theilade K, Hansen M. Phase II study of gemcitabine in previously platinum-pretreated ovarian cancer patients. *Anti-Cancer Drugs* 1995; **6**: 61–2.

11. Possinger K. Gemcitabine in advanced breast cancer. *Anti-Cancer Drugs* 1995; **6**: 55–9.
12. Carmichael J. The role of gemcitabine in the treatment of other tumours. *Br J Cancer* 1998; **78**(suppl 3): 21–5.
13. Akrivakis K, Schmid P, Flath B, *et al*. Prolonged infusion of gemcitabine in stage IV breast cancer: a phase I study. *Anti-Cancer Drugs* 1999; **10**: 525–31.
14. Pérez-Manga G, Lluch A, Alba E, *et al*. Gemcitabine in combination with doxorubicin in advanceed breast cancer: final results of a phase II pharmacokinetic trial. *J Clin Oncol* 2000; **18**: 2545–52.
15. Frasci G, Comella P, DÁiuto G, *et al*. Weekly docetaxel plus gemcitabine or vinorelbine in refractory advanced breast cancer patients: a parallel dose-finding study. *Ann Oncol* 2000; **11**: 367–71.
16. Mavroudis D, Malamos N, Alexopoulos A, *et al*. Salvage chemotherapy in anthracycline-pretreated metastatic breast cancer patients with docetaxel and gemcitabine: a multicenter phase II trial. Greek Breast Cancer Cooperative Group. *Ann Oncol* 1999; **10**: 211–5.
17. Luftner D, Flath B, Akrivakis C, *et al*. Gemcitabine plus dose-escalated epirubicin in advanced breast cancer: results of a phase I study. *Invest New Drugs* 1998; **16**: 141–6.
18. Nagourney RA, Link JS, Blitzer JB, Forsthoff C, Evens SS. Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. *J Clin Oncol* 2000; **18**: 2245–9.
19. Carmichael J, Walling J. Phase II activity of gemcitabine in advanced breast cancer. *Semin Oncol* 1996; **23**(suppl 10): 77–81.
20. Carmichael J, Walling J. Advanced breast cancer: investigational role of gemcitabine. *Eur J Cancer* 1997; **33**(suppl 1): 27–30.
21. Vermorken JB, Guastalla JP, Hatty SR, *et al*. Phase I study of gemcitabine using a once every 2 weeks schedule. *Br J Cancer* 1997; **76**: 1489–93.

(Received 25 November 2000; accepted 15 December 2000)