Gemcitabine and taxanes in metastatic breast cancer

D. Amadori1* & L. Cecconetto2
1Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola; 2Department of Medical Oncology, Morgagni-Pierantoni Hospital, Forlì, Italy

Key words: gemcitabine, metastatic breast cancer, taxanes, translational research

Gemcitabine is a deoxycytidine-analogue antimetabolite. Once incorporated into cells, it is phosphorylated into gemcitabine biphosphate and triphosphate. The former is a ribonucleotide reductase inhibitor, an enzyme involved in normal DNA synthesis. The latter competes with the natural nucleotide, deoxycytidine triphosphate for incorporation into the DNA replication chain. Once fraudulently incorporated, it determines fragmentation, with consequent cell death [1, 2].

Gemcitabine as a single agent has been the object of numerous phase II trials in patients with metastatic breast cancer, with a standard administration of 1200 mg/m² on days 1, 8 and 15 every four weeks. Objective response rates ranging from 14 to 37% have been obtained, with a time to progression varying from 5 to 8 months, an overall survival of 12 to 21 months, and acceptable toxicity. Grade 3–4 haematological toxicity has been observed in around 30% of patients. Among non haematological side-effects, asthenia, alterations in hepatic function, nausea and vomiting, and skin rash have been reported with a certain frequency [3–7]. However, gemcitabine used as a single agent has not proven effective in patients pretreated with anthracyclines and taxanes. In fact, in the only study conducted in this patient setting, no complete or partial objective responses were observed [8].

The pharmacodynamics, efficacy and good toxicity profile of gemcitabine make it an ideal agent for polychemotherapy combinations, especially with platinum derivates, vinorelbine, and taxanes.

Numerous clinical trials have investigated the activity and efficacy of gemcitabine in association with taxanes. These studies are of great importance, especially in view of the fact that about two-thirds of patients with metastatic breast cancer have already received adjuvant treatment with anthracyclines and that, in these patients, taxanes are used as standard therapeutics.

gemcitabine-paclitaxel

Preclinical studies have shown that the sequential administration of paclitaxel and gemcitabine produces an additive cytotoxic effect, independently of the sequence used [9], and that the administration of paclitaxel before gemcitabine is associated with an intracellular increase in 2′,2′-difluorodeoxycytidine-5′-triphosphate, the active metabolite of gemcitabine. This, however, results in no more than an additive effect [10].

Conversely, a study conducted by our group on human breast cancer cell lines (MCF-7 and BRC-230) reported a synergic effect when gemcitabine was administered 48 h after doxorubicin-paclitaxel sequential treatment. A possible explanation for this synergism could lie in cell cycle perturbations induced by these drugs. Our data show that the sequence doxorubicin-paclitaxel induces a G₂-M phase cell cycle block and that cells re-enter the cell cycle 8 h after paclitaxel treatment. This determines an increase in cells synchronized in G-S phase, the cycle phase in which gemcitabine exerts its cytotoxic activity [11]. In the light of these data, the paclitaxel–gemcitabine sequence has become the most widely used scheme in this treatment setting.

phase II studies

In phase II studies, the gemcitabine-paclitaxel combination has shown a good activity, with response rates varying from 40 to 69%. Studies reporting a time to progression of 8 to 9 months and an overall survival of about 12 months are further proof of its efficacy. Nausea and vomiting, myelo-depression and neuropathy are the most widely reported side-effects [12–16].

phase III study (gemcitabine-paclitaxel vs. paclitaxel)

To compare the efficacy and tolerability of the combination gemcitabine (1250 mg/m² d 1, 8)–paclitaxel (175 mg/m² d 1) with that of paclitaxel (175 mg/m² d 1 q 21) alone as first-line therapy in patients treated with anthracyclines in an adjuvant setting, a international multicentre study has been performed. The Interim Analysis of the trial, presented at the 2004 ASCO Annual Meeting, showed a statistically significant increase in response rates, time to progression, and in particular, overall response when gemcitabine was added to the taxane. Objective response rates were 22.1% for the paclitaxel arm (T) and 40.8% for the combination arm (GT) (P <0.0001). Time to progression was 2.9 months for the T arm and 5.2 months for the GT arm (P <0.0001). Median survival was 15.8 months and 18.5 months for the T and GT arms, respectively (Hazard Ratio...
0.775, \( P = 0.019 \). Both treatments were well tolerated. However, GT-arm patients reported a higher incidence of grade 3–4 neutropenia (48% vs. 11%) and febrile neutropenia (5% vs 2%) than patients in the paclitaxel arm. The combination treatment arm also showed a greater frequency of non-haematological toxicity such as asthenia (7% vs. 2%), alteration of hepatic function (7% vs. 2%) and peripheral neuropathy (6% vs. 4%) [17].

Quality of life (Rotterdam Symptom Checklist Score) was markedly better for patients who received the combination treatment, whereas there was no apparent difference in reported pain and in the use of analgesics between the two arms [18]. Thanks to its favourable risk/benefit ratio, the gemcitabine–paclitaxel association represents a new therapeutic option as first-line treatment of metastatic breast cancer patients pretreated with anthracyclines.

**three-drug combinations**

Gemcitabine has also been tested in three-drug schedules, especially in combination with paclitaxel and doxorubicin (GAT) or epirubicin (GET). Our group performed a phase II study to evaluate the activity and toxicity of the GAT scheme as first-line therapy in patients with stage IIIb-IV breast cancer. This regimen was derived from previously mentioned experimental preclinical studies and consisted of doxorubicin 50 mg/m\(^2\) on day 1, paclitaxel 160 mg/m\(^2\) on day 2 and gemcitabine 800 mg/m\(^2\) on day 6, repeated every 21–28 days. Thirty-three patients were enrolled onto the trial: all were evaluable for toxicity and 29 were assessable for response. An overall response rate of 55.2% was observed, with a median duration of 16.4 months. The median time to progression and overall survival were 10.6 and 50.6 months, respectively. The most important toxicity was haematological, with grade 3–4 neutropenia observed in 69% of patients. The strong synergism among the three drugs found in the preclinical setting was confirmed in terms of both clinical activity and haematological toxicity. Our results seem to indicate that the GAT combination is effective and feasible in anthracycline-naïve metastatic breast cancer.

The GET combination has been analysed in two important studies. A phase II study performed by Conte and co-workers on 36 patients evaluated the feasibility of this regimen as induction therapy before high-dose chemotherapy (HDCT). Treatment consisted of gemcitabine 1000 mg/m\(^2\) on days 1 and 4, epirubicin 90 mg/m\(^2\) on day 1, and paclitaxel 175 mg/m\(^2\) on day 1; every 21 days. After 6 course of GET, patients under 60 years entering a programme of high-dose chemotherapy. The overall response rate was 92%. Twenty-five patients received HDCT, leading to an overall response rate of 96%. Grade 4 neutropenia was observed in 64% of cases [19].

More recently, a multicentre international randomized phase III trial was performed to compare time to progressive disease (TTPD), overall response rate (ORR), overall survival (OS), and toxicity of GET vs. 5-fluorouracil, epirubicin, cyclophosphamide (FEC) as front-line therapy in patients with metastatic breast cancer. This trial failed to demonstrate the superiority of the GET regimen over the FEC schedule in metastatic breast cancer patients, as shown by a similar median TTPD of 9.1 and 9.0 months, respectively (\( P = 0.557 \)). In addition, ORR did not differ significantly between the two treatment arms (62.3% and 51.2% respectively; \( P = 0.93 \)) [20].

**gemcitabine-docetaxel**

Gemcitabine and docetaxel, used as single agents, are active in metastatic breast cancer, have different mechanisms of action, and have non-superimposable toxicity profiles. This would seem to indicate their potential usefulness as a combination treatment.

Our group conducted a study aimed at testing the activity of some chemotherapeutics such as docetaxel, paclitaxel, gemcitabine, oxaliplatin, and 5-fluorouracil in human gastric cancer cell lines (AKG, GK2, KKP). In this work, docetaxel and gemcitabine proved to be the most active drugs, and it was seen that the sequence docetaxel–gemcitabine was characterized by a synergistic effect, whereas the inverse sequence or simultaneous exposure to the two drugs induced an antagonistic effect. It was also observed that a 24-h exposure to docetaxel determined a cell cycle block in G2-M phase, and that after 24 h, the majority of cells had moved into G1-S, which is the most sensitive phase to the action of gemcitabine. Furthermore, the percentage of cells in apoptosis increased considerably after sequential docetaxel–gemcitabine treatment [21].

In a phase I setting, Denes and co-workers conducted a trial comparing two metastatic breast cancer patient cohorts treated with two different schedules. The first treatment arm was given sequential docetaxel–gemcitabine on the same day, whereas the second arm received gemcitabine 24 h after docetaxel administration, as reported in the preclinical study by our group. Haematological toxicity (myelodepression) was considerably higher in the latter group. Recommended doses for the docetaxel \( \rightarrow 24 \) h \( \rightarrow \) gemcitabine treatment were docetaxel 75 mg/m\(^2\) on day 1 and gemcitabine 1000 mg/m\(^2\) on day 2, every 14 days [22].

The clinical activity of this combination, in advanced breast cancer, has been tested in numerous phase II studies with different administration modalities (biweekly, triweekly, monthly). Overall, an objective response rate ranging from 36% to 75% was observed, with a time to progression of about 6 to 9 months. The most frequent side effects were myelosuppression and nausea and vomiting [23–29]. In studies conducted on the first line treatment of metastatic disease, response rates varying between 60% and 75% have been reported, with a time to progression of about 12 months [24–26]. With regard to the efficacy of docetaxel and gemcitabine in patients pretreated with anthracyclines, interesting results emerged from three studies conducted on anthracycline-resistant or refractory patients. In these trials, the combination gemcitabine-docetaxel obtained response rates ranging from 36% to 54%, with a time to progression of 7 to 8 months and an overall survival of about 12 to 16 months [27–29].

At the 2005 Annual ASCO Meeting, Chan and co-workers presented a phase III study comparing the association gemcitabine–docetaxel (GD) with the capecitabine-docetaxel (CD) combination as first and second line therapy in patients pretreated with anthracyclines. Two hundred and ninety-five
patients were randomised to receive gemcitabine and docetaxel (G 1000 mg/m² on days 1 and 8; D 75 mg/m² on day 1) or capcitabine and docetaxel (C 2500 mg/m² on days 1–14; D 75 mg/m² on day 1) every 21 days.

Response rates were 27% in the GD arm and 31% in the CD arm, and time to treatment failure was 19 and 18 weeks, respectively. Progression-free survival, the primary aim of the study, was 35 weeks in both treatment arms. The GD combination proved to be an active schedule, with an efficacy similar to that of the capcitabine-docetaxel treatment. A lower incidence of toxicity was observed in the GD arm than in the CD arm: diarrhoea (7% vs. 17%), mucositis (4% vs. 16%), hand-foot syndrome (0% vs. 24%), and febrile neutropenia (7% vs. 12%) [30].

These results are of great interest, especially if we consider that the choice of first and/or second line treatment is often a difficult one because the majority of patients receive anthracyclines and/or taxanes in previous lines. The need for active, efficacious and non cross-resistant regimens is therefore of the utmost importance.

conclusions

Despite the availability of chemotherapeutic agents, metastatic breast cancer remains essentially incurable with less than 10% of patients disease-free beyond 5 years; the main aims of chemotherapy in the metastatic setting are to relieve disease-related symptoms to improve quality of life and to prolong survival. The choice of treatment is often problematic because it is influenced by a wide range of factors such as patient age, performance status, treatment preference, and previous therapy.

In this setting, the association of gemcitabine with taxanes proved to be extremely effective, with a good toxicity profile. The combination gemcitabine–paclitaxel is a new therapeutic option, especially for anthracycline-resistant or refractory patients. The gemcitabine–docetaxel schedule, albeit a promising treatment option, requires further confirmation in larger randomised clinical trials.

disclosures

Dr Amadori has indicated that he is a member of advisory boards for Glaxo Smith-Kline and Bayer.

references


