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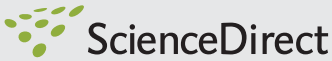

Review of gemcitabine plus taxane combination therapy in the first-line treatment of metastatic breast cancer

*Ramon Colomer**

MD Anderson Cancer Center España, Madrid, Spain

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ABSTRACT

The development of new chemotherapeutic therapies has led to an increase in treatment options for metastatic breast cancer. Using different types of agents in combination has resulted in anti-tumour activity that is greater than can be achieved with single-agent therapy, and has contributed to an increase in survival rates in the last 20 years. Some drug combinations only display synergistic effects when they are used in a certain sequence, and this is particularly true of the combination of a taxane followed by gemcitabine. Gemcitabine plus paclitaxel was recently added to the preferred combinations of the National Comprehensive Cancer Network Practice Guidelines in Oncology, as it demonstrated an increased time to disease progression and overall survival when compared with paclitaxel alone. The combination of gemcitabine plus docetaxel demonstrated similar efficacy to capecitabine plus docetaxel, but was associated with fewer drug-related discontinuations. Bi-weekly dosing regimens may optimise synergistic mechanisms and should be tested further in randomised clinical trials.

1. Introduction

Breast cancer remains the leading cause of death among women aged <65 years in Western countries. However, in the last few years information from data registries has demonstrated that the survival rate of patients with breast cancer is improving. These data mostly concern primary breast cancers, indicating that early diagnosis is having a great impact on survival. In addition, the availability of more numerous and better treatments for metastatic breast cancer (MBC) has prompted a change in practice for the treatment of advanced breast cancer and led to an improvement in survival.

The large database of patients from the MD Anderson Cancer Center in Houston, TX, USA demonstrates that the survival of MBC patients has increased in the years 1980–2000 to levels that were previously not thought possible.[1] There are several reasons for this increase in survival, one of which is related to better accuracy in diagnosis due to improved diagnostic techniques, meaning also that MBC is ascertained at an earlier stage. Additionally, improved local treatments, radiation therapy and surgery have all contributed to a survival gain. In conjunction with these advances, supportive therapies have also improved: bisphosphonates have had a considerable impact on the quality of life of patients, and cases of significant or lethal febrile neutropenia are now very rare due to the use of granulocyte colony-stimulating factors. The final reason for the recent improvement in survival is that new compounds, molecular therapies, treatment strategies

*Address for correspondence: Ramon Colomer, Director, MD Anderson Cancer Center España, Arturo Soria 270, 28033 Madrid, Spain. Tel: +34 972 426 038.
E-mail address: rcolomer@seom.org (R. Colomer).

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and combinations that have greater efficacy are being used for the treatment of MBC.

2. Therapeutic objectives

The practice of treating MBC has adapted to changing expectations. Whilst treatment should ultimately aim to improve survival, time to disease progression is an important outcome representing the ability to control disease and associated symptoms for longer periods of time. Additionally, improving the quality of life of patients can be achieved by carefully balancing treatment activity and tolerability. Therapy is now becoming more individualised, and as a result there are almost as many treatment scenarios as patients. There are several ways to individualise therapy, including selecting treatment according to a tumour's molecular characteristics, such as hormone receptor status, and clinical characteristics, such as disease-free interval or dominant disease site.

3. New agents in metastatic breast cancer

There have been several new therapeutic agents for MBC in the last 6 or 7 years, including gemcitabine, capecitabine, oral vinorelbine and liposomal doxorubicin. What all of these drugs have in common is that they are clearly less toxic than their earlier counterparts and that they have a better profile in terms of efficacy and tolerability. [2]

4. Gemcitabine combinations in metastatic breast cancer

4.1. Synergistic models

In vitro data suggest that drug combinations are particularly interesting, specifically regarding synergy between gemcitabine and the taxanes. It has been demonstrated *in vitro* that the combinations of gemcitabine plus paclitaxel, [3] and gemcitabine plus docetaxel, [4] are synergistic when combined in a particular sequence: the taxane followed by gemcitabine.

Recently published data from my research group indicate that the particular sequence used when administering paclitaxel and gemcitabine in combination is important *in vitro*: the sequence of gemcitabine followed by paclitaxel shows antagonism, whereas the sequence of paclitaxel followed by gemcitabine clearly shows synergism (see Fig. 1). [3]

There are also very interesting *in vivo* data on 50 MBC patients with either progressive or stable disease after >4 cycles of docetaxel 100 mg/m^2 as a single agent. Gemcitabine 900 mg/m^2 was added to this regimen on days 1 and 8 and a response was achieved in 46% of patients on the combination, demonstrating clinical synergism between these two compounds. [5]

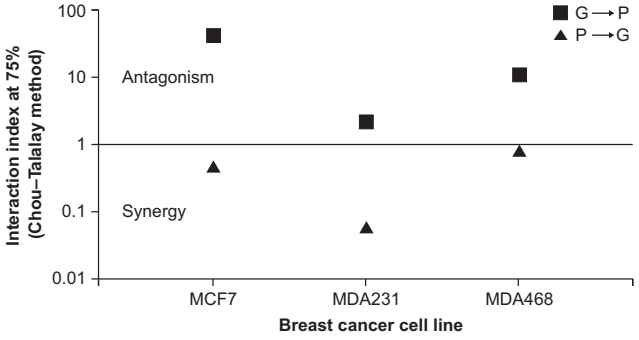

Fig. 1 – Antagonism and synergy according to the sequence of administration of gemcitabine plus a taxane in combination. [3] G, gemcitabine; P, paclitaxel.

4.2. Gemcitabine combination versus paclitaxel alone

A phase III clinical trial ($n = 529$) completed in 2007 compared gemcitabine plus paclitaxel versus paclitaxel alone in patients with unresectable, locally recurrent, or metastatic breast cancer. [6] Patients were treated with either paclitaxel 175 mg/m^2 alone or paclitaxel 175 mg/m^2 plus gemcitabine 1250 mg/m^2 on days 1 and 8, repeated every 3 weeks. The primary endpoint of this trial was overall survival, and the secondary endpoints were time to progression, overall response rate and toxicity.

The gemcitabine combination had a better time to disease progression (50% improvement, $p < 0.001$) than paclitaxel alone, and overall survival was also significantly improved in the combination arm ($p = 0.049$). The overall response rate with the gemcitabine combination was also significantly higher (41.4% vs. 26.2%, $p < 0.001$). Grade 3/4 haematological toxicities were more frequent in the combination arm, although the occurrence of febrile neutropenia requiring hospital admission was extremely low in both arms. The occurrence of some grade 3/4 non-haematological toxicities was also significantly increased in the combination arm, in particular grade 3 liver enzyme toxicity. These data led to the registration and approval of gemcitabine in combination with paclitaxel by the European Medicines Agency and the US Food and Drug Administration.

4.3. Gemcitabine in combination versus capecitabine in combination

Another important clinical trial [7] compared the combination of gemcitabine 1000 mg/m^2 plus docetaxel 75 mg/m^2 versus capecitabine 1250 mg/m^2 plus docetaxel 75 mg/m^2. This particular comparison was performed to assess whether the gemcitabine combination was superior in terms of efficacy and/or toxicity. In terms of efficacy, the

two treatments were equal for all endpoints: progression-free survival, response rate and overall survival. And in terms of haematological toxicity, there were no significant differences between the two arms. When non-haematological toxicity was analysed there was a higher proportion of toxicities, such as diarrhoea, mucositis and hand–foot syndrome, in the capecitabine combination arm. It is interesting to note that the rate of drug discontinuation due to drug-related adverse events in the gemcitabine plus docetaxel arm was approximately half of that in the capecitabine combination arm (13% vs. 27%, $p = 0.002$).

4.4. Bi-weekly schedules

In most clinical trials gemcitabine has been administered using a 3-weekly regimen, with the drug given on days 1 and 8. However, some phase I trials have demonstrated that bi-weekly dosing is possibly one of the best ways of administering gemcitabine to patients. The benefit of this dosing regimen is that up to 5 g of gemcitabine bi-weekly as a single drug can be administered without much toxicity.[8] Fewer gemcitabine dose modifications occur because it is not administered on day 8. Therefore, when gemcitabine is administered in combination with other drugs in bi-weekly schedules, a much higher dose intensity for both drugs can be achieved.[9–12] In addition to this, the synchronised timing of the two drug doses could potentially optimise the synergistic mechanism between gemcitabine and a taxane.

In Spain this approach was developed in two different multicentre clinical trials. In the first trial, gemcitabine 2500 mg/m^2 plus paclitaxel 150 mg/m^2 were administered bi-weekly to 43 previously untreated MBC patients.[13] The overall response rate was 71% and toxicity in general was very low, with only one case of febrile neutropenia observed. Pelegrí et al. used the same number of untreated MBC patients, and administered gemcitabine 2500 mg/m^2 plus docetaxel 65 mg/m^2 bi-weekly.[14] The overall response rate was 75% and the toxicity rate was also very low: only 2 patients suffered febrile neutropenia.

These new approaches to treatment with gemcitabine need randomised comparisons, and the Spanish cooperative group ACROSS is currently enrolling patients for a randomised phase II trial comparing the administration of bi-weekly gemcitabine plus docetaxel with 3-weekly gemcitabine plus docetaxel. A similar trial in the Netherlands and Belgium is also investigating bi-weekly gemcitabine plus paclitaxel dosing.

4.5. Other gemcitabine trials

There are a number of other trials in MBC investigating the combination of gemcitabine plus a taxane. A Danish study comparing the combination of gemcitabine plus docetaxel versus docetaxel alone will present its results in 2008. Comparisons of gemcitabine plus paclitaxel versus gemcitabine plus docetaxel, and gemcitabine plus bevacizumab plus paclitaxel versus bevacizumab plus paclitaxel, are currently being performed in the USA.

There are several ongoing trials that have been designed to explore the different schedules of gemcitabine plus taxane combinations. A Finnish trial is investigating the combination of gemcitabine plus docetaxel versus docetaxel alternating with gemcitabine. Another ongoing trial, performed by the Central European Cooperative Oncology Group, is comparing the sequence of docetaxel followed by gemcitabine versus docetaxel in combination with gemcitabine. The results of both studies will be presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2008.

A phase II clinical trial has also investigated gemcitabine plus albumin-bound paclitaxel, the results of which were presented at the ASCO Annual Meeting in 2006, demonstrating a 50% overall response rate in a patient population that had partly received (>40%) prior taxane treatment. In addition, a phase II clinical trial of gemcitabine in combination with the epothilone B analogue ixabepilone will start in 2008 in the USA.

5. Conclusion

What is the optimal first-line chemotherapy in MBC? From the data described above it is clear that there is no such thing as a single 'gold standard' regimen. In addition, MBC treatment depends on a huge number of characteristics, such as previously administered therapy. The treatment of advanced breast cancer needs effective low-toxicity combination chemotherapy, and gemcitabine plus a taxane is a very good combination for this. The combination of gemcitabine plus paclitaxel has recently been incorporated into the preferred combinations of the National Comprehensive Cancer Network Practice Guidelines in Oncology.[15] Therapies also need to be adapted to the molecular characteristics of tumours and the clinical characteristics of the patient. For example, patients who are positive for oestrogen or hormone receptor expression definitely need some form of hormone therapy, and a patient who is human epidermal growth factor receptor 2-positive will need treatment with trastuzumab. If she has bone metastases the patient will possibly need treatment with zoledronate.

While it is not easy to define a 'gold-standard' chemotherapy regimen for the treatment of MBC, the combination of gemcitabine plus a taxane will be appropriate in many situations, yielding efficacy with reasonable tolerability. Further work examining the scheduling of this combination may lead to improved efficacy.

Conflict of interest statement

The author declares no financial or personal conflict of interest that could inappropriately influence (bias) his work.

The study sponsors had no involvement in the manuscript design; in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

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