Advanced breast cancer: chemotherapy phase III trials that change a standard

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At the present time, there is not a standard regimen in upfront metastatic setting for breast cancer. A wide variety of regimens which includes anthracyclines, taxanes, gemcitabine or capecitabine are currently used, however, there is evidence to support the use of many of these drugs in early breast cancer and consequently limiting their use in first line treatment. The aim of this review is to evaluate every randomized phase III trials conducted in first line metastatic breast cancer. For this reason, all randomized studies that evaluated the role of chemotherapy in advanced breast cancer were analyzed and classified according to their protocol design. So far, sixteen major randomized clinical trials have evaluated the role of chemotherapy as front line in metastatic breast cancer. Some of them have analyzed a different anthracyclines-based regimen as the control arm versus new combinations or new drugs. In others, the aim is to evaluate the most effective therapy after progression to an adjuvant anthracyclines-containing regimen. The suitability of the control arm, the prospective definition of patient's subgroups as well as the statistical methodology have been taken into account. ***Anti-Cancer Drugs*** **18:843–859**

Anti-Cancer Drugs 2007, **18**:843–859

Keywords: advanced breast carcinoma, chemotherapy, optimal regimen

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Introduction

Chemotherapy of patients with metastatic breast carcinoma (MBC) has progressed significantly in recent years. Although the fundamental objective should be palliation of the symptoms caused by the tumor, prolonging survival of women with MBC is also a priority objective. The introduction of new antitumor agents with more specific therapeutical activity comparable or superior to anthracyclines and classic alkylating agents has permitted the conduct of clinical studies that attempt to integrate these new agents into more effective and less toxic treatment regimens for patients with MBC.

With the aim of reviewing the most relevant studies in this area, a group of Spanish oncologists, experienced in this disease, met in Madrid on 2 March 2006. Each expert presented and critically discussed one or more articles whose information could change standard treatment of patients with MBC.

The presentations centered on evaluating the studies, discussing their design, critically analyzing toxicity and efficacy results, and defining whether based on available data, the regimen under consideration should be regarded as standard treatment. The main questions addressed were the advantages and disadvantages of combination therapy vs. monotherapy or sequential therapy, and the regimens that are more effective and better tolerated by these patients.

This paper contains the main points discussed in this meeting. A brief summary of the most relevant data and the aspects considered most important by the panel of experts is presented for each article.

Role of taxane/anthracycline combinations in patients with metastatic breast cancer: review of six phase II/III studies

Jassem J, Pienkowski T, Pluzanska A, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol 2001; 19:1707–1715; Langley RE, Carmichael J, Jones AL, et al. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom National Cancer Research Institute trial AB01. J Clin Oncol 2005; 23:8322–8330; Biganzoli L, Cufer T, Bruning R, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European

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Organization Research and Treatment of Cancer 10961 multicenter phase III trial. J Clin Oncol 2002; 20:3114–3121; Mackey JR, Paterson A, Dirix LY, et al. Final results of the phase III randomized trial comparing (docetaxel), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer. Presented at the 2002 ASCO Annual Meeting, Abstract 137; Bonneterre J, Dieras V, Tubiana-Hulin M, et al. Phase III multicentre randomised study of docetaxel plus epirubicin vs. 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. Br J Cancer 2004; 91:1466–1471; Nabholtz JM, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003; 21:968–975.

Classical chemotherapy of patients with MBC has been based on the combination of an anthracycline (doxorubicin or epirubicin) with other drugs, such as cyclophosphamide and 5-fluorouracil. Demonstration that the taxanes, paclitaxel and docetaxel, are active both as single agents and in combination led to the conduct of randomized studies comparing the combination of a taxane with an anthracycline vs. an anthracycline-containing regimen fluorouracil-epirubicin-cyclophosphamide (FEC), fluorouracil-doxorubicin-cyclophosphamide (FAC), doxorubicin-cyclophosphamide (AC) in patients with MBC.

Six of these studies were discussed, in addition to a meta-analysis [1–7]. Three studies analyzed the inclusion of paclitaxel [1–3] and the other three were with docetaxel [3–6]. The paclitaxel studies included patients with MBC as first-line chemotherapy. A summary of the studies using paclitaxel is provided in Table 1. Only the British study by Langley *et al.* [2] permitted prior use of anthracyclines and used epirubicin as the anthracycline, whereas the other two studies used doxorubicin. The main difference between these studies was in dose and

Table 1 Paclitaxel studies: comparison of characteristics and results

	Dox + paclitaxel vs. FAC (Jassem Study) [1]	Dox + paclitaxel vs. Dox + Cyclo (EORTC study) [3]	Epi + paclitaxel vs. Epi + Cyclo (AB01 study) [2]
Inclusion criteria	First line	First line	First line
	No anthracyclines or taxanes	No anthracyclines or taxanes	Prior anthracyclines permitted. No prior taxanes
	Uni- or bidimensionally measurable disease	Uni- or bidimensionally measurable disease (excluding single bone disease)	Evaluable disease
Treatment	AT: 50 mg/m^2 followed after 24 h by P 220 mg/m^2 over 3 h	AT: 60 mg/m^2 followed after 30 min by P 175 (200) mg/m^2 over 3 h	ET: 75 mg/m^2 followed by P 200 mg/m^2 over 3 h
	FAC: 500/50/500 mg/m^2	AC: 60/600 (750) mg/m^2	EC: 75/600 mg/m^2
	Eight cycles every 3 weeks	Six cycles every 3 weeks	Six cycles every 3 weeks
Objectives	Primary: TP	Primary: TP	Primary: TP
	Secondary: OS, RR and Tx	Secondary: OS, RR and Tx	Secondary: OS, RR and Tx
Statistics	Phase III, randomized 1 : 1	Phase III, randomized 1 : 1	Phase III, randomized 1 : 1
	Sample of 260 pts. 192 events. HR of 1.5 (α=5%, 80% power)	Sample of 260 pts	Sample of 700 pts
	Stratified by prior adjuvant therapy and bone mts	50% improvement in TP (α=5%, 80% power) from 8 to 12 months	Improvement in TP (α=5%, 80% power) from 3 to 5 months
			Stratified by center, previous anthracyclines, site of mts, measurable/evaluable disease and PS
Measurement of response	WHO criteria: CR, PR, SD, PD	WHO criteria: CR, PR, SD, PD	WHO criteria: CR, PR, SD, PD
	TP: randomization to progression or death	TP: randomization to evidence p rogression or death	TP: randomization to progression or death
Population included	259 evaluable pts	275 evaluable pts	705 pts
	66% with visceral involvement and 36% with bone mts	80% with visceral involvement	65% with visceral involvement
	35% with 3 or + mts	25% with 3 or + mts	Prior anthracyclines, 7% in both arms
	45% with prior adjuvant therapy	45% with prior adjuvant therapy	49% with prior adjuvant therapy
Treatment after progression	AT 82% and FAC 74% received some second-line therapy	NA	85% of pts received some treatment
	AT 44% and FAC 48% received CT		ET (6%) and EC (20%) received taxanes after DP
	FAC 24% received taxane		
Results:	TP: AT 8.3 vs. 6.2 months (P=0.034)	TP: AT 6 vs. 6 months (P=0.65)	TP: ET 7 vs. 7.1 months
	OS: AT 23.3 vs. 18.3 months (P=0.013)	OS: AT 20.6 vs. 20.5 months (P=0.49)	OS: 13 vs. 14 months
	RR: AT 68 vs. 55% (P=0.032)	RR: AT 58 vs. 54% (P=0.51)	RR: ET 65 vs. EC 55% (P=0.015)
	Tx: grade 3/4 neutropenia more frequent with AT 89 vs. 65% (P<0.001)	Tx: grade 3/4 neutropenia similar, but more febrile neutropenia with AT (P > 0.001)	Tx: more grade 3/4 toxicity with ET (48%) vs. 38%
		QoL: NA	QoL: not analyzed

AT, doxorubicin-paclitaxel; AC, doxorubicin-cyclophosphamide; CR, complete response; Dox, doxorubicin; EC, epirubicin-cyclophosphamide; EORTC, European Organization for Research and Treatment of Cancer; Epi, epirubicin; ET, epirubicin-paclitaxel; FAC, fluorouracil-doxorubicin-cyclophosphamide; HR, Hazard ratio; mts, metastases; NA, not applicable; OS, Overall survival; PD, progressive disease; PR, partial response; pts, patients; QoL, Quality of Life; RR, Response rate; SD, stable disease; TP, Time to progression; Tx, Toxicity; WHO, World Health Organization.

Table 2 Docetaxel studies: comparison of characteristics and results

	Epi + docetaxel vs. FEC (Bonaterre Study) [5]	Dox + docetaxel vs. Dox + Cyclo (TAX 306 Study Group) [6]	TAC vs. FAC (Mackey study) [4]
Inclusion criteria	First line Prior anthracyclines	First line No anthracyclines or taxanes	First line Prior anthracyclines permitted. No prior taxanes
	Bidimensionally measurable disease	Measurable or evaluable disease	Evaluable disease
Treatment	ET: 75 mg/m^2 followed by T 75 mg/m^2 over 1 h	AT: 50 mg/m^2 followed by T 75 mg/m^2 (200) over 1 h	TAC: 75/50/500 mg/m^2 FAC: 500/50/500 mg/m^2
	FEC: 500/75/500 mg/m^2 Eight cycles every 3 weeks	AC: 60/600 mg/m^2 Eight cycles every 3 weeks	6–8 cycles every 3 weeks
Objectives	Primary: RR Secondary: OS, TP and Tx	Primary: TP Secondary: OS, RR and Tx	Primary: TP Secondary: OS, RR and Tx
Statistics	Phase II, randomized Sample of 200 pts	Phase III, randomized 1 : 1 Sample of 428 pts to ensure improvement in TP (α = 5%, 80% power) from 9 to 13 months	Phase III, randomized 1 : 1 NA
	RR of 65% (α = 5%, 95% power)		
Measurement of response	WHO criteria: CR, PR, SD, PD TP: randomization to evidence of progression or death	WHO criteria: CR, PR, SD, PD TP: randomization to evidence of progression or death	WHO criteria: CR, PR, SD, PD TP: randomization to evidence of progression or death
Population included	142 pts 49% with prior adjuvant therapy and 42% with anthracyclines ET 64% with > 3 mts vs. FEC 44%	423 evaluable pts 62% with visceral involvement 40% with 3 or + mts 42% with prior adjuvant therapy	484 pts 71% with visceral involvement Prior anthracyclines, 11% in both arms 39% with prior adjuvant therapy
Treatment after progression	Received some second-line therapy. NA ET 67.1% and FEC 79.1% received CT Docetaxel as second line in 56.9% of FEC	60% received additional CT AC 40% and AT 12% received taxanes AC 29% received docetaxel	TAC 11% and FAC 38% received docetaxel after progression
Results:	TP: ET 7.8 vs. 5.9 months	TP: AT 37.3 weeks vs. 31.9 months (P = 0.014)	TP: TAC 31 vs. 29 weeks
	OS: ET 34 vs. 28 months RR: ET 59 vs. 32% Tx: febrile neutropenia more frequent with ET 18.6 vs. 0%	OS: AT 22.5 vs. 21.7 months RR: AT 59 vs. 47% (P = 0.009) Tx: higher incidence of grade 3/4 neutropenia and febrile neutropenia with AT (P > 0.01)	OS: 21 vs. 22 months RR: TAC 55 vs. 44% (P = 0.02) Tx: more grade 3/4 neutropenia with TAC (94%) vs. 81%. Febrile neutropenia 29 vs. 5%
	QoL: NA	QoL: similar	QoL: NA

AT, doxorubicin-paclitaxel; AC, doxorubicin-cyclophosphamide; CR, complete response; CT, chemotherapy; Dox, doxorubicin; EC, epirubicin-cyclophosphamide; EORTC, European Organization for Research and Treatment of Cancer; Epi, epirubicin; ET, epirubicin-paclitaxel; FAC, fluorouracil-doxorubicin-cyclophosphamide; FEC, fluorouracil-epirubicin-cyclophosphamide; HR, Hazard ratio; mts, metastases; NA, not applicable; OS, Overall survival; PD, progressive disease; PR, partial response; pts, patients; QoL, Quality of Life; RR, Response rate; SD, stable disease; TAC, docetaxel-doxorubicin-cyclophosphamide; TP, Time to progression; Tx, Toxicity; WHO, World Health Organization.

dosing schedule used for paclitaxel (175–220 mg/m^2), and the time between administration of the anthracycline and the taxane (3–24 h).

All were phase III randomized studies and similar in design. In addition, the primary objective in all six studies was time to progression. The number of patients included ranged from 260 patients in the studies by Jassem and the European Organisation for Research and Treatment of Cancer (EORTC) study to 700 patients in the British study [1–3]. Patient characteristics were well balanced between the different treatment groups and studies, except for the frequency of visceral disease in the EORTC study, which was 80% compared with 65–66% in the other studies. The results obtained varied from one study to the other. In the Israeli study, the doxorubicin-paclitaxel (AT) arm was superior to the control arm in terms of time to progression, response rate and overall survival. The authors attributed these differences in all study parameters to the prolonged interval (24 h) between administration of the anthracycline and paclitaxel [1]. All efficacy parameters were negative in the EORTC study, whereas the British study obtained a higher response rate but a similar time to progression and overall survival with the epuribicin-paclitaxel (ET) combination [2,3]. Hematologic toxicity was superior in patients treated with paclitaxel.

The docetaxel studies were also for first-line therapy and consisted of one randomized phase II study and two phase III studies (Table 2) [4–6]. Unlike the paclitaxel studies, docetaxel was administered in a dose of 75 mg/m^2 1 h after the anthracycline in these three studies. The phase II study by Bonneterre *et al.* [5] included patients with measurable disease who could have received prior anthracycline therapy and compared ET vs. FEC. The primary endpoint of the study was response rate and only 142 of the planned 200 patients were included. The results were favorable to ET in terms of response rate, time to progression and overall survival. Fifty-nine percent of patients treated with FEC received paclitaxel at progression. The other two studies used doxorubicin as

the anthracycline and were phase III randomized studies with time to progression as the primary endpoint. The study by Mackey *et al.* [4] is only available as an abstract and therefore many important details of its design and results are lacking. The TAX 306 study is the only phase III study published to date [6]. The study included 429 anthracycline-naive patients and was designed to detect an increase in time to progression from 9 to 13 months. Treatment with docetaxel resulted in an increase in time to progression from 31.9 to 37.3 weeks ($P = 0.014$), overall survival from 21.7 to 22.5 months ($P = $ NS), and response rate from 47 to 59% ($P = 0.009$). Grade 3/4 neutropenia and febrile neutropenia were more frequent in patients treated with AT.

To put these studies in perspective, the results of a recent review of the literature published by Ghersi *et al.* [7] on the value of taxanes for the treatment of MBC should be considered. The results of this review, which included 6300 patients treated in 21 trials, indicated that women treated with taxane-containing regimens have a higher hazard ratio (HR) for overall survival (HR 0.93, 95% confidence interval: 0.86–1.00, $P = 0.05$), and an improvement in time to progression and response rate. Taxanes were also associated with a higher incidence of hematologic toxicity (leukopenia) and neurotoxicity, but a lower incidence of nausea and vomiting.

Discussion of these studies centered on their design and applicability of the results to daily clinical practice. The study population and primary endpoints selected seem appropriate, but some considerations should be made. Inclusion of patients with measurable disease (in general, patients with visceral disease) may result in higher enrollment of patients with a worse prognosis. Patients with MBC and carcinomatous lymphangitis, ascites or pleural effusion are not included in studies, but make up a significant number of women seen in daily clinical practice. It was also mentioned that the presence of visceral disease is not very informative in itself, as the prognosis of a patient is influenced not only by the presence of visceral disease, but by its volume and location.

Another point discussed was that, from a statistical point of view, the studies were designed to detect very large differences and therefore included a small number of patients, which may have been insufficient to detect small but clinically significant differences. This is based on the belief, as yet insufficiently proven, that taxanes have synergistic activity when combined with anthracyclines in breast cancer. Regarding this, the data from the meta-analysis are very interesting. The primary endpoint in all the studies was time to progression, which was generally well defined. This endpoint allows the inclusion of patients with or without measurable disease, bringing it closer to usual clinical practice. A problem with time to progression is that it is affected by how often patients are evaluated and as these are studies in which the differences are very small, differences in this aspect may be important. Only one study showed an increase in overall survival, the most important clinical parameter [1]. The increase in overall survival in the meta-analysis was minimal and very close to being not significant. A problem with the use of overall survival as the primary endpoint is that many patients receive taxane-containing regimens at progression, which masks the effects on overall survival. This may be the reason why the only study with an increase in overall survival was conducted when taxanes were still not commercially available.

The critical question is whether standard treatment of MBC patients requiring chemotherapy should be the combination of an anthracycline and a taxane. The experts agreed that the key objective in this situation is quality of life. Whereas AT combinations result in a higher response rate and may also improve time to progression, they are associated with higher toxicity. Given that there is no significant impact on overall survival, toxicity is an important factor to be considered.

Some patients may benefit from very aggressive initial treatments. These are patients with very aggressive tumors, visceral disease, good performance status and a poor prognosis. Analysis of the studies, however, does not allow these patients to be clearly identified and therefore the experience of the attending physician still has the greatest weight when deciding treatment. Nevertheless, the available data seem to indicate that it is still reasonable to treat certain patients with single agents or nontaxane-containing combinations.

Superior survival with capecitabine and docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: results of a phase III trial

O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002; 20:2812–2823.

This phase III randomized trial compared single-agent docetaxel 100 mg/m^2 administered on day 1 every 3 weeks with the combination of capecitabine 1250 mg/m^2 twice daily on days 1–14 with docetaxel 75 mg/m^2 on day 1 [8]. The primary objective of the study was time to progression, and secondary objectives included objective response rate, overall survival and quality of life.

A total of 256 patients were included in the control arm and 255 patients in the experimental arm. Patients were comparable in terms of baseline characteristics at randomization. Thus, 39 and 42%, respectively, of

patients were estrogen receptor-positive, and a high number of patients were also observed to have developed metastatic visceral disease, with locally advanced disease being detected in 3 and 2%, respectively, of patients. A similar distribution was observed in both groups with regard to previous treatments (10 and 9%, respectively, of patients had received prior paclitaxel therapy). With regard to the treatment assigned in the two study arms, 35 and 31%, respectively, of patients received study therapy as first-line treatment, and 48 and 53%, respectively, of patients received study therapy as second-line treatment.

The study results showed that capecitabine/docetaxel combination therapy was superior to single-agent docetaxel in terms of the primary endpoint of time to progression (6.1 vs. 4.2 months, $P = 0.0001$), objective response rate (42 vs. 30%, $P = 0.006$) and overall survival (14.5 vs. 11.5 months, $P = 0.01$). Comparing the results of this study with those conducted in patients with similar characteristics but using other treatment regimens, it can be seen that the overall survival of 14.5 months associated with the administration of capecitabine in combination with docetaxel is superior to that of previously available treatments.

Regarding toxicity, the experimental treatment had higher toxicity, with a significantly higher incidence of stomatitis, diarrhea and hand–foot syndrome of approximately 20–30%, compared with less than 5% in patients who received single-agent docetaxel. The lower incidence of febrile neutropenia was also notable, as the dose of docetaxel used in the combination was lower.

Strikingly, the quality of life tests carried out after 18 weeks of combined administration of capecitabine and docetaxel showed no reduction in the quality of life of the patients.

With regard to dose reductions, 65% of patients in the experimental group required a dose reduction compared with 36% of patients who received docetaxel alone. Seventy-eight percent of dose reductions were made in both drugs and most were required during the first cycle.

Discussion of the article focused on analyzing the validity of the study using the importance of the results and applicability of the study as assessment criteria.

It is a valid study in terms of its design, execution and analysis of the results, although it is important to point out that no comment was included on the results in patients who had received prior taxane therapy, which was one of the stratification criteria. The results of the study were positive in all its parameters, which included time to progression, objective response rate, and overall survival. The high incidence of adverse effects, however, is an important barrier to the use of this combination in daily clinical practice. Improved patient selection, based either on clinical criteria or on genetic criteria such as the presence of polymorphisms, is needed to improve tolerance of the combination regimen.

It is important to note the difficulty in analyzing the results of the study in terms of toxicity, because the dose used in the combination was clearly superior to the dose tolerated and used in clinical practice. The most frequently used dose was 1000 mg/m^2. Although it is not known whether reducing the dose to this level would have compromised the study results, on the basis of large proportion of patients who required dose reduction of the combination, the study results most likely reflect the effects of a 1000 mg/m^2 rather than a 1250 mg/m^2 dose.

Although combined administration of capecitabine and docetaxel has high toxicity, the correct information provided to patients on when they should reduce or discontinue treatment allowed this regimen to be administered in higher doses in many cases, depending on the participants' experience.

The results of the study show that despite the higher toxicity of the combination, quality of life of the patients was unaffected. It should be taken into account that analyzing quality of life in this type of trials presents large difficulties. Many of the patients not responding to quality of life tests are patients who withdrew from the study owing to greater toxicity and thus cannot be assessed for quality of life when they probably have the lowest value. Therefore, the results of quality of life tests should be analyzed with caution, as they may show better results than those actually obtained by the patients. Mention was also made of the need to revise the quality of life tests used in these patients because most currently accepted questionnaires are completed in the week before receiving a new cycle, presumably when the patient has recovered from side effects of the treatment.

Gemcitabine and docetaxel vs. capecitabine plus docetaxel for anthracycline-pretreated patients with advanced breast cancer: preliminary results of a phase III trial

Chan S, Romieu G, Huober J, et al. Gemcitabine plus docetaxel (GD) versus capecitabine plus docetaxel (CD) for anthracycline-pretreated metastatic breast cancer (MBC) patients (pts): Results of a European phase III study. Proc Am Soc Clin Oncol 2005, Abstract 581

This was a phase III study comparing gemcitabine plus docetaxel (GD) vs. capecitabine plus docetaxel (CD) in anthracycline-pretreated patients with advanced breast cancer [9]. The rationale for this study was based on

available data at the time of design of the study indicating that combination therapy with either gemcitabine or capecitabine plus taxane was superior to taxane alone in monotherapy. It was also thought, perhaps optimistically, that both the hematologic and nonhematologic toxicity profile of these combination regimens was optimal. The results of phase II trials were also available that indicated that both CD and GD were highly active drugs in anthracycline-pretreated MBC patients. Therefore, the proposed trial comparing the combination of GD vs. CD would provide important information that would allow the optimum treatment to be chosen.

The primary objective of the study was progression-free survival, and secondary objectives included time to treatment failure, objective response rate, and toxicity.

This was a randomized study stratified by first-line or second-line therapy, presence or not of visceral disease, adequate Karnofsky index and patients with or without prior taxane therapy. Patients were randomized to two groups: docetaxel 75 mg/m^2 on day 1 combined with gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days, or docetaxel in the same dose and schedule combined with capecitabine 1250 mg/m^2 twice daily on days 1–14, every 21 days.

The main inclusion criteria were the standard criteria for this type of study, permitting the inclusion of patients who had received neoadjuvant or adjuvant pretreatment with taxanes provided that time to progression was more than 6 months. Statistical design of the study was based on progression-free survival using a design to demonstrate superiority (6 vs. 8.2 months) with a power of 80%.

A total of 305 evaluable patients were included, 153 in the GD arm and 152 in the CD arm. Baseline patient characteristics were comparable in both arms. Four percent and 3%, respectively, of patients had locally advanced disease, and a high percentage of patients (63 and 64%, respectively) had visceral disease of the liver and were estrogen receptor-positive (60 and 65%, respectively). Eleven percent and 9% of patients had received prior taxane treatment.

The results showed equivalence in terms of efficacy parameters, with identical progression-free survival (35 weeks, $P = 0.2$), identical objective response rate (32%, $P = 0.9$), and similar median times to treatment failure of 19 and 18 weeks, respectively ($P = 0.5$). No differences in efficacy parameters were found when patients receiving first-line or second-line therapy or pretreatment with taxanes were compared.

Docetaxel doses were similar in both groups, but there were differences in the relative doses of gemcitabine (73%) and capecitabine (60%) ($P < 0.0001$).

Hematologic toxicity was similar in both arms, but nonhematologic toxicity was higher in the CD arm, especially hand–foot syndrome (26%), diarrhea (17%) and mucositis (13%). The possibility of continuing treatment with taxanes in patients treated in the CD arm after discontinuation of capecitabine owing to toxicity was considered, although this continuation could complicate analysis of the study results.

Overall safety data showed that the incidence of treatment discontinuations owing to treatment-related adverse events was 28% in the capecitabine/docetaxel arm vs. 13% in the gemcitabine/docetaxel arm.

Therefore, comparison of all efficacy measures showed similar results in both treatment arms, with a more favorable toxicity profile in the gemcitabine/docetaxel arm.

Discussion of this study centered on the study design. As previously mentioned, a superiority design was used in the study. Therefore, it was criticized that both combinations were considered equivalent in efficacy in the study conclusions. An equivalence study would have required a much higher number of patients. Consequently, the real conclusion of the study should have been that GD was not superior to CD and not that they were equivalent, because the sample size was insufficient to demonstrate equivalence.

Regarding the inclusion of patients previously treated with taxanes in this type of studies, it was considered appropriate provided that time to progression was more than 6 or 12 months.

Another important point of this study was the greater toxicity of CD, which may have been related to use of a very high dose of capecitabine. The dose chosen for the study, 1250 mg/m^2 twice daily on days 1–14, was based on the approved prescribing information for the product at the time of the study. Subsequent studies showed that this dose was too high and recommended a dose of 1000 mg/m^2, which is the dose currently indicated in the revised prescribing information. The question that remains unanswered is whether the toxicity profile would have been more favorable if a lower dose of capecitabine had been used. The experts discussed the need for clinical studies to use the drug doses and schedules used in daily clinical practice, and not to be limited by the data provided in the product prescribing information, which are not always applicable.

Global phase III study of gemcitabine plus paclitaxel vs. paclitaxel as first-line therapy for metastatic breast carcinoma

Albain KS, Nag S, Calderillo-Ruiz G, et al. Global phase III study of gemcitabine plus paclitaxel versus paclitaxel as frontline

therapy for metastatic breast cancer. Proc Am Soc Clin Oncol 2004, Abstract 510

This was a phase III randomized study comparing gemcitabine plus paclitaxel vs. paclitaxel alone as first-line therapy for patients with MBC [10]. The presentation of the study centered on interim analysis of overall survival. The rationale for this study was based on the activity of gemcitabine as single-agent therapy for this disease, with objective response rates ranging from 22 to 44% and an increase in response rates from 40 to 55% when combined with paclitaxel [11–15].

The study hypothesis was that combined administration of gemcitabine plus paclitaxel to anthracycline-pretreated MBC patients would result in a significantly longer time to progression, higher objective response rates, tolerability and quality of life, and a significant overall survival advantage over paclitaxel alone.

The primary endpoint of the study was overall survival and the coprimary endpoint was time to progression, whose data were previously presented at ASCO 2003. Secondary endpoints included objective response rate, disease-free progression, pain, use of analgesics, and quality of life. In this oral abstract presentation at the 2005 ASCO Annual Meeting, the results of interim analysis of survival were presented.

Patients with locally recurrent or metastatic breast cancer, good performance status, no prior chemotherapy for advanced disease and prior adjuvant chemotherapy with anthracyclines unless contraindicated were included in the study.

The treatment regimens used were paclitaxel (175 mg/m^2 in a 3-h infusion) vs. the same regimen of paclitaxel plus gemcitabine (1250 mg/m^2, days 1 and 8), both administered every 21 days. Treatment was maintained to progression, and disease was evaluated every 8 weeks.

The interim analysis included in this presentation centered on overall survival data. A significance level of 0.0001 was required to conclude that the experimental regimen was superior to paclitaxel alone. The study was conducted from August 1999 to April 2002 and 98 centers from 19 countries participated in the study. A total of 529 patients with similar baseline characteristics were randomized. The majority of patients (96.6% in the gemcitabine and paclitaxel group vs. 95.8% in the paclitaxel group, respectively) had received prior anthracycline therapy and a large proportion (over 40%) had more than three sites of disease, which indicates that it was a population with very advanced disease.

The most important toxicities were grade 3 and 4 neutropenia, which occurred in 31 and 17%, respectively, of patients treated with gemcitabine plus paclitaxel vs. 4 and 7%, respectively, of patients treated with paclitaxel alone. A higher incidence of asthenia was observed in patients treated with the combination (grade 3 in 6%), compared with 1% in patients from the control group.

Efficacy data showed a statistically significant increase in both objective response rate (40.8 vs. 22.1%) and time to progression (5.2 months in the experimental group vs. 2.9 months in the control group).

The data included in the presentation showed an improvement in median overall survival in patients treated in the experimental arm vs. the control arm (18.5 vs. 15.8 months). Although significant ($P = 0.018$), the result of the interim analysis did not reach the previously mentioned statistical significance level of 0.0001 required to conclude superiority of the experimental arm.

The study conclusions indicated that the combination of gemcitabine and paclitaxel is a very promising regimen in terms of overall survival, but it is necessary to wait until completion of the study before definitive conclusions can be made on the efficacy parameters analyzed. The authors concluded that the combination of gemcitabine and paclitaxel can be considered a doublet regimen with similar activity in patients with MBC to other combinations such as capecitabine and docetaxel or herceptin and taxanes.

The discussion of this study centered on various aspects. First, attention was called to the wide diversity of regimens and doses of gemcitabine used in breast cancer patients in clinical practice, which complicated justification of the regimen selected and dose used in this study. Second, it should be emphasized that selection of single-agent paclitaxel as the control arm is debatable because previous studies have shown that paclitaxel in this dose and dosing schedule has very limited activity in patients with MBC, weekly administration being a more appropriate regimen for this type of patient. It should, however, also be mentioned that the data on the superiority of weekly paclitaxel vs. 3-weekly regimens were not known at the time of the design of this study.

The experts also discussed the fact that both the oral presentation and previous presentation of the same study in 2003 showed considerable confusion regarding the primary and secondary endpoints of the study. It is striking that analysis of toxicity was not considered a secondary endpoint in this presentation. Selection of an 8-week interval for performing efficacy analysis in the study using a 3-weekly dosing regimen was also criticized.

The most important point in the presentation was that as it was an interim analysis, the level of significance required to conclude that the experimental arm was superior to the control arm was greater than the usual 5%, with a value of 0.0001 being chosen in this study. We will see later that this statistical detail has great relevance for the real conclusions of the study.

The patients randomized in this study were representative of women with advanced breast cancer and comprised a population with a large metastatic burden as a large proportion of patients had three or more sites of metastasis. The inclusion of patients who had not received prior anthracycline therapy is questionable because it was a very small group (3–4%) and only confounded the study results.

As previously mentioned, the presentation did not include a statistical analysis of the experimental regimen vs. paclitaxel alone with regard to toxicity, when the data showed a clearly higher incidence of asthenia and neutropenia with the combination.

Although the authors' conclusion that combination therapy was associated with increased survival has a *P* value that meets conventional criteria for statistical significance, it should not be forgotten that it was an interim analysis and did not reach the prespecified significance level. Therefore, the result of the interim analysis would conventionally be viewed as negative, which is not consistent with the optimism of the authors who present the combination regimen as another option for the treatment of patients with MBC.

Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: intergroup trial (E1193)

Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: and intergroup trial (E1193). J Clin Oncol 2003; 21:588–592.

This was a randomized study conducted by the US Eastern Cooperative Oncology Group (ECOG) [16]. The rationale for the study was based on the following points: (1) doxorubicin was considered the most efficacious and active drug in MBC patients until the arrival of taxanes, and (2) at the time when this study was designed 10 years ago, phase II studies with taxanes had shown a high objective response rate (about 50% for paclitaxel), and it was thought that polychemotherapy was associated with a higher objective response rate, a longer time to progression, and increased overall survival and therapeutic efficacy [17,18]. This study therefore attempted to answer the question of whether the combination of doxorubicin with a taxane was superior to either of these two drugs administered as single agents.

It was a randomized trial with three arms including doxorubicin (60 mg/m^2), paclitaxel (175 mg/m^2) and the combination of doxorubicin (50 mg/m^2) and paclitaxel (150 mg/m^2) administered every 3 weeks. Although specific details are not given in the article, administration of granulocyte colony-stimulating factor (G-CSF) was permitted in the combination arm, which may have influenced the development of hematologic toxicity, as shown by the results.

Patients randomized to anthracycline could receive up to eight cycles or until disease progression. The study had a crossover design and patients receiving single-agent doxorubicin or paclitaxel were crossed over to the other agent at the time of progression. The number of cycles was not limited in the study.

The study objectives included objective response rate, time to treatment failure, overall survival and quality of life. The article did not specify which of these were primary endpoints and which were secondary endpoints.

Inclusion criteria were the standard criteria in this type of study and included: patients with MBC, although inclusion of some patients with stage III disease was permitted; measurable or evaluable disease; good performance status and adequate bone marrow, renal and hepatic function; adjuvant chemotherapy, although a progression-free interval of 6 months was required; both adjuvant and first-line hormonal therapy in patients with advanced disease.

Patients with ischemic heart disease, cardiac conduction abnormalities, thromboembolic disease, pregnancy or other neoplasms were excluded. Use of adjuvant anthracycline or taxane regimens was not permitted. Prior administration of radiotherapy was initially prohibited, but the protocol was subsequently amended to permit the inclusion of patients who had received radiotherapy to less than 25% of bone marrow reserve.

The study was designed to detect a 15% improvement in overall response rate between any pairwise comparison of treatments and a 50% improvement in time to treatment failure in any of the pairwise comparisons.

Baseline efficacy of doxorubicin treatment was set at an objective response rate of 30–35%, with a median time to treatment failure of 6–8 months. Bonferroni correction was used for multiple comparisons. It was determined that a total of 220 patients were required in each study arm to detect with a power of 84% and a *P* of 0.05 using a one-sided test an increase in the objective response rate from 35–50% and an increase in time to progression from 6 to 9 months.

A total of 739 patients were entered in the trial, of which eight were not evaluable. Therefore, the total number of evaluable patients in the three study arms was distributed as follows: 245 patients in the doxorubicin arm, 242 in the paclitaxel arm, and 244 in the combination arm. Patients' characteristics were similar in the three arms. The median age was 56–58 years, and 25–27% of patients were estrogen-receptor negative. Hormone receptor status was unknown in nearly 30% of patients. Sixty to seventy percent of patients had visceral disease, and 47–53% had metastatic disease in more than three sites. Regarding previous treatment, 67–69% of patients had received prior hormonal therapy.

With respect to toxicity, all three treatments were well tolerated. The most common toxicity was leukopenia (49–59%), with no significant differences between the three arms. It is important to note that prophylactic treatment with colony-stimulating factors was permitted in the combination arm. Other toxicities, such as anemia and thrombocytopenia, were more frequent in the combination arm.

Regarding efficacy results, the combination arm was associated with a statistically significant higher objective response rate of 47 vs. 36% (doxorubicin arm) vs. 34% (paclitaxel), as well as an increased time to treatment failure [8.2 months (combination) vs. 6 months (doxorubicin) vs. 6.3 months (paclitaxel)]. No significant differences were observed in overall survival between the three arms (22.4 vs. 19.1 vs. 22.5 months, respectively).

Multivariate analysis of survival indicated that the factors associated with decreased survival were negative estrogen receptor status, visceral dominant disease, three or more sites of metastatic disease, shorter progression-free interval and having received prior systemic treatment.

A total of 129 patients initially receiving doxorubicin were crossed over to paclitaxel. Similarly, a total of 128 patients initially receiving paclitaxel were crossed over to doxorubicin. The article does not give details on the number of cycles received before or after crossover. It is not specified whether patients receiving doxorubicin were crossed over because they had received the maximum of eight cycles or because they had progressed. The objective response rate in patients who received crossover therapy was 22% (crossover from doxorubicin to paclitaxel) and 20% (crossover from paclitaxel to doxorubicin), respectively; time to treatment failure was 4.5 and 4.2 months, respectively. Overall survival was 14.9 and 12.7 months.

No significant differences were observed in quality of life in the three arms and the scant variation in the quality of life parameters studied was notable.

The study conclusion was that polychemotherapy with anthracyclines and taxanes did not have a significant impact on overall survival compared with sequential therapy with either drug class alone. Factors specific to the biology of the tumor adversely affect survival and not the treatment modality selected. Coadministration of anthracyclines and taxanes is more toxic, and although it improves the objective response rate and time to treatment failure, it does not improve quality of life scores. Therefore, it appears that it cannot be concluded from this study that anthracyclines and taxanes act synergistically when administered concomitantly for the treatment of MBC.

Although this was an ambitious study in attempting to answer the question on the use of monotherapy vs. polychemotherapy for MBC, it lacks many specific details that are now considered necessary for randomized phase III studies published in international journals. It should be stressed that the article provides very few details on treatment during crossover and it is unclear whether the crossover criterion used was time to treatment failure or time to disease progression. It is not clearly indicated whether patients who discontinued owing to toxicity were crossed over or not. Moreover, the use of CSFs in the combination arm clearly confounded the incidence of neutropenia. It is also striking that use of G-CSF is mentioned in the abstract but not referred to later in the article in the description of the treatment used and the references to toxicity.

Phase III study of intravenous vinorelbine in combination with epirubicin vs. epirubicin alone in patients with metastatic breast cancer: Scandinavian Breast Group Trial (SBG 9403)

Ejlertsen B, Mouridsen HT, Langkjer ST, et al. Phase III study of intravenous vinorelbine in combination with epirubicin versus epirubicin alone in patients with advanced breast cancer: A Scandinavian Breast Group Trial (SBG9403). J Clin Oncol 2004; 12:2313–2320.

This was a phase III randomized study comparing the efficacy of a combined regimen of vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 90 mg/m^2 on day 1 vs. epirubicin 90 mg/m^2 on day 1 as first-line therapy for patients with MBC [19]. The primary objective of the study was progression-free survival, whereas response rate, toxicity and overall survival were secondary objectives. Sample size calculation was performed according to the so-called triangular test method in which sample size is estimated at every 50 events on the basis of progression-free survival in both arms using the PEST computer program. Time-dependent events were analyzed using the log-rank test and the multivariate

Cox regression model was used to analyze prognostic factors.

A total of 387 patients were enrolled who met standard inclusion criteria such as women 18–75 years of age with MBC, measurable or evaluable disease, good Karnofsky index (< 2), and adequate hepatic, cardiac and renal function. Patients with peripheral neuropathy, prior radiotherapy of more than 25% of bone marrow reserve and those who had received prior anthracycline therapy were excluded. The two treatment groups were comparable, with a median age of 55 years, the only significant difference being that the number of patients with positive estrogen receptors was 10% higher in the epirubicin group. Both groups received very high dose intensities, which were comparable between groups, with a median of eight to nine cycles. Efficacy analysis was evaluated by an external committee. Progression-free survival was superior in the vinorelbine plus epirubicin arm, with a median of 10.1 vs. 8.2 months in the epirubicin arm ($P = 0.019$). Correction of the progression-free survival analysis for interim analyses and stratification factors reduced the P value ($P = 0.038$), but it remained significant.

The multivariate analysis identified tumor stage at diagnosis, performance status, number of organs involved, presence or not of visceral involvement and treatment with vinorelbine. Patients who received treatment with vinorelbine had a HR for progression-free survival of 0.75 (95% confidence interval: 0.61–0.92). The response rate was also superior in the combination arm (50 vs. 42%), but did not reach statistical significance. It is interesting to observe that patients in the combination had a 7% higher complete response rate. Overall survival was 19.1 vs. 18 months, with no significant difference between the two arms. The combination arm was more toxic, with a significant higher incidence of hematologic toxicity, infections, stomatitis and peripheral neuropathy ($P < 0.05$ in all cases).

The discussion centered on the following points: the study was positive in that it met the primary study endpoint of progression-free survival. The statistical design of the study, however, was very peculiar because it used a method for calculation of sample size that is not commonly used in oncology. It is also important to note that combined therapy was more toxic and was not associated with increased overall survival.

The key question is whether there is a group of patients whose personal characteristics, tumor extension, visceral metastases and rapidly progressive disease (or patients in whom rapid cytoreduction is desired) make it recommendable to use more aggressive combination regimens as initial therapy. No studies exist at present that allow this group of patients to be clearly identified.

Concomitant vs. sequential administration of epirubicin and paclitaxel as first-line therapy in patients with metastatic breast carcinoma: results for the Gruppo Oncologico Nord Ovest randomized trial

Conte PF, Guameri V, Bruzzi P, et al. Concomitant versus sequential administration of epirubicin and paclitaxel as first-line therapy in metastatic breast carcinoma: results for the Gruppo Oncologico Nord Ovest randomized trial. Cancer 2004; 101: 704–12.

This was a phase III randomized open-label study of first-line therapy for MBC in 18 centers, with one clearly dominant center where the majority of patients were enrolled and other centers where the enrollment rate was much more limited [20]. The study hypothesis was that concomitant treatment with anthracyclines and taxanes is associated with a higher objective response rate and greater toxicity, whereas sequential treatment with the same drugs has a lower objective response rate, less toxicity and a lower cost, with no significant difference in terms of impact on survival between the two treatment strategies.

A noninferiority design was used to evaluate sequential vs. concomitant treatment ($\delta = 15\%$), but with a better toxicity profile and quality of life. The justification for this selection was based on the fact that a less than 15% difference in response rates would not result in differences in survival, whereas sequential treatment would be associated with a better toxicity profile and quality of life. The study had a statistical power of 80% and an α error of 0.05 (one-tailed). It was determined to include a total of 266 patients.

The primary objective of the study was the objective response rate, and secondary objectives included complete responses at 4 and 8 months of treatment, progression-free interval, overall survival, and quality of life.

The statistical design of the study presents two basic problems: (1) the 15% increase in objective response rates is slightly higher than what is usually expected with these treatments and therefore not very realistic, and (2) use of a one-tailed statistical test is not usual in this type of studies, with two-tailed statistical tests being generally preferred.

The results of the study were analyzed by intent-to-treat. Toxicity monitoring was performed during the study. No interim analyses were performed. Responses were analyzed using the Mantel–Hansel test. The study design was stratified by centers and results were evaluated every two cycles, with the measurement of left ventricular ejection function every two cycles.

Survival analysis was performed using the log-rank test, and quality of life using the EORTC C-30 test at baseline and after two, four and eight cycles.

The doses used in concomitant treatment were epirubicin (90 mg/m^2) plus paclitaxel (200 mg/m^2) in a 3-h infusion, up to a maximum of eight cycles. The doses used in sequential treatment were epirubicin (120 mg/m^2) for four cycles followed by paclitaxel (250 mg/m^2) for four cycles. One of the major problems of this study was the use of the maximum tolerated doses of the drugs in sequential treatment and that dose adjustments were not considered for the toxicities observed. Consequently, a large number of patients in this arm could experience severe grade 3/4 toxicities, preventing them from completing treatment owing to the design of the study itself. It is important to take into account this point in the analysis of the study results.

Prior use of adjuvant anthracyclines was permitted, with a maximum dose of doxorubicin of 240 and 360 mg/m^2 of epirubicin, although the doses of anthracyclines to be received were not adjusted according to the doses previously received – another important point for analysis of the results.

A total of 202 patients were included. The study was prematurely closed after 4.5 years of recruitment because it failed to demonstrate the hypothesis for which it was designed. Seventy-six percent of patients had an ECOG performance status of 0, 38% had not received adjuvant chemotherapy, whereas 49% had received adjuvant chemotherapy, which in 50% of these patients consisted of epirubicin. Overall, 74.2% of patients had visceral metastases. The median disease-free interval was 28.5 and 36.6 months, which is within the expected range for a population of patients with MBC.

Patient characteristics were similar in both groups, although small differences were observed in the percentages of patients with metastasis at baseline, which was higher in the concomitant arm.

The results of the study indicated, contrary to what was planned, that sequential treatment was not less effective. In fact, objective response rates were nearly identical (58.5 vs. 57.6%, $P = 0.023$), and progression-free (11 and 10.8 months) and median overall survival (20 and 26 months) were also similar.

Two points related to the efficacy analysis should be noted. (1) The publication of the study is rather confusing regarding the efficacy evaluation. The probability value of 0.023 provided by the authors does not indicate that there are statistically significant differences between the two treatments, but that the probability that the treatments are significantly different is very small, and in fact the difference between the two treatments was only 2.3%. (2) The difference of 6 months in median survival (20 vs. 26 months) did not reach statistical significance, suggesting that the sample size was very small.

It should be noted that sequential treatment was more toxic than concomitant treatment, with a higher incidence of neutropenia and neuropathy ($P = 0.003$), although no differences were observed in quality of life tests. This is reasonable because the doses of the drugs used in the sequential arm were very high, the maximum tolerated doses, and the study did not include any procedure for dose adjustment. Therefore, it is very likely that if lower doses or dose adjustment procedures had been used in patients who developed toxicity, the incidence of toxic effects would have been smaller. For reasons that are not clearly explained, the study was closed prematurely.

Regarding tolerability, 33.7% of patients in the sequential arm and 14.1% in the concomitant arm were able to receive the complete treatment. A high incidence of grade 3/4 neutropenia was experienced by 62.2% of patients in the sequential arm and 50.6% in the concomitant arm. A very high incidence of grade 2/4 neuropathy (45.5% in the sequential arm and 30.4% in the concomitant arm) was observed. A total of nine patients, six with congestive heart failure (concomitant arm) and eight patients (sequential arm) experienced severe adverse effects.

Despite the fact that neither one of the two premises proposed in the initial hypothesis were met, the study authors considered that both treatment options were valid for the management of patients with MBC.

Some limitations are related to this study. For example, no left ventricular ejection function data were presented, although it is indicated that they were collected every two cycles; no dose adjustment was made according to the cumulative doses of anthracyclines; the doses chosen for doxorubicin and paclitaxel were not sufficiently justified; no toxicities requiring dose adjustment were anticipated, and, finally, no data were provided on the proportion of the dose received of each drug.

Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: Spanish Breast Cancer Study Group (GEICAM-9903) phase III study

Alba E, Martín M, Ramos M, et al. Multicenter randomized trial comparing sequential with concomitant administration of

doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: a Spanish Breast Cancer Study Group (GEICAM-9903) phase III study. J Clin Oncol 2004; 22:2587–2583.

This was a phase III, multicenter, prospective, open-label study conducted by the Spanish Breast Cancer Study Group (GEICAM), which included patients from 25 Spanish centers recruited in the period from December 1999 to December 2001 [21].

The rationale for conducting this study was based on the data available in 1998 showing that taxanes were very active as single agents in breast carcinoma and that docetaxel was the most active taxane. It had also been shown that the combination of taxanes and doxorubicin had an adequate tolerance profile and superior efficacy to the classic combination of doxorubicin and cyclophosphamide, although long-term results were not available and are still not available, especially on superiority in terms of survival.

It was also notable that these regimens had greater toxicity, with an incidence of febrile neutropenia of around 30–40%. Subsequently, phase II studies were conducted in which the combination of anthracyclines and taxanes was administered sequentially instead of concomitantly, and it was shown that these regimens had less toxicity when administered every 3 months, with comparable efficacy.

Patients were randomized in this study to two arms: sequential treatment with doxorubicin 75 mg/m^2 followed by docetaxel 100 mg/m^2 (sequential arm) or concomitant administration of doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 (concomitant arm). Inclusion of patients previously treated with anthracyclines was permitted, but dose modifications were required in these patients. Thus, the cycles of anthracyclines were reduced from three to two in the sequential arm, whereas the cycles of the combination were reduced from six to three in the concomitant arm, administering docetaxel as a single agent in the last three cycles.

Treatments were administered every 3 weeks, accompanied by premedication with corticosteroids for docetaxel. Use of CSFs was not permitted, except for secondary prophylaxis of febrile neutropenia.

The primary objective of the study was to evaluate whether sequential doxorubicin and docetaxel reduced hematological toxicity, especially febrile neutropenia, compared with concomitant administration of the same drugs. Secondary objectives included objective response rate, time to progression, duration of response and overall survival.

Sample size calculation was carried out to detect a reduction in the incidence of febrile neutropenia in the sequential arm from 36 to 19%. This required the inclusion of 72 patients per arm to obtain a power of 80% ($\alpha = 0.05$, one-tailed).

One of the problems in the design of this study was that inclusion of patients previously treated with anthracyclines could cause confusion regarding toxicity, because the cycles were not exactly the same between patients previously treated or not with anthracyclines in the two treatment arms.

The inclusion criteria were the standard criteria for this type of studies, i.e. patients with MBC; good performance status; good bone marrow, renal, hepatic and cardiac function; patients who had not received prior chemotherapy for metastatic disease; and time to progression more than 6 months since last adjuvant treatment.

Patients who had received a cumulative dose of doxorubicin or equivalent dose of epirubicin exceeding 300 mg/m^2 were excluded.

Baseline patient characteristics were comparable in both groups; the only significant difference was the higher percentage of patients previously treated with anthracyclines in the sequential arm.

Eighty-one percent of patients in the sequential arm completed treatment, compared with 67% of patients in the concomitant arm.

Regarding the primary study endpoint, patients receiving sequential treatment had a significantly lower incidence of febrile neutropenia, both per patient (47.8 vs. 29.3%) and per cycle (14.8 vs. 6.9%). Overall, patients in the sequential arm had a lower incidence of adverse effects. The incidence of adverse effects requiring withdrawal of treatment was 1.2% in the sequential arm vs. 14.5% in the concomitant arm ($P = 0.0027$). A significantly lower incidence of asthenia (15.9 vs. 6.7%, $P = 0.05$) and fever of other etiologies (5.8 vs. 1.3%, $P = 0.04$) was also observed.

Regarding secondary endpoints, no significant differences were observed in any of the efficacy parameters between the sequential and concomitant arms, including objective response rates (61 vs. 51%), time to progression (10.5 vs. 9.2 months) and overall survival (22.3 vs. 21.8 months).

It can be concluded from the study results that (1) the sequential regimen significantly reduced the number of febrile neutropenia episodes compared with concomitant AT administration; (2) the efficacy of both treatments

Table 3 Comparison of characteristics and results of the three studies

Author	*N*	Scheme	Primary endpoint	Febrile neutropenia (%)	RR (%)	TTP	G-CSF prophylaxis
Conte [20]	202	EP	Phase III	7.3	58	11 months	No
		E→P	RR	5.7	57.6	10.8 months	
Cresta [22]	123	AT	Randomized	22	63	36 weeks	No
		Alternating T/A	Phase II	7	52	34 weeks	Ciprofloxacin prophylaxis in second randomization
		Sequential A→T	RR	0	61	33 weeks	
Alba [21]	144	AT	Phase III	47.8	51	9.2 months	No
		A→T	Febrile neutropenia	29.3	61	10.5 months	

G-CSF, granulocyte colony stimulating factor, TTP, time to tumour progression; RR, response rate.

was similar, although the study did not have sufficient statistical power to detect moderate differences; and (3) the sequential regimen is a safe alternative to concomitant administration in first-line chemotherapy of MBC.

The discussion centered on the quality of the study, which successfully answered an important question chosen as the primary objective of the study. The design of the study was adequate, with a sufficient sample size to analyze the proposed primary endpoint. The patient groups were comparable, and both the scientific and methodological quality of the study was of high standard. Therefore, it can be concluded that the results of the study were valid.

The results of this study was put in perspective by comparing them to the results of two other randomized studies carried out by Conte *et al.* and Cresta *et al.* [20,22]. These authors reached virtually identical conclusions that sequential treatment significantly reduced febrile neutropenia compared with concomitant treatment, without altering the objective response rate or other efficacy parameters (Table 3).

The most relevant question is whether or not these drugs are the treatment of choice for patients with MBC. It appears clear that it was for the patients included in this study and that sequential administration may also be the appropriate treatment in patients with more aggressive disease, where the trend is to use combined treatments.

Phase III study of weekly paclitaxel via 1-h infusion vs. standard 3-h infusion every third week in the treatment of metastatic breast cancer, with trastuzumab for HER2 + metastatic breast cancer and randomized for trastuzumab for HER2 normal metastatic breast cancer

Seidman A, Berry D, Cirrincione L, et al. Phase III study of weekly paclitaxel via 1-hr infusion vs. Standard 3-hr infusion every third week in the treatment of metastatic breast cancer, with trastuzumab for HER2 + MBC and randomized for trastuzumab for HER2 normal. CALGB 9840. Presented at the 2004 ASCO Annual Meeting, Abstract 512.

This phase III randomized study (CALGB 9840) attempted to answer two questions: (1) to determine the efficacy of weekly paclitaxel 1-h infusion vs. 3-h infusion every third week in patients with MBC and (2) to assess the effect of trastuzumab in patients with HER2-negative MBC [23]. The rationale for this study was based on the documented efficacy of weekly taxanes in patients with MBC and the lack of data on the efficacy of trastuzumab in patients with HER2-negative MBC. In fact, the presence of a HER2-negative tumor does not mean that the membrane receptor is totally lacking, but that the receptor is present in a smaller amount.

The primary study endpoint was response rate, whereas secondary objectives included progression-free survival, overall survival and toxicity. The study also included a number of correlative studies including measurement of circulating levels of HER2, differences in determination of HER2 levels depending on the use of a central or local laboratories and quality of life. Patients were stratified by first or second-line therapy and HER2 overexpression (positive/negative).

The study design was modified several times during the course of the study, which complicates analysis of the results. The study was initiated in 1998 as a randomized study of weekly paclitaxel and paclitaxel every 3 weeks. First, when trastuzumab was introduced in 2000, all patients with HER2-positive MBC were treated with this drug, whereas patients with HER2-negative MBC were randomized to trastuzumab. Second, the dose of weekly paclitaxel was modified from 100 to 80 mg/m^2 weekly owing to the incidence of neurotoxicity. Finally, predesigned study analyses included patients treated with paclitaxel 175 mg/m^2 enrolled in another study (study CALGB 9342) [24]. This study, which compared the efficacy of three dose levels of paclitaxel (175, 210 and 250 mg/m^2) in patients with MBC, showed no benefit with higher doses of paclitaxel.

A total 700 patients were included, 350 per arm, assuming that 580 patients would be from this study and 120 patients from study CALGB 9342. As all patients from CALGB 9342 had received paclitaxel every 3 weeks,

randomization of this study was performed in a 6 : 4 ratio so that the different arms would be balanced.

Regarding patient characteristics, it is important to note that while only 20% of patients from the CALGB 9840 study received second-line therapy, 75% of patients from the CALGB 9342 study received second-line therapy. This created an imbalance between the two arms as the number of patients who had received second-line therapy in the paclitaxel 3-weekly arm was higher. A multivariate analysis was performed to attempt to correct this disproportion.

The results showed that weekly paclitaxel was associated with a significantly higher response rate (40 vs. 28%) and that trastuzumab played no role in patients with HER2-negative tumors. These results were maintained after multivariate analysis, indicating that the dosing regimen had a significant impact on objective response rates, whereas line of therapy and addition of trastuzumab did not. When patients from the CALBG 9342 study were excluded from the analysis, however, the results, were not as positive for weekly paclitaxel and thus may have influenced the results obtained. Weekly paclitaxel was associated with a significant improvement in time to progression (9 vs. 5.1 months) and overall survival from 16 to 24 months (not significant). If patients from CALGB 9342 are excluded, however, overall survival of patients treated with paclitaxel every 3 weeks was 22 months and not 16 months, indicating that inclusion of the group of patients led to a worsening of efficacy parameters in the control group.

Regarding toxicity, the data showed that patients treated with paclitaxel every 3 weeks had more hematologic toxicity, with a significant difference in the incidence of neutropenia (15 vs. 5%, $P = 0.013$), whereas patients who received paclitaxel on a weekly schedule had more neurosensory (23 vs. 12%, $P = 0.0019$) and neuromotor toxicity (8 vs. 4%, $P = 0.04$).

It is important to note that, as previously mentioned, when toxicity and efficacy data were analyzed in patients treated with 80 mg/m^2 vs. those who received 100 mg/m^2, a lower incidence of neurotoxicity (30 vs. 19%) and a higher response rate (29 vs. 45%) was observed.

The authors concluded that weekly paclitaxel was more effective in response rate and time to progression in patients with MBC, and has a different toxicity profile. On the other hand, the data indicated that trastuzumab was not effective in patients with HER2-negative MBC.

The most important finding on which the discussion focused was that HER2-negative patients did not benefit from trastuzumab treatment. The superior efficacy of weekly paclitaxel to paclitaxel every 3 weeks is complicated by the inclusion of patients from the CALGB 9342 study who had received paclitaxel as second-line therapy. This created a disproportion in the number of patients treated in first-line or second-line therapy, which most likely significantly modified the efficacy of the treatments.

Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer

Jones SE, Erban J, Overmoyer B, et al. Randomized Phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005; 23:5542–51.

This randomized phase III study compared the efficacy and safety of docetaxel 100 mg/m^2 every 3 weeks vs. paclitaxel 175 mg/m^2 in a 3-h infusion every 3 weeks in patients with MBC, either as second-line therapy after systemic anthracycline-based chemotherapy for metastatic disease or in patients who had progressed after a progression-free interval of less than 1 year after adjuvant anthracycline therapy [25].

The primary objectives of the study included objective response rate and toxicity. Secondary objectives of the study were treatment duration, time to progression, overall survival and quality of life.

In the analysis of the study, the experts noted the long recruitment period of 7 years required to recruit a total of 449 patients in 53 centers.

Regarding patient characteristics, the most striking aspect was the difference in expression of estrogen markers between the patients randomized to the two treatment groups (51% in the docetaxel group vs. 42% in the paclitaxel group), although the difference did not reach statistical significance. The impact of this difference on the final results, however, is not really known.

The efficacy analysis showed that patients in the docetaxel group had a higher objective response rate (32 vs. 26%, $P = 0.1$; difference not significant), and longer duration of response (7.5 vs. 4.6 months; $P = 0.01$) and time to progression (5.7 vs. 3.6 months; $P < 0.001$). Median overall survival was of 15.4 months in the docetaxel group compared with 12.7 months in the paclitaxel group ($P = 0.03$).

Regarding treatment duration, it is interesting to observe that patients in the paclitaxel group received a median of four cycles compared with six cycles in the docetaxel group. The reasons for discontinuing treatment included disease progression (75% in the paclitaxel group vs. 47% in the docetaxel group), whereas discontinuations owing

to toxicity showed the opposite distribution, with 26% of patients discontinuing treatment owing to toxicity secondary to docetaxel vs. 8% of patients in the paclitaxel group. It is also important to note that 15% of patients in the docetaxel group discontinued treatment by their own decision vs. 7% of patients in the paclitaxel group.

The discussion on efficacy centered on the relevance of the increase in survival with a significance value of 0.03. This value is below the significance level of 0.05 usually required in phase III randomized clinical trials and there has recently been a trend to consider only studies having a significance level below 0.01 as truly significant. Although this significant level of 0.03 is acceptable for the primary endpoints of the study, a more rigorous significant level of 0.01 tends to be required for analysis of secondary endpoints, including survival.

Regarding toxicity, patients in the docetaxel group had a higher incidence of febrile neutropenia (15 vs. 1.8%, $P < 0.001$), and neurotoxicity and asthenia were also more common in this group.

Analysis of quality of life was carried out using the FACT-B questionnaire, with no significant differences being observed between the two groups.

The authors of the study concluded that docetaxel every 3 weeks was superior to paclitaxel every 3 weeks in terms of response rate and time to progression. Docetaxel showed a trend to improve overall survival and the greater toxicity of docetaxel was not associated with a worsening of quality of life.

To put in perspective the results of this study, the experts discussed the preliminary results of the E-1999 study presented at the Breast Cancer Symposium held in San Antonio, Texas, USA, in December 2005.

In this trial, patients who had received adjuvant therapy were randomized after four cycles of anthracycline/cyclophosphamide to four different taxane regimens: docetaxel every 3 weeks; weekly docetaxel; paclitaxel every 3 weeks or weekly paclitaxel.

Although the study results are preliminary, after a follow-up of 4 years, the authors demonstrated that progression-free survival was approximately 80% in the four study arms. Notable in this study was the trend toward better tolerance and a longer progression-free interval in patients treated with weekly paclitaxel, whereas patients treated with weekly docetaxel experienced a significant increase in toxicity.

Consequently, the results of the study by Jones *et al.* [25] should be analyzed with caution. Probably, weekly administration is the best scheme for paclitaxel treatment. Although docetaxel administrated every 3 weeks is superior to paclitaxel at the same interval, a comparison is warranted between 3 weeks docetaxel and weekly paclitaxel.

A randomized phase III trial of paclitaxel vs. paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer

Miller KD. E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab for metastatic breast cancer. Clin Breast Cancer 2003; 3:421–422.

This randomized phase III trial conducted by the ECOG compared the efficacy and safety of the combination of paclitaxel and bevacizumab as first-line therapy in patients with MBC [26]. The rationale for the conduct of this study was based on: (1) the universality of angiogenesis as the pathogenic mechanism in carcinogenic tumors; (2) the efficacy of bevacizumab as single-agent therapy in patients with MBC, with a 9% objective response rate; and (3) the results of a previous study comparing the efficacy of bevacizumab in combination with capecitabine vs. capecitabine alone in patients with MBC, which showed that the combination doubled the response rate from 9 to 19%, although it did not have a significant impact on time to progression because the patients were heavily pretreated.

The primary objective of the study was progression-free survival, establishing an increase from 6 to 8 months as statistically significant. To detect this difference with a type I error of 2.5%, inclusion of at least 650 patients was required. The study compared administration of paclitaxel at a dose of 90 mg/m^2 on days 1, 8 and 15, every 28 days alone or in combination with bevacizumab at a dose of 10 mg/m^2 on days 1 and 8.

The study started in December 2001 and ended in March 2004. In total, 680 patients with locally recurrent or MBC, good performance status and absence of proteinuria were enrolled. Patients with a previous history of hypertension were excluded. Patients were stratified by progression-free interval (more than or less than 24 months), number of sites of metastatic lesions, prior adjuvant therapy and hormonal receptor status.

The results presented, which include the analysis performed in September 2005, included a total of 484 events. The patients analyzed had similar prognostic characteristics in both groups and it was significant that a small number of patients with HER2-positive tumors were included in the study. The combination had a higher response rate than paclitaxel alone (37.7 vs. 15%) in patients with measurable disease. A significant increase in

time to progression (11.4 vs. 6.11 months) was also observed in all patient groups analyzed. No significant differences were observed in overall survival (25.2 vs. 28.4 months).

With respect to toxicity, there was a higher incidence of grade 3 hypertension (15% in the experimental group vs. 2% in the control group), and proteinuria and bleeding episodes were more frequent with combination therapy, although the frequency of these events was less than 2%. A higher, although moderate, incidence of tiredness was also observed in patients treated with the combination. Analysis of quality of life showed a similar profile in both treatment groups.

The most relevant aspects of this study included selection of paclitaxel as the control arm, and applicability of the results to daily clinical practice. Objective response rates in the control arm were apparently lower than those obtained when this regimen is used as first-line therapy for the treatment of MBC, but in a large phase II study conducted by Perez *et al.* [27] only 21% of the patients registered a response with weekly administration of paclitaxel.

It is also important to take into account the high cost of this medication and that its clinical applications will necessarily be related to improvements in knowledge of the factors that make patients more susceptible to treatment with antiangiogenic agents, which are presently unknown.

Conclusion

This point is also related to duration of bevacizumab treatment in patients receiving the drug. Although treatment was discontinued in this study at disease progression, in other diseases, such as colon cancer, there is a tendency to continued bevacizumab treatment for prolonged periods after progression. The impact of treatment duration on overall survival is not known. Given the importance of other mediators of angiogenesis in patients with breast cancer as the disease progresses, it has been postulated that blockade of a single mediator via administration of bevacizumab is unlikely to have a very prolonged effect on time to progression in these patients.

The trend in the adjuvant setting is to incorporate drugs that have demonstrated to be active in advanced disease, therefore limiting the available therapeutic resources once disease relapses. Enough evidence exists to support the routine use of taxanes and anthracyclines for the adjuvant treatment of node-positive breast cancer patients. Patients that may be excluded from this recommendation are defined by the exclusion criteria of the corresponding clinical trials. For the group of patients that receive taxanes and anthracyclines in the adjuvant treatment, the recommendations for first-line metastatic disease are some of the polychemotherapy regimens extensively discussed in this article that include active drugs such as capecitabine, gemcitabine or vinorelbine. The re-introduction of taxanes is left to the investigator's criteria, taking into the account the disease-free survival and side effects.

With regard to high-risk node-negative breast cancer patients, the antracycline-based regimens are considered the standard option. At this point, there is not enough evidence to justify the routine use of taxanes. Several clinical trials are currently testing the role of anthracyclines and taxanes in node-negative breast cancer patients. These trials are still ongoing and the results will be available very soon. The preliminary results are very promising and in the near future it is possible that the standard of care in early breast cancer will be most likely anthracyclines and taxanes. Consequently, the first line of chemotherapy in MBC is likely to change and drugs that are currently administered as a second or third line such as capecitabine, vinorelbine or gemcitabine will be definitely moved to upfront therapy. Capecitabine is one of the most effective drugs after failure to anthracyclines and taxanes treatment. It, however, has been evaluated as second, third or subsequently lines.

One of the most necessary research projects is the search for new predictive factors of response (gene expression profile, polymorphisms) in the metastatic disease in such a way that we could look for the maximum potential benefit of a certain drug (alone or in combination) with the minimum related side effects. Hence, for instance, a woman with liver metastasis could benefit from either the combination of gemcitabine and vinorelbine or the monotherapy administration.

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