27
Advanced Breast Cancer: Treatment with Docetaxel/Epirubicin

A.G. Pallis, V. Georgoulias, and V. Mavroudis

INTRODUCTION

Metastatic breast cancer (MBC) remains a fatal disease despite the great amount of research performed in recent years and the progress achieved. The median survival of patients with MBC is ~ 18–24 months after the initial diagnosis of metastases (Dickson *et al*., 2005). Hence, the principal goals of treatment are palliation of symptoms and prolongation of survival while maintaining or improving the quality of life. Many drugs have been approved for the treatment of MBC and among them the taxanes and anthracyclines represent the two major chemotherapy classes commonly used in daily practice.

EPIRUBICIN

Anthracyclines are considered to be the most active drugs in the treatment of MBC. Single agent doxorubicin has significant activity against MBC, with overall response rates (ORR) ranging from 35% to 50%, in chemotherapy-naïve patients (Ellis *et al*., 2000). Until recently, doxorubicin was one of the most active single agents available against MBC and doxorubicin-containing regimens were considered the "standard" of care in first and second line treatments (A'Hern *et al*., 1993). Epirubicin, another anthracycline agent, has similar single agent activity with doxorubicin as first-line treatment in MBC with response rates of 25–62% (Launchbury and Habboubi, 1993); but its toxicity profile is more favorable, especially in terms of cardiotoxicity, compared to doxorubicin (Ganzina, 1983; Launchbury and Habboubi, 1993). Due to its faster elimination leading to a reduced area under the curve than equimolar doses of doxorubicin, epirubicin can be given at higher doses (120–180 mg/m^2 every 3 weeks) (Feld *et al*., 1992) and with a dose-response curve favoring dose intensification (Bastholt *et al*., 1996; Brufman *et al*., 1997).

DOCETAXEL

The taxanes, paclitaxel, and docetaxel, exert their antineoplastic properties by promoting the *in vitro* assembly of stable

microtubules in the absence of guanosine triphosphate and thus, inducing microtubule-bundle formation inside the cells (Rowinsky, 1997). Paclitaxel was the first taxane proven to be active against MBC (Holmes *et al*., 1991; Nabholtz *et al*., 1996). Docetaxel is a semi-synthetic taxane derived from 10-deacetyl bacatin III (Gueritte-Voegelein *et al*., 1991) and was developed later. Several clinical phase II and III trials reported significant activity as 1st- and 2nd-line therapy in MBC, as well as in patients previously exposed or resistant to anthracyclines (Chan *et al*., 1999; Crown, 2001; Nabholtz *et al*., 1999). As a single agent, docetaxel has achieved response rates of 54–68% in previously untreated patients (Cortes and Pazdur, 1995) and 41% in patients with anthracycline-resistant disease (Ravdin, 1997), suggesting that there is no significant cross resistance with anthracyclines. Moreover, docetaxel is active even in patients with paclitaxel-refractory disease (Valero *et al*., 1998). In randomized phase III studies, docetaxel, but not paclitaxel, was more active than doxorubicin in patients with MBC (Chan *et al*., 1999; Paridaens *et al*., 2000). Furthermore, docetaxel seems to be less cardiotoxic than paclitaxel (Verweij *et al*., 1994). Taken together, these data indicate that docetaxel is a highly active chemotherapeutic agent for the treatment of MBC.

ANTHRACYCLINE-TAXANE COMBINATION

Given that both taxanes and anthracyclines lack cross resistance and are both highly active agents against MBC, their combined use is a logical step. A randomized phase III Intergroup trial, evaluating doxorubicin (60 mg/m^2) versus paclitaxel (175 mg/m^2) versus doxorubicin/paclitaxel combination (50/150 mg/m^2), reported a higher response rate in favor of the doxorubicin/paclitaxel doublet. Response rate was 36% for doxorubicin, 34% for paclitaxel, and 47% for the combination ($p = 0.84$ for doxorubicin vs paclitaxel, $p = 0.007$ for doxorubicin vs doxorubicin/paclitaxel, $p = 0.004$ for paclitaxel vs doxorubicin/paclitaxel combination). However, no significant difference regarding overall survival and quality of life was reported. Patients receiving single agent doxorubicin or paclitaxel crossed over to the other agent, and this may have diluted any survival benefit (Sledge *et al*., 2003). Furthermore, the paclitaxel/doxorubicin combination has been associated with a high incidence of cardiotoxicity (Gehl *et al*., 1996).

On the contrary, docetaxel has not been associated with cardiotoxicity (Verweij *et al*., 1994). Doxorubicin has also been combined with docetaxel in the setting of randomized phase III trials. TAX 306 randomized 429 patients to doxorubicin/docetaxel (50/75 mg/m^2) versus doxorubicin/cyclophosphamide (50/600 mg/m^2) combinations (Nabholtz *et al*., 2003). Time to tumor progression (TTP) was the primary end point. Doxorubicin/docetaxel doublet was more active than doxorubicin/cyclophosphamide in terms of response rate (59% vs 47%, $p = 0.009$) and TTP (median TTP, 37.3 v 31.9 weeks; log-rank $p = 0.014$); however, overall survival (OS) was similar in the two arms. Given the significant activity of the docetaxel/doxorubicin combination in MBC and the fact that epirubicin has similar single agent activity with doxorubicin although

with a more favorable toxicity profile, the docetaxel/epirubicin combination is a logical doublet to study.

Docetaxel-Epirubicin Combination

Phase I studies

Several phase I studies have evaluated the maximum tolerated doses (MTD) and the dose limiting toxicities (DLT) of docetaxel in combination with epirubicin. First, the Greek Breast Cancer Cooperative group (GBCCG) enrolled 47 chemotherapy-naïve patients in a phase I study, to determine the MTD and the DLT of the Docetaxel/Epirubicin doublet (Kouroussis *et al*., 1999). Docetaxel was given as a 1-h infusion after appropriate premedication on either day 1 or 2 in escalated doses with increments of 10 mg/m^2. Epirubicin was given first as a 5-min bolus i.v., infusion on day 1 in escalated doses with increments of 10 mg/m^2. When the two drugs were given on the same day, the MTD was reached at the doses of Epirubicin 60 mg/m^2 and Docetaxel 80 mg/m^2; administration of prophylactic G-CSF could not result in further dose intensification. When the drugs were given on two consecutive days, the MTD2 was reached at the doses of Epirubicin 80 mg/m^2 (d1) and Docetaxel 90 mg/m^2 (d2). The dose-limiting events were febrile neutropenia and grade 4 neutropenia, which developed in 30 (64%) patients during the study; among 227 delivered cycles, grade 3–4 neutropenia occurred in 64 (28%) cycles but only 22 (10%) of them were complicated by fever. There were no septic deaths. Grade 1–2 neurosensory toxicity occurred in nine (19%) patients. Four (9%) patients presented a greater than 10% decrease of LVEF and treatment discontinuation was required in two of them. However, none of the patients developed congestive heart failure. Nevertheless, one patient suddenly died 10 days after treatment initiation of myocardial ischemia, and this death was considered treatment-related. Regarding efficacy, five (14.7%) complete and thirteen (38.2%) partial responses (ORR: 53.9%; 95% confidence interval: 36.1–69.7%) were observed in 34 evaluable patients.

At the same time an Italian group (Pagani *et al*., 1999) conducted a dose-finding study to determine the MTD of the combination with or without granulocyte-colony stimulating factor (G-CSF) support. Forty-two patients who had previously received neither palliative chemotherapy nor adjuvant anthracyclines, were treated on four dose escalating levels with Epirubicin 75–120mg/m^2 and Docetaxel 75–85 mg/m^2 given on the same day with epirubicin administered first. Cardiac toxicity was monitored at baseline and after every second course by echocardiography. Febrile neutropenia and prolonged, severe neutropenia (absolute neutrophil count (ANC) $< 0.1 \times 10^9$/l for more than 3 days) were the DLT. The MTD of the combination without G-CSF support was Epirubicin 90 mg/m^2 and Docetaxel 75 mg/m^2. With the subsequent administration of G-CSF, the MTD was established at Epirubicin 120 mg/m^2 and Docetaxel 85 mg/m^2. No severe neurotoxicity, mucositis, or fluid retention were observed and there were no clinical signs of cardiotoxicity. The overall response rate in 40 evaluable patients was 60% (95% CI: 43–75%) with no apparent dose-response effect.

A third study published later by Venturini *et al*. recommended for future

phase II studies the Epirubicin 75 mg/m^2 and docetaxel 80 mg/m^2 combination (Venturini *et al*., 2001). Fifty-eight women with locally advanced or metastatic breast cancer were included in that study. Docetaxel administration was started at 60 mg/m^2 with escalated increments of 10 mg/m^2, in association with two fixed doses of epirubicin (90 mg/m^2, and 75 mg/m^2). The authors also studied a third group with prophylactic G-CSF support in order to determine the MTD of docetaxel in combination with a fixed dose of 90 mg/m^2 of epirubicin. In the first group, the MTD was docetaxel 60 mg/m^2 and epirubicin 90 mg/m^2. Dose limiting toxicities were neutropenia, febrile neutropenia, while there was one toxic death. In the second group (75 mg/m^2 of epirubicin) the MTD for docetaxel was 80 mg/m^2. Neutropenia and febrile neutropenia were again the DLTs, while one patient developed grade III mucositis. In the third group (epirubicin 90 mg/m^2) with G-CSF administration, docetaxel was escalated up to 90 mg/m^2. DLTs were febrile neutropenia and grade III myalgia. Most frequent non-hematological adverse effects were asthenia (45%), nausea (39%) and mucositis (36%). No patient developed congestive heart failure. Two toxic deaths occurred. Overall response rate was 73% (42 out of 58 patients) with no apparent epirubicin dose-response effect.

Finally, a study by Viens *et al*. (2001) included 27 women with MBC having measurable and/or evaluable disease. Epirubicin was escalated from 60 to 110 mg/m^2 according to five different dose levels, in combination with a fixed dose of 75 mg/m^2 docetaxel. Dose-limiting toxicities consisted of grade III asthenia and febrile neutropenia (epirubicin 75 mg/m^2), grade IV thrombocytopenia and grade III asthenia (epirubicin 90 mg/m^2), grade IV stomatitis and grade III diarrhea (epirubicin 100 mg/m^2), and grade III diarrhea (epirubicin 110 mg/m^2). In three patients a decrease of left ventricular ejection was observed, which normalized during follow-up. Based on the above data, the recommended doses were epirubicin 100 mg/m^2 epirubicin and 75 mg/m^2 docetaxel.

TOXICITY OF THE DOCETAXEL-EPIRUBICIN COMBINATION

In terms of toxicity and safety, the phase I studies cited above (Kouroussis *et al*., 1999; Pagani *et al*., 1999; Venturini *et al*., 2001; Viens *et al*., 2001) indicated that the major toxicity of the combination was haematological. Neutropenia and its consequences were the main toxicities associated with the combination. Approximately, 28–87% of chemotherapy cycles were complicated with grade III–IV neutropenia. However, febrile neutropenia was less frequent and septic deaths were rare. Secondly, non-hematological toxicities were relatively mild. The most common non-hematological toxicities were asthenia, mucositis, and diarrhea. Thirdly, and perhaps most importantly, the docetaxel/epirubicin combination did not result in any significant increase in anthracycline cardiotoxicity.

This was further confirmed by a Finnish study (Salminen *et al*., 2003). The aim of that study was to evaluate clinical and subclinical cardiac toxicity of docetaxel/epirubicin combination. Previously untreated breast cancer patients were given epirubicin (75 mg/m^2 for 15 min), followed

1 h later by a 1-h infusion of docetaxel (75 mg/m^2). Cardiac function was monitored using a 24-h ambulatory electrocardiogram (ECG), left ventricular ejection fraction (LVEF), physical examination, and chest radiography. The median LVEF did not decrease during the course of the treatment: pretreatment median LVEF was 64% prior to treatment and 68% after cycle 8, while the 24-h ECG did not reveal any considerable changes in heart rate variability. Furthermore, the number of extrasystoles or cardiac arrhythmias did not increase with the epirubicin-docetaxel treatment. No patient experienced congestive heart failure during treatment or after a mean follow-up of 34 months.

PHARMACOKINETIC DATA

In a phase I/II study of the paclitaxel with epirubicin combination, it was observed that the pharmacokinetics of paclitaxel were not modified by the administration of epirubicin; on the contrary, the metabolism of epirubicin was affected, with a reduction of epirubicinol levels as the paclitaxel dose increased (Conte *et al*., 1997). This observation justified the evaluation of pharmacokinetic interactions in the docetaxel/epirubicin combination. In order to study these interactions, Ceruti *et al*. (1999) administered epirubicin (75 mg/m^2) and docetaxel (75 mg/m^2) to 16 patients with MBC according to two different schedules: (1) docetaxel as infusion given 1 h after epirubicin administration (schedule A); and (2) docetaxel as infusion given immediately (10 min) after the end of epirubicin i.v., bolus administration (schedule B). The conclusion was that a significant increase in epirubicin clearance was seen when moving from schedule A to schedule B. The difference in docetaxel clearance was less evident and statistically non significant.

1. Phase II studies of the Docetaxel/Epirubicin combination

Based on the encouraging results of phase I studies, the docetaxel/epirubicin combination was evaluated in phase II studies. The phase I study by the GBCCG, was further expanded into a multicenter phase II study. Fifty four women with advanced breast cancer (stage IIIB/IV) were treated with epirubicin (70 mg/m^2, day 1) and docetaxel (90 mg/m^2, day 2), as first line treatment (Mavroudis *et al*., 2000). The median age of patients was 55 years, while the vast majority (91%) had performance status of 0–1. In an intent to treat analysis, the overall response rate (ORR) was 66% (95% confidence interval 54–79%), with five patients (9%) achieving complete response (CR) and 31 (57%) partial response (PR). Stable disease (SD) was observed in nine (17%) and progressive disease (PD) in nine (17%) patients. After a median follow-up period of 11.5 months, the authors reported a median duration of response of 8 months, a median TTP of 11.5 months, while the median overall survival (OS) had not been reached at the time of publication of that study. The probability of 1-year survival was calculated at 65%. The major haematological toxicity was grade III/IV neutropenia, which was observed in eight (15%) and 31 (57%) patients, respectively. Febrile neutropenia, was also common, occurring in 19 (35%) patients; however, it was always successfully treated with intravenous antibiotics.

Prophylactic G-CSF was used in 45 (83%) patients, or 226 (74%) cycles. The major non-hematological toxicity was grade III and IV diarrhea, occurring in four (7%) and one (2%) patients, respectively. All other toxicities were generally mild. Five patients (9%) presented a more than 10% decrease of LVEF during treatment; however, none of the patients developed congestive heart failure or had to stop therapy due to cardiotoxicity. During treatment there were two deaths, due to respiratory insufficiency, without associated neutropenia. The authors considered those deaths possibly treatment-related either due to the immunosuppressive properties of the regimen, or due to a probable pulmonary toxicity of the combination (Mavroudis *et al*., 2000).

A second phase II study of the combination was reported by Milla-Santos *et al*. (2001). They used high dose epirubicin (130 mg/m^2, day 1) with docetaxel administered 1 h following epirubicin at a dose of 100 mg/m^2, with prophylactic administration of G-CSF on days 4–13. A total of 32 patients were included in the study and 236 chemotherapy cycles were administered. The ORR was 87.5% (95% confidence interval 77–98) with 11 (34.4%) patients achieving a CR and 17 (53.1%) patients with PR. The major toxicity was neutropenia (2.9% of cycles were delayed 3–6 days because of neutropenia) despite the prophylactic administration of G-CSF. After a median follow-up of 490 days, the authors reported a median TTP of 490 days and a median OS of 604 days. The significantly higher response rate yielded in this study, compared with the above mentioned Greek study, could be attributed to the higher epirubicin dose used. A clear dose-response relationship for single agent epirubicin (up to a dose of 90 mg/m^2) has been shown in postmenopausal women with MBC (Bastholt *et al*., 1996). Furthermore, doubling of the epirubicin dose intensity (100 mg/m^2 versus 50 mg/m^2) in the FEC regimen, significantly increased the complete and overall response rates but not the overall survival, especially in patients with visceral metastases or multiple metastatic organ sites (Brufman *et al*., 1997).

In an Italian phase I–II, the docetaxel/epirubicin combination was administered (in the phase II part) at the doses of 75 mg/m^2 and 90 mg/m^2, respectively. A total of 70 patients were included in both parts of the study (Pagani *et al*., 2000). The ORR in 68 evaluable patients was 66% (95% confidence interval: 54–73%). After a median follow-up time of 22 months (range 4–39+), the median TTP was 4.5 months and the median duration of response was 8 months (range 3–16).

Another phase II study including 38 women with MBC was reported by a Finnish group (Salminen *et al*., 2002). This study used a regimen of epirubicin (75 mg/m^2) and docetaxel (75 mg/m^2), both drugs administered on day 1. The ORR reported 54% (95% confidence interval 37–71), with a median duration of response of 14.8 months (95% confidence intervals 8.8–27.8). Median TTP was 12 months and median OS 26 months. Neutropenia grade IV was observed in 113 (39%) of the 285 chemotherapy cycles administered; 21 patients were hospitalized due to febrile neutropenia. The authors' conclusion was that epirubicin/docetaxel regimen needed further dose reduction and tailoring in order to avoid the high incidence of grade IV neutropenia.

The same regimen (epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2) was used in a

large phase II study reported by Morales *et al*. (2004), which included 133 patients with MBC. This study also reported a high ORR of 67%, with an impressive CR rate of 23%. The median TTP was 10.8 months (95% confidence interval: 9.7–12.6) and the median OS was 19.5 months. The major toxicity was grade III/IV neutropenia which occurred in 35%, while febrile neutropenia was observed in 19% of patients. Granulocyte colony-stimulating factor support was administered to 32% of patients and in 22% of cycles. The most frequent grade 3/4 non-hematological toxicities were asthenia (6%), vomiting (5%) and nausea (5%). No patients developed congestive heart failure.

An Italian group used higher doses of both drugs in a small phase II study of 25 patients with MBC (Fabi *et al*., 2004). Patients were treated with the combination of epirubicin 90 mg/m^2 plus docetaxel 90 mg/m^2, with prophylactic G-CSF administration. Overall response rate was 79%, with 21% of these patients achieving CR. The median response duration was 10 months (range: 3–16). The main toxicity was grade III/IV neutropenia (41% of cycles) regardless of the use of G-CSF; while febrile neutropenia was observed in 14% of cycles necessitating a dose reduction of both drugs in 30% of patients. The median TTP was 11 months and the overall 3-year survival was 49.7%. Despite the use of higher doses, the ORR observed in this series was comparable with that seen in other studies of epirubicin/docetaxel combination. However, as the authors comment, the degree of myelosuppression was severe, despite the prophylactic administration of G-CSF, and therefore, they recommend a lower dose of both drugs.

Finally, the Minnie Pearl Cancer Research Network reported a small phase II study (Hainsworth *et al*., 2006). Thirty patients with MBC were treated with docetaxel 60 mg/m^2 and epirubicin 90 mg/m^2 as first line treatment; both drugs were repeated at 21-day intervals. Objective responses were observed in 50%; an additional 20% of patients had stable disease of more than 6 months duration. The median and 2-year progression-free survival (PFS) was 12 months and the 2-year PFS rate 34%. The median survival was 18 months and the 2-year overall survival rate 42%. Myelosuppression was the most common grade III/IV toxicity, with two (6%) treatment-related deaths due to sepsis.

Based on the high activity of the docetaxel/epirubicin combination reported in the above mentioned studies, Bonneterre *et al*. (2004) conducted a multicenter randomized phase II study in order to compare the efficacy and safety of docetaxel plus epirubicin (ET) combination versus the 5-fluorouracil plus epirubicin and cyclophosphamide (FEC) regimen as first-line chemotherapy for MBC. A total of 142 patients were randomised to receive either docetaxel 75 mg/m^2 plus epirubicin 75 mg/m^2 or 5-fluorouracil 500 mg/m^2 plus epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2, once every 3 weeks for up to eight cycles. Prophylactic granulocyte-colony-stimulating factor was only permitted after the first cycle, if required. In an intent-to-treat analysis, the ORR for docetaxel plus epirubicin combination was 59% (95% CI, 47–70%) and for FEC 32% (95% CI, 21–43%) after a median of seven and six cycles, respectively. The median response duration for ET was 8.6 months (95% CI, 7.2–9.6 months) and for FEC 7.8 months (95% CI, 6.5–10.4 months).

The median TTP for docetaxel plus epirubicin combination was 7.8 months (95% CI, 5.8–9.6 months) and for FEC 5.9 months (95% CI, 4.6–7.8 months). After a median follow-up period of 23.8 months, median OS for docetaxel plus epirubicin and FEC combinations were 34 and 28 months, respectively. Nonhaematologic grade 3–4 toxicities were infrequent in both arms. Hematologic toxicity was more common with ET combination and febrile neutropenia was reported in 13 patients (18.6%) in that group. Two deaths in the docetaxel plus epirubicin group were possibly related to study treatment. The authors concluded that the toxicity of both arms was acceptable, while the taxane/anthracycline combination was significantly more active.

The above mentioned studies confirmed that the docetaxel/epirubicin combination is a highly active regimen as first line treatment of patients with MBC, with observed RR from 50% to 87.5% (Fabi *et al*., 2004; Hainsworth *et al*., 2006; Mavroudis *et al*., 2000; Milla-Santos *et al*., 2001; Morales *et al*., 2004; Pagani *et al*., 2000; Salminen *et al*., 2002). The doses used ranged from 60 mg/m^2 (Hainsworth *et al*., 2006) to 100 mg/m^2 (Milla-Santos *et al*., 2001) for docetaxel and from 70 mg/m^2 (Mavroudis *et al*., 2000) to 130 mg/m^2 (Milla-Santos *et al*., 2001) for epirubicin. Despite the previously reported dose-response relationship for single agent epirubicin (up to a dose of 90 mg/m^2) (Bastholt *et al*., 1996), and the significantly increased ORR by doubling the epirubicin dose (100 mg/m^2 versus 50 mg/m^2) in the FEC regimen (Brufman *et al*., 1997), there were no major differences regarding ORR in the above mentioned studies, using different dose intensities for both drugs. The only exception was the Spanish study, which used the higher doses of both drugs (docetaxel 100 mg/m^2 and epirubicin 130 mg/m^2) (Milla-Santos *et al*., 2001), and reported a high ORR of 87.5%, with 34.3% CR.

The most frequently reported toxicity for the docetaxel-epirubicin combination was neutropenia, as observed in both phase I and II studies. However, febrile neutropenia was much less frequent and septic deaths were rare. All other toxicities were, in general, mild and easily manageable. An interesting observation regarding a higher incidence of central nervous system (CNS) involvement in patients treated with docetaxel/epirubicin was reported by an Italian group, based on a pooled analysis of their phase I and II studies (Pagani *et al*., 1999, 2000). A total of 92 patients were included in these two studies and the authors reported that 28 (30%) of the 92 patients treated with this combination developed CNS metastases; 25 patients developed cerebral metastasis, two leptomeningeal, and one both (Crivellari *et al*., 2001). Median time for the development of CNS metastases from the start of chemotherapy was 15 months (range 5–42), when the six patients presenting CNS progression within 3 months from start of treatment were excluded. It is noteworthy that 11 patients (39%) had disease progression only in the CNS. Although, this observation could be easily explained by the sanctuary site 'hypothesis', as a consequence of an intact blood-brain barrier, this is not proven and the exact explanation remains to be elucidated. The authors conclude that as anthracycline- and taxane-containing regimens are increasingly used both in the metastatic and in the adjuvant setting, a careful monitoring of any neurological symptoms should be advisable.

Taken together, the results of all aforementioned reports clearly indicate that the docetaxel/epirubicin combination is very effective and with manageable toxicity and therefore merits further evaluation in the context of phase III randomized studies. These studies should compare this regimen with other taxane-anthracycline combinations or "standard" anthracycline-based therapies.

REFERENCES

A'Hern, R.P., Smith, I.E., and Ebbs, S.R. 1993. Chemotherapy and survival in advanced breast cancer: the inclusion of doxorubicin in Cooper type regimens. *Br. J. Cancer 67*: 801–805.

Bastholt, L., Dalmark, M., Gjedde, S.B., Pfeiffer, P., Pedersen, D., Sandberg, E., Kjaer, M., Mouridsen, H.T., Rose, C., Nielsen, O.S., Jakobsen, P., and Bentzen, S.M. 1996. Dose-response relationship of epirubicin in the treatment of postmenopausal patients with metastatic breast cancer: a randomized study of epirubicin at four different dose levels performed by the Danish Breast Cancer Cooperative Group. *J. Clin. Oncol. 14*: 1146–1155.

Bonneterre, J., Dieras, V., Tubiana-Hulin, M., Bougnoux, P., Bonneterre, M.E., Delozier, T., Mayer, F., Culine, S., Dohoulou, N., and Bendahmane, B. 2004. Phase II multicentre randomised study of docetaxel plus epirubicin vs 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. *Br. J. Cancer 91*: 1466–1471.

Brufman, G., Colajori, E., Ghilezan, N., Lassus, M., Martoni, A., Perevodchikova, N., Tosello, C., Viaro, D., and Zielinski, C. 1997. Doubling epirubicin dose intensity (100 mg/m2 versus 50 mg/m2) in the FEC regimen significantly increases response rates. An international randomised phase III study in metastatic breast cancer. The Epirubicin High Dose (HEPI 010) Study Group. *Ann. Oncol. 8*: 155–162.

Ceruti, M., Tagini, V., Recalenda, V., Arpicco, S., Cattel, L., Airoldi, M., and Bumma, C. 1999. Docetaxel in combination with epirubicin in metastatic breast cancer: pharmacokinetic interactions. *Farmaco 54*: 733–739.

Chan, S., Friedrichs, K., Noel, D., Pinter, T., VanBelle, S., Vorobiof, D., Duarte, R., Gil, G.M., Bodrogi, I., Murray, E., Yelle, L., von Minckwitz, G., Korec, S., Simmonds, P., Buzzi, F., Gonzalez, M.R., Richardson, G., Walpole, E., Ronzoni, M., Murawsky, M., Alakl, M., Riva, A., and Crown, J. 1999. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J. Clin. Oncol. 17*: 2341–2354.

Conte, P.F., Baldini, E., Gennari, A., Michelotti, A., Salvadori, B., Tibaldi, C., Danesi, R., Innocenti, F., Gentile, A., Dell'Anna, R., Biadi, O., Mariani, M., and DelTacca, M. 1997. Dose-finding study and pharmacokinetics of epirubicin and paclitaxel over 3 hours: a regimen with high activity and low cardiotoxicity in advanced breast cancer. *J. Clin. Oncol. 15*: 2510–2517.

Cortes, J.E., and Pazdur, R. 1995. Docetaxel. *J. Clin. Oncol. 13*: 2643–2655.

Crivellari, D., Pagani, O., Veronesi, A., Lombardi, D., Nole, F., Thurlimann, B., Hess, D., Borner, M., Bauer, J., Martinelli, G., Graffeo, R., Sessa, C., and Goldhirsch, A. 2001. High incidence of central nervous system involvement in patients with metastatic or locally advanced breast cancer treated with epirubicin and docetaxel. *Ann. Oncol. 12*: 353–356.

Crown, J. 2001. Docetaxel: overview of an active drug for breast cancer. *Oncologist 6*: 1–4.

Dickson, R.B., Pestell, R.G., and Lippman, M.E. 2005. Cancer of the Breast. in: Principles and Practice of Oncology, DeVita, V.T., Hellman, S., and Rosenberg, S.A. Eds Lippincott Williams & Wilkins, Philadelphia, 7th Edition: 1399–1487.

Ellis, M.J., Hayes, D.F., and Lippman, M.E. 2000. Treatment of metastatic breast cancer. in: Diseases of the Breast, Lippman, M.E., Morrow, M., and Osborne, C.K., Eds Lippincott, Williams & Willkins, Philadelphia: 749–797.

Fabi, A., Papaldo, P., Pino, M.S., Ferretti, G., Carlini, P., Pacetti, U., Di Cosimo, S., Nardoni, C., Giannarelli, D., Sacchi, I., and Cognetti, F. 2004. Epirubicin plus docetaxel in metastatic breast cancer: escalating dose does not improve efficacy. A phase II study. *Anticancer Res. 24*: 1963–1967.

Feld, R., Wierzbicki, R., Walde, P.L., Shepherd, F.A., Evans, W.K., Gupta, S., Shannon, P., and Lassus, M. 1992. Phase I-II study of high-dose epirubicin

in advanced non-small-cell lung cancer. *J. Clin. Oncol. 10*: 297–303.

Ganzina, F. 1983. 4´-epi-doxorubicin, a new analogue of doxorubicin: a preliminary overview of preclinical and clinical data. *Cancer Treat. Rev. 10*: 1–22.

Gehl, J., Boesgaard, M., Paaske, T., Vittrup, J.B., and Dombernowsky, P. 1996. Combined doxorubicin and paclitaxel in advanced breast cancer: effective and cardiotoxic. *Ann. Oncol. 7*: 687–693.

Gueritte-Voegelein, F., Guenard, D., Lavelle, F., Le Goff, M.T., Mangatal, L., and Potier, P. 1991. Relationships between the structure of taxol analogues and their antimitotic activity. *J. Med. Chem. 34*: 992–998.

Hainsworth, J.D., Yardley, D.A., Spigel, D.R., Meluch, A.A., Rinaldi, D., Schnell, F.M., and Greco, F.A. 2006. Docetaxel and epirubicin as first-line treatment for patients with metastatic breast cancer: a Minnie Pearl Cancer Research Network Phase II trial. *Cancer Invest. 24*: 469–473.

Holmes, F.A., Walters, R.S., Theriault, R.L., Forman, A.D., Newton, L.K., Raber, M.N., Buzdar, A.U., Frye, D.K., and Hortobagyi, G.N. 1991. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J. Natl. Cancer Inst. 83*: 1797–1805.

Kouroussis, C., Xydakis, E., Potamianou, A., Giannakakis, T., Kakolyris, S., Agelaki, S., Sara, E., Malamos, N., Alexopoulos, A., Mavroudis, D., Samonis, G., Papadouris, S., Georgoulias, V., and Panagos, G. 1999. Front-line treatment of metastatic breast cancer with docetaxel and epirubicin: a multicenter dose-escalation study. The Greek Breast Cancer Cooperative Group (GBCCG). *Ann. Oncol. 10*: 547–552.

Launchbury, A.P., and Habboubi, N. 1993. Epirubicin and doxorubicin: a comparison of their characteristics, therapeutic activity and toxicity. *Cancer Treat. Rev. 19*: 197–228.

Mavroudis, D., Alexopoulos, A., Ziras, N., Malamos, N., Kouroussis, C., Kakolyris, S., Agelaki, S., Kalbakis, K., Tsavaris, N., Potamianou, A., Rigatos, G., and Georgoulias, V. 2000. Front-line treatment of advanced breast cancer with docetaxel and epirubicin: a multicenter phase II study. *Ann. Oncol. 11*: 1249–1254.

Milla-Santos, A., Milla, L., Rallo, L., and Solano, V. 2001. High-dose epirubicin plus docetaxel at standard dose with lenograstim support as first-line therapy in advanced breast cancer. *Am. J. Clin. Oncol. 24*: 138–142.

Morales, S., Lorenzo, A., Ramos, M., Ballesteros, P., Mendez, M., Almanza, C., Castellanos, J., Moreno-Nogueira, J.A., Casal, J., Lizon, J., Oltra, A., Frau, A., Machengs, I., Galan, A., Belon, J., and Llorca, C. 2004. Docetaxel plus epirubicin is a highly active, well-tolerated, first-line chemotherapy for metastatic breast cancer: results of a large, multicentre phase II study. *Cancer Chemother. Pharmacol. 53*: 75–81.

Nabholtz, J.M., Gelmon, K., Bontenbal, M., Spielmann, M., Catimel, G., Conte, P., Klaassen, U., Namer, M., Bonneterre, J., Fumoleau, P., and Winograd, B. 1996. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. *J. Clin. Oncol. 14*: 1858–1867.

Nabholtz, J.M., Senn, H.J., Bezwoda, W.R., Melnychuk, D., Deschenes, L., Douma, J., Vandenberg, T.A., Rapoport, B., Rosso, R., Trillet-Lenoir, V., Drbal, J., Molino, A., Nortier, J.W., Richel, D.J., Nagykalnai, T., Siedlecki, P., Wilking, N., Genot, J.Y., Hupperets, P.S., Pannuti, F., Skarlos, D., Tomiak, E.M., Murawsky, M., Alakl, M., and Aapro, M. 1999. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. *J. Clin. Oncol. 17*: 1413–1424.

Nabholtz, J.M., Falkson, C., Campos, D., Szanto, J., Martin, M., Chan, S., Pienkowski, T., Zaluski, J., Pinter, T., Krzakowski, M., Vorobiof, D., Leonard, R., Kennedy, I., Azli, N., Murawsky, M., Riva, A., and Pouillart, P. 2003. 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. 21*: 968–975.

Pagani, O., Sessa, C., Martinelli, G., Crivellari, D., Buonadonna, A., Thurlimann, B., Hess, D., Borner, M., Bauer, J., Zampino, G., Zimatore, M., Graffeo, R., Riva, A., and Goldhirsch, A. 1999. Dose-finding study of epidoxorubicin and docetaxel as first-line chemotherapy in patients with advanced breast cancer. *Ann. Oncol. 10*: 539–545.

Pagani, O., Sessa, C., Nole, F., Crivellari, D., Lombardi, D., Thurlimann, B., Hess, D., Borner, M., Bauer, J., Martinelli, G., Graffeo, R., Zucchetti, M., D'Incalci, M., and Goldhirsch, A. 2000. Epidoxorubicin and docetaxel as first-line chemotherapy in patients with advanced breast cancer: a multicentric phase I-II study. *Ann. Oncol. 11*: 985–991.

Paridaens, R., Biganzoli, L., Bruning, P., Klijn, J.G., Gamucci, T., Houston, S., Coleman, R., Schachter, J., Van Vreckem, A., Sylvester, R., Awada, A., Wildiers, J., and Piccart, M. 2000. Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer Randomized Study with cross-over. *J. Clin. Oncol. 18*: 724–733.

Ravdin, P.M. 1997. Docetaxel (Taxotere) for the treatment of anthracycline-resistant breast cancer. *Semin. Oncol. 24*: 10–17.

Rowinsky, E.K. 1997. The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. *Ann. Rev. Med. 48*: 353–374.

Salminen, E., Korpela, J., Varpula, M., Asola, R., Varjo, P., Pyrhonen, S., Mali, P., Hinkka, S., and Ekholm, E. 2002. Epirubicin/docetaxel regimen in progressive breast cancer-a phase II study. *Anticancer Drugs 13*: 925–929.

Salminen, E., Syvanen, K., Korpela, J., Varpula, M., Antila, K., Varjo, P., and Ekholm, E. 2003. Docetaxel with epirubicin–investigations on cardiac safety. *Anticancer Drugs 14*: 73–77.

Sledge, G.W., Neuberg, D., Bernardo, P., Ingle, J.N., Martino, S., Rowinsky, E.K., and Wood, W.C. 2003. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J. Clin. Oncol. 21*: 588–592.

Valero, V., Jones, S.E., Von Hoff, D.D., Booser, D.J., Mennel, R.G., Ravdin, P.M., Holmes, F.A., Rahman, Z., Schottstaedt, M.W., Erban, J.K., Esparza-Guerra, L., Earhart, R.H., Hortobagyi, G.N., and Burris, H.A. III. 1998. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J. Clin. Oncol. 16*: 3362–3368.

Venturini, M., Michelotti, A., Papaldo, P., Del Mastro, L., Bergaglio, M., Lionetto, R., Lunardi, G., Sguotti, C., Frevola, L., Donati, S., Rosso, R., and Cognetti, F. 2001. Identification of the highest dose of docetaxel associable with active doses of epirubicin. Results from a dose-finding study in advanced breast cancer patients. *Ann. Oncol. 12*: 1097–1106.

Verweij, J., Clavel, M., and Chevalier, B. 1994. Paclitaxel (Taxol) and docetaxel (Taxotere): not simply two of a kind. *Ann. Oncol. 5*: 495–505.

Viens, P., Roche, H., Kerbrat, P., Fumoleau, P., Guastalla, J.P., and Delozier, T. 2001. Epirubicin–docetaxel combination in first-line chemotherapy for patients with metastatic breast cancer: final results of a dose-finding and efficacy study. *Am. J. Clin. Oncol. 24*: 328–335.