

## Extending Survival with Chemotherapy in Metastatic Breast Cancer

JOYCE O'SHAUGHNESSY

Baylor-Sammons Cancer Center, Dallas, Texas, USA

**Key Words.** Metastatic • Overall survival • Docetaxel • Paclitaxel • Trastuzumab • Bevacizumab

### LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify trials that have demonstrated a survival benefit with a modern chemotherapeutic agent or regimen in MBC.
2. Summarize recent findings of randomized trials showing survival benefits with targeted therapy–chemotherapy combinations in MBC.
3. Discuss quality-of-life findings and their implications in clinical practice.

CME

Access and take the CME test online and receive 1 AMA PRA category 1 credit at [CME.TheOncologist.com](http://CME.TheOncologist.com)

### ABSTRACT

Metastatic breast cancer (MBC) remains essentially incurable, and goals of therapy include the palliation of symptoms, delay of disease progression, and prolongation of overall survival time without negatively impacting quality of life. Anthracycline and taxane-based therapies have traditionally shown the highest degree of activity in MBC. Though numerous randomized clinical trials have shown improvements in overall response rates, few have found clear survival benefits. In recent years, however, there has been a small but growing series of clinical trials demonstrating modest, but

meaningful survival advantages in metastatic disease. A common feature in many of these trials has been the use of a taxane, and more recently, a taxane combined with an antimetabolite. In addition, the development of targeted biologic agents active against MBC, such as trastuzumab and bevacizumab, has demonstrated great potential for enhancing the effects of chemotherapy and producing meaningful survival improvements. The role of the taxanes, antimetabolites, and biologics in extending survival in MBC is discussed. *The Oncologist* 2005;10(suppl 3):20–29

### INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women in the U.S. In 2005, an estimated 211,240 new cases of invasive breast cancer are expected to occur [1]. Continuing on a trend established over the past decade, the overall incidence of breast cancer continues to gradually increase. The mortality rate from breast cancer declined approximately 2.3% per year from 1990 through 2001, due in large part to increased awareness, earlier detection, and improved therapies [1]. Nonetheless, it is estimated that 40,410 women in the U.S. will die of breast cancer in 2005,

with breast cancer ranking second only to lung cancer in cancer-related mortality in women.

The majority of breast cancer-related deaths are a result of complications from recurrent or metastatic disease. As an initial presentation, metastatic breast cancer (MBC) is uncommon, occurring in only about 6% of newly diagnosed cases [2]. Despite advances in the treatment of breast cancer, approximately 30% of women initially diagnosed with earlier stages of breast cancer eventually develop recurrent advanced or metastatic disease.

Correspondence: Joyce O'Shaughnessy, M.D., Baylor-Sammons Cancer Center, 3535 Worth St., Collins 5, Dallas, Texas 75246, USA. Telephone: 214-370-1795; Fax: 214-370-1850; e-mail: [joyce.o'shaughnessy@usoncology.com](mailto:joyce.o'shaughnessy@usoncology.com) Received October 3, 2005; accepted for publication October 7, 2005. ©AlphaMed Press 1083-7159/2005/\$12.00/0

There is no single standard of care for patients with MBC, as treatment plans require an individualized approach based on multiple factors. These include specific tumor biology, growth rate of disease, presence of visceral metastases, history of prior therapy and response, risk for toxicity, and patient preference. MBC remains essentially incurable, and current goals of therapy are to ameliorate symptoms, delay disease progression, improve or at least maintain quality of life (QoL), and prolong overall survival.

Chemotherapy is a treatment option for many patients with MBC. There are a number of agents with established single-agent activity, with the anthracyclines and taxanes generally considered the most active. In addition, capecitabine (Xeloda<sup>®</sup>; Hoffmann-La Roche Inc., Nutley, NJ, <http://www.rocheusa.com>), gemcitabine (Gemzar<sup>®</sup>; Eli Lilly and Company, Indianapolis, <http://www.lilly.com>), and vinorelbine (Navelbine<sup>®</sup>; GlaxoSmithKline, Philadelphia, <http://www.gsk.com>) have also demonstrated substantial activity in the metastatic setting [3].

Selection of agents for treatment is an individualized process. The relative benefits and toxicities of individual agents or combinations must be considered as well as the treatment history and clinical status of the patient. Many patients with recurrent disease will already have had substantial anthracycline exposure from adjuvant chemotherapy, and retreatment with doxorubicin (Adriamycin<sup>®</sup>; Bedford Laboratories, Bedford, OH, <http://www.bedfordlabs.com>) or epirubicin (Ellence<sup>®</sup>; Pfizer Pharmaceuticals, New York, <http://www.pfizer.com>) is generally avoided. Taxane-based therapy is often considered for patients with anthracycline-pretreated breast cancer; however, it is becoming increasingly common for patients to have received both an anthracycline and a taxane in the adjuvant setting. Time to recurrence is also an important consideration. If time to recurrence is several years following adjuvant therapy, retreatment with prior active agents may be desirable. If progression or disease recurrence takes place in a relatively short time (i.e., <12 months), the use of different classes of classes of agents is generally preferable.

Capecitabine, a novel, oral fluoropyrimidine carbamate, has been extensively evaluated in anthracycline- and taxane-pretreated MBC. Four large, multicenter trials have evaluated single-agent capecitabine in patients with MBC that has progressed during or following anthracycline and taxane therapy [4–8], showing consistent efficacy and safety data. Response rates of 15%–26% were demonstrated, with a median survival time of approximately 1 year. Capecitabine demonstrated a favorable safety profile in those trials, with predominant adverse events of cutaneous and gastrointestinal events. Myelosuppression was particularly rare, as was alopecia.

The use of combination therapy versus monotherapy or sequential single agents remains a controversial issue [9]. Depending on the individual patient and specific treatment goals, either can be appropriate. Combination therapies generally result in higher overall response rates and times to disease progression than with sequential single agents, but usually at a cost of greater toxicity. In addition, the higher overall response rates with combination therapy versus sequential single agents may not necessarily translate into superior survival outcomes.

Demonstrating this point are the results of Intergroup trial E1193, in which patients were randomized to receive either paclitaxel (Taxol<sup>®</sup>; Bristol-Myers Squibb, Princeton, NJ, <http://www.bms.com>), docetaxel (Taxotere<sup>®</sup>; Aventis Pharmaceuticals Inc., Bridgewater, NJ, <http://www.avenispharma-us.com>), or a combination of the two as first-line treatment of MBC [10]. In both the single-agent arms, patients were crossed over to treatment with the alternate single agent at the time of disease progression. Combination therapy produced a significantly higher overall response rate and longer time to treatment failure than either single agent arm; however, there were no differences in overall survival times among the three arms (Table 1). Other groups have compared combination chemotherapy with sequential therapy in randomized trials (Table 1), showing similar outcomes in terms of response rate and progression-free and overall survival [11–13]. Toxicity was in general less with sequential administration.

Combinations of traditional chemotherapeutics with targeted biologic agents, such as trastuzumab (Herceptin<sup>®</sup>; Genentech, Inc., South San Francisco, CA, <http://www.gene.com>) and more recently bevacizumab (Avastin<sup>®</sup>; Genentech, Inc.), appear to present a new dimension. With the potential to realize clinical synergism between chemotherapy and the biologics, significant improvements in overall survival with the use of these agents in combination have been seen [14–16].

Optimization of chemotherapy for the treatment of MBC remains an ongoing effort. While it is generally accepted that chemotherapy can provide substantial clinical benefit, the potential to positively impact overall survival and QoL remains the subject of debate. This manuscript provides an overview of recent randomized trials in MBC, focusing on survival outcomes and QoL issues.

## CHEMOTHERAPY AND SURVIVAL OUTCOMES IN MBC

In the treatment of MBC, there is an underlying assumption that improvements in overall response rates would translate into long-term survival benefits. While there is indirect evidence to support a relationship between response and

**Table 1.** Results of selected trials of sequential single-agent versus combination chemotherapy as first-line therapy for metastatic breast cancer

Study	Regimen	No. of patients	Median response rate	Median overall time to treatment failure (months)	Survival (months)
Sledge et al. [10]	Paclitaxel	229	34%	6	22.2
	Doxorubicin	224	36%	5.8	18.9
	Doxorubicin + paclitaxel	230	47% <sup>a</sup>	8 <sup>b</sup>	22
Cresta et al. [11]	Docetaxel → doxorubicin	42	52%	7.8	34 <sup>c</sup>
	Doxorubicin → docetaxel	39	61%	7.6	
	Doxorubicin + docetaxel	42	63%	8.3	
Conte et al. [12]	Epirubicin → paclitaxel	94	58%	10.8	26
	Epirubicin + paclitaxel	108	59%	11 <sup>d</sup>	20
Alba et al. [13]	Doxorubicin → docetaxel	54	61%	10.5	22.3
	Doxorubicin + docetaxel	54	51%	9.2	21.8

<sup>a</sup> $p = .017$  for the combination versus doxorubicin;  $p = .006$  for the combination versus paclitaxel.

<sup>b</sup> $p = .0022$  for doxorubicin versus AT;  $p = .0567$  for the combination versus paclitaxel.

<sup>c</sup>Median overall survival time for all groups combined.

<sup>d</sup>Progression-free survival.

overall survival [17–20], few randomized trials have provided direct evidence.

There are indications, though, that with modern chemotherapeutic agents and biologics, progress has been made toward improving survival outcomes in women with MBC. In a population-based analysis of survival outcomes in MBC conducted in British Columbia, the introduction of new agents over the past decade, such as the taxanes, aromatase inhibitors, and trastuzumab, was associated with significant improvements in overall survival times across the population [21].

In addition, there is a small but growing number of randomized clinical trials reporting statistically significant survival improvements in women with MBC [14, 15, 22–30]. A common feature of these studies has been the use of a taxane or combination therapy with a targeted biologic agent such as trastuzumab.

### Taxanes in Anthracycline-Pretreated Patients with MBC

The taxanes docetaxel and paclitaxel are highly active in MBC and have established activity in patients who have been previously treated with anthracyclines, including patients with anthracycline-refractory disease [31, 32]. Taxane-based therapy, therefore, is often a primary option for patients who have previously been treated with anthracycline-based therapy and present with disease progression or recurrence.

A survival advantage with the use of single-agent docetaxel in women with anthracycline-pretreated MBC has been observed in two of four randomized phase III tri-

als (Table 2) [22, 23, 33, 34]. In the first of these studies, 392 patients with progressive MBC following anthracycline-based chemotherapy were randomized to receive either single-agent docetaxel (100 mg/m<sup>2</sup>) or combination therapy with mitomycin (Mutamycin<sup>®</sup>; Bristol-Myers Squibb) (12 mg/m<sup>2</sup>) and vinblastine (Velban<sup>®</sup>; Eli Lilly and Company) (6 mg/m<sup>2</sup>) [22]. The overall response rate, median time to disease progression, and overall survival time were all significantly greater with docetaxel. The median overall survival time with docetaxel was 11.4 months, 2.7 months longer than with mitomycin and vinblastine. While grade 3–4 neutropenia occurred more frequently with docetaxel, other acute adverse events were similar in the two treatment arms. A QoL analysis was conducted, and though interpretation of the results was limited, there were no apparent differences in QoL between treatment groups.

The second study compared single-agent docetaxel (100 mg/m<sup>2</sup>) with single-agent paclitaxel (175 mg/m<sup>2</sup>) in 449 patients with MBC who had previously received first-line metastatic therapy with an anthracycline-based regimen or had disease progression within 12 months of completing anthracycline-based adjuvant or neoadjuvant therapy [23]. The overall response rate in the intent-to-treat population was 32% with docetaxel, compared with 25% with paclitaxel; this difference did not reach statistical significance. The median time to disease progression and median overall survival time were statistically significantly longer in the docetaxel arm (Table 2). Docetaxel was associated with more toxicities than paclitaxel, including grade 3–4 neutropenia, asthenia, edema, infection, and stomatitis.

**Table 2.** Phase III trials with single-agent taxanes in anthracycline-pretreated metastatic breast cancer

Study	Regimen	No. of patients	Overall response rate	Median time to progression (months)	Median overall survival (months)
Nabholtz et al. [22]	Docetaxel	203	30% ( $p < .0001$ )	4.4 ( $p = .001$ )	11.4 ( $p = .0097$ )
	Mitomycin/vinblastine	189	12%	2.5	8.7
Jones et al. [23]	Docetaxel	225	32%	5.7 ( $p < .0001$ )	15.4 ( $p = .03$ )
	Paclitaxel	224	25%	3.6	12.7
Sjöström et al. [33]	Docetaxel	143	42% ( $p < .001$ )	6.3 ( $p < .001$ )	10.4
	Methotrexate/5-fluorouracil	139	21%	3	11.1
Bonnetterre et al. [34]	Docetaxel	86	43%	6.5	16
	5-fluorouracil/vinorelbine	90	34%	5.1	15

Interestingly, there were no statistically significant differences in global QoL scores (as assessed by the Functional Assessment of Cancer Therapy tool) between treatment groups over time, suggesting that toxicity differences did not affect QoL.

Paclitaxel was also directly compared with albumin-bound paclitaxel (ABI-007) in 460 patients with MBC (who had not received prior paclitaxel or docetaxel for MBC) in a randomized phase III trial [35]. ABI-007 was associated with a significantly greater response rate (33% vs. 19%;  $p = .001$ ) and time to tumor progression (23 weeks vs. 16.9 weeks;  $p = .006$ ) than paclitaxel, but median survival rates were similar in the two treatment groups (65 weeks vs. 55.7 weeks, respectively).

Two additional phase III trials compared single-agent docetaxel with either sequential methotrexate and 5-fluorouracil or 5-fluorouracil in combination with vinorelbine (Table 2) [33, 34]. In comparison with sequential methotrexate and 5-fluorouracil, docetaxel produced a significantly higher overall response rate and longer time

to disease progression, but median overall survival was not different between the two treatment groups. Grade 3–4 toxicities, including fatigue, alopecia, and infection, were more frequent with docetaxel. In comparison with the combination of 5-fluorouracil and vinorelbine, no significant differences in response or survival outcomes were seen between study arms, though overall tolerability was greater with docetaxel.

Clinical outcomes with taxane combination regimens in anthracycline-pretreated breast cancer patients have been very encouraging, with significant survival benefits observed in two phase III trials [24–26]. The first of those trials compared the combination of docetaxel (75 mg/m<sup>2</sup>) and capecitabine (2,500 mg/m<sup>2</sup>) with docetaxel alone (100 mg/m<sup>2</sup>) in 511 patients with disease progression or recurrence following anthracycline-based chemotherapy (Table 3) [24]. The overall response rate, median time to disease progression, and median overall survival time were all statistically superior with the combination, with an absolute improvement in median overall survival time of 3 months.

**Table 3.** Phase III trials with taxane combinations in anthracycline-pretreated metastatic breast cancer

Study	Regimen	No. of patients	Overall response rate	Median time to progression (months)	Median overall survival (months)
O'Shaughnessy et al. [24]	Docetaxel and capecitabine	255	42% ( $p = .006$ )	6.1 ( $p = .0001$ )	14.5 ( $p = .0126$ )
	Docetaxel	256	30%	4.2	11.5
Albain et al. [25] and O'Shaughnessy et al. [26]	Paclitaxel and gemcitabine	267	39% ( $p = .0007$ )	5.4 ( $p = .0013$ )	18.5 (HR 0.775; $p = .018$ )
	Paclitaxel	262	26%	3.5	15.8

Abbreviation: HR, hazard ratio.

The incidences of grade 3–4 adverse events were similar in both treatment groups, and though these rates were relatively high, treatment was generally tolerable. Gastrointestinal adverse events and hand-foot syndrome were more common with combination therapy, whereas febrile neutropenia, sepsis, arthralgia, and myalgia were more common with single-agent docetaxel. QoL scores were similar in the two treatment arms, and overall global health quality was generally maintained over time.

For patients treated with docetaxel alone, crossover to single-agent capecitabine was not mandatory. A subsequent survival analysis suggested that patients who received capecitabine following docetaxel had a longer median survival time than patients receiving other poststudy chemotherapy agents [36]. Although retrospective, these data suggest that sequential administration of docetaxel and capecitabine may also have favorable survival outcomes.

The second phase III trial compared the combination of paclitaxel (175 mg/m<sup>2</sup>) and gemcitabine (1,250 mg/m<sup>2</sup>) with single-agent paclitaxel (175 mg/m<sup>2</sup>) in 529 patients with MBC who had previously received an anthracycline but had no prior chemotherapy for metastatic disease [25, 26]. Combination therapy resulted in a significantly higher overall response rate and longer progression-free and overall survival times than single-agent paclitaxel (Table 3). The median overall survival time with the combination was 18.5 months, 2.7 months higher than that seen with single-agent paclitaxel. Again, crossover was not mandated, and the potential impact of sequential therapy on survival outcomes has not been evaluated. Although grade 4 neutropenia was more common with the combination, overall toxicities in both arms were manageable. A QoL analysis indicated better global scores for patients receiving combination therapy than for those receiving single-agent paclitaxel [37].

### TAXANES IN PATIENTS WITH MBC AND NO PRIOR ANTHRACYCLINE THERAPY

In addition to the E1193 trial, two randomized phase III trials have evaluated a single-agent taxane therapy versus single-agent doxorubicin for patients with MBC without prior anthracycline exposure [38, 39]. The first of these trials compared docetaxel (100 mg/m<sup>2</sup>) with doxorubicin (75 mg/m<sup>2</sup>) in 326 patients who had previously received alkylating agent-based therapy, either in the adjuvant setting or for advanced disease [38]. There was no planned crossover design, and further treatment at the time of disease progression was at the investigator's discretion. The overall response rate with docetaxel was significantly higher than the rate with doxorubicin, though there were no differences in median time to disease progression or overall survival time (Table 4). Subgroup analyses showed that docetaxel produced substantially higher response rates than did doxorubicin in patients with negative prognostic factors, including visceral metastases and resistance to prior chemotherapy. The incidence of neutropenia was similar for both groups, although febrile neutropenia and severe infection occurred more frequently with doxorubicin.

A second phase III trial compared paclitaxel (200 mg/m<sup>2</sup>) with doxorubicin (75 mg/m<sup>2</sup>) in 331 patients as first-line chemotherapy for metastatic disease [39]. Patients could not have received any prior anthracycline therapy, though prior alkylating agent-based chemotherapy in the adjuvant setting was permitted. At the time of disease progression, patients were to be crossed over to the alternate treatment. The overall response rate and time to disease progression were significantly greater for patients randomized to doxorubicin than for those given paclitaxel, but there was no statistical difference in overall survival time between groups (Table 4). Neutropenia, febrile neutropenia, and

**Table 4.** Phase III trials of single-agent taxanes in metastatic breast cancer with no or minimal prior anthracycline exposure

Study	Regimen	No. of patients	Overall response rate	Median time to progression (months)	Median overall survival (months)
Chan et al. [38]	Docetaxel	161	42% ( $p = .008$ )	6	15
	Doxorubicin	165	30%	4.8	14
Paridaens et al. [39]	Paclitaxel	166	25%	3.9	15.6
	Doxorubicin	165	41% ( $p = .003$ )	7.5 ( $p < .001$ )	18.3
Bishop et al. [27]	Paclitaxel	107	29%	5.3	17.3 ( $p = .025$ ) <sup>a</sup>
	CMFP	102	35%	6.4	13.9

<sup>a</sup>By multivariate analysis.

Abbreviation: CMFP, cyclophosphamide, methotrexate, fluorouracil, and prednisone.

infections occurred more frequently with doxorubicin. A QoL analysis showed no differences in global health scores between the two arms after the third cycle of therapy.

An additional phase III trial compared single-agent paclitaxel (200 mg/m<sup>2</sup>) with the alkylating agent-based combination of cyclophosphamide, methotrexate, fluorouracil, and prednisone (Deltasone®; Pfizer Pharmaceuticals) (CMFP) in 209 patients as first-line therapy for metastatic disease [27]. Prior adjuvant chemotherapy was permitted. Overall response rates and times to disease progression were not different between the two study arms (Table 4). The absolute difference in median overall survival was 3.4 months in favor of paclitaxel, but this difference did not achieve statistical significance on univariate analysis. In a multivariate model that factored in significant prognostic factors, however, this difference was found to be significant ( $p = .025$ ). Leukopenia, thrombocytopenia, nausea and vomiting, and mucositis occurred more frequently with CMFP. Overall QoL assessments were similar for both treatment arms.

Seven phase III trials have evaluated a taxane in combination with an anthracycline versus a standard anthracycline-based combination in patients with MBC (Table 5) [28, 29, 40–44]. Three trials evaluated a docetaxel-based combination and four trials evaluated a paclitaxel-based combination.

The combination of doxorubicin (50 mg/m<sup>2</sup>) and docetaxel (75 mg/m<sup>2</sup>) (AD) was compared with doxorubicin (60 mg/m<sup>2</sup>) and cyclophosphamide (500 mg/m<sup>2</sup>) (AC) as first-line chemotherapy in 429 women with MBC [40]. Prior nonanthracycline-based adjuvant chemotherapy was allowed. The overall response rate and median time to disease progression were statistically superior with AD than with AC, though the median overall survival time did not differ between the two treatment arms (Table 5). Of the 60% of patients who received additional chemotherapy, 29% in the AC group received docetaxel as additional treatment versus 6% in the AD group. Grade 3–4 neutropenia occurred frequently in both treatment arms, and febrile neutropenia and infection occurred more commonly with the AD combination.

A second phase III trial compared docetaxel, doxorubicin, and cyclophosphamide (TAC) at doses of 75/50/500 mg/m<sup>2</sup>, respectively, with the combination of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC, 500/50/500 mg/m<sup>2</sup>) as first-line chemotherapy for metastatic disease in 484 women [41]. Prior adjuvant chemotherapy was allowed, and patients could have received prior doxorubicin up to a cumulative dose of 240 mg/m<sup>2</sup>. While the overall response rate with TAC was significantly higher, time to disease progression and overall sur-

**Table 5.** Phase III trials of taxane combinations in metastatic breast cancer with no or minimal prior anthracycline exposure

Study	Regimen	No. of patients	Overall response	Median time to progression (months)	Median overall survival (months)
Nabholtz et al. [40]	AD	214	59% ( $p = .009$ )	8.6 ( $p = .014$ )	22.5
	AC	215	47%	7.3	21.7
Mackey et al. [41]	DAC	242	55% ( $p = .02$ )	7.2	21
	FAC	242	44%	6.7	22
Bontenbal et al. [28]	AD	108	64% ( $p = .002$ )	8.1 ( $p = .002$ )	22.6 ( $p = .02$ )
	FAC	107	41%	6.6	16.1
Jassem et al. [29]	AP	134	68% ( $p = .032$ )	8.3 ( $p = .034$ )	22.3 ( $p = .013$ )
	FAC	133	55%	6.2	18.3
Biganzoli et al. [42]	AP	138	58%	6.0	20.6
	AC	137	54%	6.0	20.5
Carmichael [43]	EP	705 (total)	67%	6.5	13.7
	EC		56%	6.7	13.8
Lück et al. [44]	EP	429 (total)	46%	9.0	NR
	EC		41%	7.6	NR

Abbreviations: AC, doxorubicin and cyclophosphamide; AD, doxorubicin and docetaxel; AP, paclitaxel and doxorubicin; DAC, docetaxel, doxorubicin, cyclophosphamide; EC, epirubicin and cyclophosphamide; EP, epirubicin and paclitaxel; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; NR, not reported.

vival times were similar in the two treatment groups. A greater percentage of patients in the FAC group received crossover treatment with a taxane than those in the TAC group (46.2% vs. 16.5%). Both regimens were associated with a high rate of grade 3–4 hematologic toxicities, though neutropenia and febrile neutropenia occurred more frequently with TAC.

A randomized phase II study compared AD (50/75 mg/m<sup>2</sup>) with FAC (500/50/500 mg/m<sup>2</sup>) as first-line chemotherapy in 215 MBC patients [28]. That study permitted limited prior doxorubicin exposure in the adjuvant setting. In contrast to the previous trial, significant differences in time to disease progression and overall survival time along with a superior overall response rate were seen with AD versus FAC. The absolute median survival difference was 6.5 months, representing a 40% longer survival time than in the FAC arm. The incidences of grade 3–4 neutropenia were similar for both arms, although febrile neutropenia occurred more frequently with AD.

Among the three trials evaluating paclitaxel-based combinations, one demonstrated significantly better outcomes favoring the taxane combination. That trial compared doxorubicin and paclitaxel (50/220 mg/m<sup>2</sup>) with FAC (500/50/500 mg/m<sup>2</sup>) as first-line chemotherapy in 267 anthracycline-naïve MBC patients [29]. The overall response rate, median time to disease progression, and overall survival time were significantly better with AP than with FAC, with AP producing a median survival time that was 4 months longer. Approximately the same number of patients on the FAC and AP arms received second-line chemotherapy (44% and 48%, respectively). Paclitaxel and docetaxel were administered to 10% and 14% of patients, respectively, in the FAC group and each was administered to 1% of patients in the AP group. Grade 3–4 neutropenia occurred more frequently with AP, although the incidence of febrile neutropenia was low in both arms. Overall QoL measures were similar in the two treatment arms. Symptom scales of pain, fatigue, insomnia, and diarrhea favored FAC therapy, while the nausea and vomiting symptom scale favored AP therapy.

In a phase III trial comparing AP (60/175 mg/m<sup>2</sup>) with AC (60/600 mg/m<sup>2</sup>) as first-line chemotherapy in 265 anthracycline-naïve patients, no differences in response or survival outcomes were seen between treatment arms [42]. A QoL analysis found no difference between treatment groups, and overall QoL was maintained.

In two similar comparisons of epirubicin and paclitaxel versus epirubicin and cyclophosphamide in women with MBC, there were also no differences in either overall response rates or survival times [43, 44].

## CHEMOTHERAPY IN COMBINATION WITH TARGETED BIOLOGIC AGENTS IN MBC

Targeted biologic therapies offer an entirely new treatment dimension for patients with MBC. The monoclonal antibody trastuzumab targets an extracellular domain of the HER-2 receptor [45]. Overexpression of HER-2 is associated with clinically aggressive disease and a shorter survival time. Synergistic activity has been observed in cellular models between trastuzumab and several chemotherapeutic agents, including docetaxel and carboplatin (Paraplatin®; Bristol-Myers Squibb), while additive activity has been observed with paclitaxel, doxorubicin, and epirubicin [45].

Clinically, trastuzumab therapy is generally well tolerated. One important caveat, however, is the potential for congestive heart failure. As the risk for congestive heart failure is much greater when trastuzumab is given with doxorubicin, this combination is generally avoided [14].

Two important phase III trials have evaluated the addition of trastuzumab to chemotherapy in women with HER-2–overexpressing MBC [14, 15]. In a pivotal clinical trial reported by Slamon et al., patients received chemotherapy with either doxorubicin and cyclophosphamide (AC) or single-agent paclitaxel with or without trastuzumab. The combination of chemotherapy and trastuzumab resulted in significantly higher overall response rates with a longer median time to disease progression and overall survival time than with chemotherapy alone (Table 6). An absolute survival advantage of 4.8 months was seen with the addition of trastuzumab. Approximately two thirds of the patients in the chemotherapy-alone arm crossed over to receive trastuzumab at disease progression. The most important adverse event was a higher incidence of congestive heart failure in patients receiving trastuzumab with AC.

In a separate study, a QoL analysis was performed in a sample of 400 patients who received either chemotherapy with trastuzumab (n = 208) or chemotherapy alone as first-line therapy for MBC [46]. After completion of therapy, fatigue scores were significantly better than baseline scores in patients receiving chemotherapy and trastuzumab (p < .05). In addition, patients who received trastuzumab had a significant improvement in global QoL scores (p < .05).

The results of a phase III trial evaluating single-agent docetaxel (100 mg/m<sup>2</sup>) with or without trastuzumab as first-line therapy for MBC have also shown a significant benefit from the addition of trastuzumab (Table 6) [15]. The overall response rate, median time to disease progression, and median overall survival time were all statistically superior with the combination than with single-agent therapy. Both the overall response rate and median time to disease progression were nearly doubled by the addition of trastuzumab. The absolute difference in median survival time

**Table 6.** Randomized trials of chemotherapy and biologic combinations in metastatic breast cancer

Study	Regimen	No. of patients	Overall response rate	Median time to progression (months)	Median overall survival (months)
Slamon et al. [14]	AC or paclitaxel + trastuzumab	235	50% ( $p < .0001$ )	7.4 ( $p < .0001$ )	25.1 ( $p = .046$ )
	AC or paclitaxel	234	32%	4.6	20.3
Marty et al. [15]	Docetaxel + trastuzumab	92	61% ( $p = .002$ )	11.7 ( $p = 0.0001$ )	31.2 ( $p = .0325$ )
	Docetaxel	94	34%	6.1	22.7
Miller et al. [50]	Capecitabine + bevacizumab	232	19.8% ( $p = .001$ )	4.9	15.1
	Capecitabine	230	9.1%	4.2	14.5
Miller et al. [16]	Paclitaxel + bevacizumab	350	28.2% ( $p = .0001$ )	11.0 ( $p < .001$ )	NA
	Paclitaxel	365	14.2%	6.1	NA

Abbreviations: AC, doxorubicin and cyclophosphamide; NA, not available.

in this study was impressive, at 8.5 months, 37% higher than with docetaxel alone. Of note, patients who received docetaxel first, followed by trastuzumab at progression, had worse survival than those who received the combination initially. Overall, toxicities were consistent with those expected, with the combination producing more grade 3–4 neutropenia than single-agent docetaxel. Both the trastuzumab–taxane randomized trials demonstrated that overall survival is optimized in HER-2–positive MBC patients by beginning trastuzumab along with the first chemotherapy regimen given for MBC rather than giving trastuzumab following first-line chemotherapy.

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). Angiogenesis is essential for cancer growth and metastasis. The consequent hyperpermeable, irregular vessels cause irregular blood flow and high interstitial fluid pressure within the tumor, which can impair the delivery of oxygen (a known radiation sensitizer) and drugs to the tumor site. Bevacizumab decreases interstitial fluid pressure in tumors, improving drug delivery and penetration [47]. Preclinical data indicate that breast cancer invasiveness and metastasis is dependent on the establishment of new blood vessels, and VEGF is a potent stimulator of angiogenesis [48].

Phase II data indicate a modest response rate of 9% for bevacizumab alone in previously treated MBC patients [49]. Building on this, a phase III trial comparing the combination of bevacizumab and capecitabine with capecitabine alone was conducted, enrolling MBC patients who had previously received both an anthracycline and a taxane (Table 6) [50]. The addition of bevacizumab produced a significantly higher overall response rate; however, there were no differences in median progression-free or overall survival times. There were no differences between treatment groups with respect to the incidence of diarrhea, hand-foot syndrome,

thromboembolic events, or serious bleeding episodes, though hypertension requiring medical intervention was more common in the bevacizumab arm. Global QoL measures were similar for both treatment arms.

Preliminary results from a phase III trial of paclitaxel with or without bevacizumab as first-line treatment of 715 patients with MBC appear very promising [16]. Significantly greater overall response rate and median time to disease progression were seen with the combination (Table 6). Overall survival also favored the addition of bevacizumab, but median values had not yet been reached.

## SUMMARY

The assessment of the true survival benefits from chemotherapy in MBC can be difficult, given the potential for confounding issues, such as the impact of subsequent therapies. Nonetheless, there is an increasing number of randomized clinical trials that have documented significant survival differences.

With chemotherapy regimens, the taxanes have figured prominently in those trials exhibiting a survival benefit. When present, the improvement in survival time has usually been on the order of 3 months, representing a survival time that is about 20%–30% longer. It is interesting to note that, among all these trials, in no case has a docetaxel-based regimen been inferior with respect to overall survival outcome.

Capecitabine and gemcitabine, two antimetabolite cytotoxic agents, have shown high activity and acceptable tolerability in a range of settings for MBC. These include single-agent and combination regimens, including in patients with anthracycline- and/or taxane-pretreated disease.

The debate concerning combination therapy versus sequential single agents continues. Combination therapies are associated with higher overall response rates, albeit at a cost of greater toxicities. And aside from the E1193

trial, well-defined comparisons of combination regimens with the same agents in sequence are not available, and the ultimate impact on survival outcomes between the two approaches remains to be seen.

With targeted biologics, such as trastuzumab and bevacizumab, the potential for enhanced or synergistic activity is a compelling argument for the use of these agents in combination with traditional chemotherapeutics. In randomized studies, response and survival benefits have been impressive, with combination therapies resulting in substantially higher overall response rates. Trials with chemotherapy and trastuzumab have also demonstrated substantial improvements in overall survival ranging from 4 to 8 months, representing increases of 24% and 37% in survival time. Early data from the combination of paclitaxel and bevacizumab also appear to support a survival benefit.

With respect to QoL measures, in general, treatment regimens for MBC do not appear to impair overall QoL. With trastuzumab therapy, there has even been an indication of an improvement in overall QoL following treatment.

Overall, there is a growing body of phase III data on MBC that demonstrates that the introduction of modern chemotherapeutic agents, such as the taxanes, antimetabolites, and targeted biologic agents, has helped to improve survival outcomes in MBC.

#### DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Dr. O'Shaughnessy has acted as a consultant for Eli Lilly, Pfizer, Roche, sanofi-aventis, Abraxis, and Genentech and has received support from Roche, sanofi-aventis, Lilly, Genentech, and Abraxis.

#### REFERENCES

- American Cancer Society. Cancer Facts and Figures 2005. Atlanta, GA: American Cancer Society, 2005:9–11.
- Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). SEER\*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2004 Sub (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.
- Gralow JR. Optimizing the treatment of metastatic breast cancer. *Breast Cancer Res Treat* 2005;89(suppl 1):S9–S15.
- Blum JL, Jones SE, Buzdar AU et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;17:485–493.
- Blum JL, Jones SE, Buzdar A. Capecitabine (Xeloda) in 162 patients with paclitaxel-pretreated MBC: updated results and analysis of dose modification. *Eur J Cancer* 2001;37:S190a.
- Blum JL, Dieras V, Lo Russo PM et al. Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. *Cancer* 2001;92:1759–1768.
- Reichardt P, Von Minckwitz G, Luck HJ et al. Capecitabine: the new standard in metastatic breast cancer failing anthracycline and taxane containing chemotherapy? Mature results of a large multicenter phase II trial. *Eur J Cancer* 2001;37(suppl 6):S191a.
- Fumoleau P, Largillier R, Trillet-Lenoir V et al. Phase II study of capecitabine (Xeloda®) in patients with advanced breast cancer (ABC), previously treated with anthracyclines and taxanes. *Breast Cancer Res Treat* 2001;69:285a.
- Miles D, von Minckwitz G, Seidman AD. Combination versus sequential single-agent therapy in metastatic breast cancer. *The Oncologist* 2002;7(suppl 6):13–16.
- Sledge GW, Neuberger 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: an intergroup trial (E1193). *J Clin Oncol* 2003;21:588–592.
- Cresta S, Grasselli G, Mansutti M et al. A randomized phase II study of combination, alternating and sequential regimens of doxorubicin and docetaxel as first-line chemotherapy for women with metastatic breast cancer. *Ann Oncol* 2004;15:433–439.
- Conte PF, Guarneri 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;101:704–712.
- Alba E, Martin 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 Research Group (GEICAM-9903) phase III study. *J Clin Oncol* 2004;22:2587–2593.
- Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–792.
- Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;23:4265–4274.
- Miller KD, Wang M, Gralow J et al. E2100: a randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Presented at the 41st Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 13–17, 2004.
- Greenberg PA, Hortobagyi GN, Smith TL et al. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996;14:2197–2205.
- Fossati R, Confalonieri C, Torri V et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *J Clin Oncol* 1998;16:3439–3460.
- Pierga JY, Robain M, Jouve M et al. Response to chemotherapy is a major parameter influencing long-term survival of metastatic breast cancer patients. *Ann Oncol* 2001;12:231–237.
- Bruzzi P, Del Mastro L, Sormani MP et al. Objective response to chemotherapy as a potential surrogate end point of survival in metastatic breast cancer patients. *J Clin Oncol* 2005;23:5117–5125.

- 21 Chia SK, Speers C, Kang A et al. The impact of new chemotherapeutic and hormonal agents on the survival of women with metastatic breast cancer in a population based cohort. *Proc Am Soc Clin Oncol* 2003;22:6.
- 22 Nabholz JM, Senn HJ, Bezwoda WR et al. 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* 1999;17:1413–1424.
- 23 Jones S, Erban J, Overmoyer B et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 2005;23:5542–5551.
- 24 O'Shaughnessy J, Miles D, Vukelja S et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pre-treated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;20:2812–2823.
- 25 Albain KS, Nag S, Calderillo-Ruiz G et al. Global phase III study of gemcitabine plus paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): first report of overall survival. *J Clin Oncol* 2004;22:5S.
- 26 O'Shaughnessy J, Nag S, Calderillo-Ruiz G et al. Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): interim results of a global phase III study. *Proc Am Soc Clin Oncol* 2003;22:7.
- 27 Bishop JF, Dewar J, Toner GC et al. Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. *J Clin Oncol* 1999;17:2355–2364.
- 28 Bontenbal M, Braun JJ, Creemers GJ et al. Phase II study comparing AT to FAC as first line chemotherapy in patients with MBC. *Eur J Cancer* 2003;1(suppl 1):S201.
- 29 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.
- 30 Feher O, Vodvarka P, Jassem J et al. First-line gemcitabine versus epirubicin in postmenopausal women aged 60 or older with metastatic breast cancer: a multicenter, randomized, phase III study. *Ann Oncol* 2005;16:899–908.
- 31 Perez EA. Paclitaxel in breast cancer. *The Oncologist* 1998;3:373–389.
- 32 Figgitt DP, Wiseman LR. Docetaxel: an update of its use in advanced breast cancer. *Drugs* 2000;59:621–651.
- 33 Sjöström J, Blomqvist C, Mouridsen H et al. Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. *Eur J Cancer* 1999;35:1194–1201.
- 34 Bonnetterre J, Roche H, Monnier A et al. Docetaxel vs 5-fluorouracil plus vinorelbine in metastatic breast cancer after anthracycline therapy failure. *Br J Cancer* 2002;87:1210–1215.
- 35 Gradishar WJ, Tjulandin S, Davidson N et al. Superior efficacy of albumin-bound paclitaxel, ABI-007, compared with polyethylated castor oil-based paclitaxel in women with metastatic breast cancer: results of a phase III trial. *J Clin Oncol*. 2005;23. Epub on September 19, 2005 as 10.1200/JCO.2005.04.937.
- 36 Miles D, Vukelja S, Moiseyenko V et al. Survival benefit with capecitabine/docetaxel versus docetaxel alone: analysis of therapy in a randomized phase III trial. *Clin Breast Cancer* 2004;5:273–278.
- 37 Moinpour C, Wu J, Donaldson G et al. Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): quality of life (QoL) and pain palliation results from the global phase III study. *J Clin Oncol* 2004;22:22:621.
- 38 Chan S, Friedrichs K, Noel D et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999;8:2341–2354.
- 39 Paridaens R, Biganzoli L, Bruning P et al. 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* 2000;18:724–733.
- 40 Nabholz 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.
- 41 Mackey JR, Paterson A, Dirix LY et al. Final results of the phase III randomized trial comparing docetaxel (T) doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 2002;21:35a.
- 42 Biganzoli L, Cufer T, Bruning P et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 multicenter phase III trial. *J Clin Oncol* 2002;20:3114–3121.
- 43 Carmichael J. UKCCCR trial of epirubicin and cyclophosphamide (EC) versus epirubicin and Taxol (ET) in the first-line treatment of women with metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 2001;20:22.
- 44 Lück HJ, Thomssen C, Untch M et al. Multicentric phase III study in first line treatment of advanced metastatic breast cancer (ABC). Epirubicin/paclitaxel (ET) vs epirubicin/cyclophosphamide (EC). A study of the AGO Breast Cancer Group. *Proc Am Soc Clin Oncol* 2000;19:73a.
- 45 Pegram MD, Konecny GE, O'Callaghan C et al. Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. *J Natl Cancer Inst* 2004;96:739–749.
- 46 Osoba D, Slamon DJ, Burchmore M et al. Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. *J Clin Oncol* 2002;20:3106–3133.
- 47 Jain RK. Antiangiogenic therapy of cancer: current and emerging concepts. *Oncology* 2005;19:7–16.
- 48 Kim KJ, Li B, Winer J et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* 1993;362:841–844.
- 49 Cobleigh M, Langmuir VK, Sledge GW et al. A phase II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. *Semin Oncol* 2003;30(suppl 16):117–124.
- 50 Miller KD, Chap LI, Holmes FA et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer patients. *J Clin Oncol* 2005;23:792–799.

DrFarrahCancerCenter.com

**Extending Survival with Chemotherapy in Metastatic Breast Cancer**  
Joyce O'Shaughnessy

*The Oncologist* 2005, 10:20-29.  
doi: 10.1634/theoncologist.10-90003-20

The online version of this article, along with updated information and services, is located on  
the World Wide Web at:

[http://theoncologist.alphamedpress.org/content/10/suppl\\_3/20](http://theoncologist.alphamedpress.org/content/10/suppl_3/20)

DrFarrahCancerCenter.com