COMMENTARY

International Guidelines for Management of Metastatic Breast Cancer: Combination vs Sequential Single-Agent Chemotherapy

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Compared with treatment options for early-stage breast cancer, few data exist regarding the optimal use of chemotherapy for metastatic breast cancer (MBC). The choice of using a combination of cytotoxic chemotherapies vs sequential single agents is controversial. At the 6th European Breast Cancer Conference, the European School of Oncology Metastatic Breast Cancer Task Force convened an open debate on the relative benefits of combination vs sequential therapy. Based on the available data, the Task Force recommends sequential monotherapy as the preferred choice in advanced disease, in the absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control. Patient- and disease-related factors should be used to choose between combination and sequential single-agent chemotherapy for MBC. Additional research is needed to determine the impact of therapy on patient-rated quality of life and to identify predictive factors that can be used to guide therapy.

Many challenges exist in the management of metastatic breast cancer (MBC). As opposed to early disease, for which level 1 evidence exists for the majority of treatment alternatives, there are few recognized therapeutic standards for MBC, particularly following initial chemotherapy (1). Randomized controlled trials in MBC are usually conducted in the first-line setting and address specific questions regarding the efficacy, safety, and tolerability of individual drugs. The design of these trials is sometimes at odds with the questions clinical oncologists face in daily practice. Several international guidelines for adjuvant therapy are widely used (2–4), but consensus statements regarding the management of MBC are lacking (5). Acknowledging the urgent need for these initiatives, the European School of Oncology (ESO) joined with the European Breast Cancer Conference (EBCC) to create an MBC Task Force in 2005. The task force held its first open meeting at the EBCC-5 in Nice in March 2006. This interactive session addressed many of the main issues in MBC, and 12 consensus statements regarding MBC management were subsequently published (1).

At the EBCC-6 in Berlin in April 2008, the second public session on MBC Guidelines was held. During this session, three of the most controversial issues outlined in the 12 statements were selected for further discussion. Here, we summarize the discussion and the related recommendations regarding the optimal use of chemotherapy in MBC, focusing on the still unresolved issue of whether it is better to treat MBC patients sequentially with single cytoxic agents or to treat them simultaneously with a combination of drugs.

The initial consensus statement regarding this subject (consensus statement 9) from the ESO-MBC Task Force guidelines reads: "The choice between sequential use of single cytotoxic drugs and combination chemotherapy should be taken after consideration of the factors mentioned in [Table 1], with greatest emphasis on the need for a rapid and significant response and on quality of life (QoL). For the majority of patients, overall survival (OS) outcomes from sequential use of single cytotoxic drugs are equivalent to combination chemotherapy. Duration of each regimen and number of regimens should be tailored to each individual patient" (1).

Although the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview established the survival benefit of adjuvant polychemotherapy (6), the role of polychemotherapy in MBC remains largely unsettled. Unlike the adjuvant setting, in which the goal of therapy is cure, the aim of therapy in the setting of MBC is essentially palliation. Stepwise advances in chemotherapy have produced statistically significant improvements in survival (7). Nevertheless, tolerability and QoL are important factors

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Table 1. Factors to consider when choosing between sequential and combination chemotherapy

Patient related	Disease related
Menopausal status	Endocrine responsiveness
Biological age and comorbidities (including organ dysfunction)	HER2 status
Performance status and adverse effects of prior therapy	Disease-free interval
Socioeconomic and psychological factors	Previous therapies and response obtained
Patient preference	Tumor burden (defined as number and site of metastases)
Available therapies in the patient's country	Need for rapid disease and/or symptom control

in therapeutic decision making that must be balanced with any potential gains in disease response or survival.

Objective improvements in OS are difficult to demonstrate in individual trials (8), leading some authors to question whether OS is an appropriate endpoint for clinical trials testing novel therapeutic approaches for metastatic disease (9). Accordingly, many recent registration trials were designed to detect improvements in progression-free interval and were not adequately powered to evaluate the impact of new treatments on OS (10–12). Crossover to the novel agent following progression in the monotherapy arm was not mandated, limiting the application of these studies to the clinically important question of the relative benefits of combination vs sequential monotherapy. Recent data from single-institution series and population-based registries demonstrate that the survival of patients with MBC has improved over time, coincident with the widespread availability of newer and more effective systemic therapies (13,14). Although these data suggest a possible change in the natural history or staging procedures of MBC, they do not provide insight regarding the optimal timing, sequence, or combination of systemic agents in the treatment of MBC.

In particular, few appropriately powered randomized clinical trials have addressed the question of the sequential use of single cytotoxic agents vs upfront combination chemotherapy for MBC, with evaluation of the comparative impact of these palliative strategies on patients' QoL. In contrast to adjuvant therapy, for which trials are designed to include thousands of patients to identify small absolute differences in disease-free survival, most studies that address MBC involve smaller numbers of participants and are underpowered to detect potentially meaningful differences in progression-free interval and/or OS between combination and sequential approaches.

A Cochrane Review (15) of 28 trials with 5707 MBC patients who were randomly assigned to either single-agent or combination chemotherapy found that combination chemotherapy was associated with a higher response rate (RR) (odds ratio for tumor response = 1.28, 95% confidence interval [CI] = 1.15 to 1.42, $P < .001$), longer time to progression (hazard ratio [HR] for disease progression = 0.78, 95% CI = 0.73 to 0.83, $P < .001$), and longer OS (HR for death = 0.88, 95% CI = 0.83 to 0.94, $P < .001$) when compared with single-agent therapy. More toxicity (nausea and vomiting, leucopenia, and alopecia) was also observed with combination therapy. Few studies included in the Cochrane analysis formally assessed differences in QoL between combination and single-agent therapy.

In addition, most trials included in the Cochrane meta-analysis did not systematically investigate the combination vs the sequential approach. Very few trials included in the overview reported the rate of "crossover" to an additional agent following progression in the monotherapy arm. Such studies test the value of two agents vs a single agent but do not address whether a combination or sequential monotherapy strategy should be pursued.

It is also important to remember that the terms *sequential* and *combination* chemotherapy are often used to encompass a variety of different therapeutic approaches. For example, sequential therapy may refer to the consecutive administration of several chemotherapies, with each successive regimen introduced following either radiographic and/or symptomatic disease progression. Alternatively, it may refer to a planned multicourse sequence of chemotherapies without interruption between treatment regimens (16). Combination therapy may also involve the pairing of a cytotoxic drug with a novel biological therapy, such as a taxane and trastuzumab in women with HER2-positive MBC. This ESO-MBC Task Force publication, however, will focus exclusively on the combination of cytotoxic chemotherapies vs sequential single-agent therapies and will not address the optimal addition of biological therapies to chemotherapy.

Literature Review

Anthracycline Alone vs Combination Therapy

Anthracyclines are among the most active agents against breast cancer. The EBCTCG overview demonstrated that the addition of an anthracycline to adjuvant systemic therapy was associated with a 16% reduction in relative risk of breast cancer mortality (HR for breast cancer mortality = 0.84; $P < .001$), when compared with cyclophosphamide-methotrexate-5-fluorouracil (CMF) (6). In the metastatic setting, anthracyclines have been used for the past 30 years and are widely considered as the standard first-line therapy for MBC. Given their established role, many trials have compared single vs combination strategies using an anthracycline as the standard single-agent reference regimen (Supplementary Tables 1 and 2, available online). An anthracycline is often combined with cyclophosphamide and 5-fluorouracil (5-FU) because of their partial lack of cross-resistance and nonoverlapping toxicity profiles. The addition of 5-FU and cyclophosphamide to epirubicin (FEC) was associated with an increase in RR: RRs for epirubicin (75 mg/m²) alone, FEC50 (epirubicin at 50 mg/m²), and FEC75 (epirubicin at 75 mg/m²) were 30.6%, 44.6%, and 44.7%, respectively; $P = .04$ (FEC50 vs epirubicin alone) and $P = .006$ (FEC75 vs epirubicin alone). However, compared with epirubicin alone, use of these combinations did not prolong progression-free interval or OS (17). Comparable results have also been reported in a study in Finland (18) with a similar design and in a study in Germany (19) using single-agent mitoxantrone as the reference regimen. The study in Finland (18) was one of the few studies to

clearly compare a sequential single-agent strategy with a combination approach throughout the course of illness. Patients who were randomly assigned to receive single-agent epirubicin as first-line therapy were subsequently treated with single-agent mitomycin C (MMC) following progression. Patients who were randomly assigned to receive first-line FEC received combination MMC–vinblastine following progression. This study (18) was also one of the few trials to formally examine differences in QoL between patients who were treated with combination vs single-agent therapy. It confirmed that combination therapy improves disease response with no improvement in progression-free interval or OS, at the expense of increased treatment-related toxicity and poorer self-assessed QoL (18).

More recently, the taxanes have been shown to have comparable antitumor activity to anthracyclines in MBC patients who have not received previous chemotherapy (20). This observation has led to many trials investigating combinations of anthracyclines and taxanes. It should be recognized that anthracyclines and taxanes have overlapping toxicity profiles, because both classes of agents are known to be potent myelosuppressors. The Eastern Cooperative Oncology Group 1193 study randomly assigned 739 patients with untreated MBC to either doxorubicin (A) or paclitaxel (P) alone or to a combination of doxorubicin and paclitaxel (AP) (21). RRs and time to treatment failure (TTF) were increased with combination therapy (RR for A, P, and AP was 36%, 34%, and 47%, respectively; $P = .84$ [A vs P], $P = .007$ [A vs AP], and $P = .004$ [P vs AP] and median TTF for A vs P vs AP was = 5.8 vs 6.0 vs 8.0 months, respectively; $P = .68$ [A vs P], $P = .003$ [A vs AP], and $P = .009$ [P vs AP]). However, there was no improvement in median OS (A vs P vs AP, 18.9 vs 22.2 vs 22.0 months; $P = .60$ [A vs P], $P = .82$ [A vs AP], and $P = .49$ [P vs AP]) or QoL (change in FACT-B baseline to 16 weeks; A vs P vs AP, −1.7 vs −2.8 vs −3.0; $P = $ not statistically significant) with combination therapy. In a similar study, Conte et al. (22) compared a preplanned schedule of four cycles of single-agent epirubicin followed by four cycles of single-agent paclitaxel with eight cycles of the combination regimen and found no statistically significant difference in RR, progression-free interval, or OS between the two approaches. Both of these studies (21,22) used a 3-weekly paclitaxel administration schedule, which was subsequently shown to be inferior to weekly paclitaxel or 3-weekly docetaxel (23–26). In a smaller study conducted by the Spanish Breast Cancer Research Group (GEICAM 9903) (27), 144 MBC patients were randomly assigned to three cycles of single-agent doxorubicin followed by three cycles of single-agent docetaxel, given on a 3-weekly schedule, or to six cycles of the doxorubicin–docetaxel combination (27). Again, no differences in RR, progression-free interval, or OS were observed between the two groups, but more febrile neutropenia, asthenia, and diarrhea were reported in the combination arm. Likewise, a randomized phase II study of two different doxorubicin–docetaxel combination regimens failed to show a benefit in RR, progression-free interval, OS, or toxicity when compared with docetaxel followed by doxorubicin in the sequential monotherapy group (28).

Other trials comparing single-agent anthracyclines with anthracycline-based regimens with either vinca alkaloids (29–34), platinum analogs (32,35), MMC (36), or etoposide (37) have also failed to show a survival benefit in favor of the combination

approach, but the majority of these studies were underpowered to detect small differences in survival.

Taxane Monotherapy vs Combination Regimens

A variety of studies have examined taxane monotherapy against combination regimens. Older studies compared single-agent taxanes with combination regimens, including agents with limited clinical activity no longer widely used in the management of MBC (Supplementary Table 3, available online). For example, Nabholtz et al. (38) compared docetaxel with the combination of MMC and vinblastine in a population of patients who had been previously treated with anthracyclines. In this trial, docetaxel monotherapy was associated with better RR, progression-free interval, and OS. Similarly in another trial, single-agent treatment with docetaxel improved RR and time to progression (TTP) when compared with methotrexate and 5-FU, but not OS, with less toxicity (39). Bonneterre et al. (40) showed that docetaxel has similar antitumor efficacy as the combination of 5-FU and vinorelbine with a more favorable toxicity profile. In a study in Australia, 3-weekly paclitaxel monotherapy was associated with a similar RR, TTF, and QoL when compared with cyclophosphamide-methotrexate-5-FU-prednisone, with a trend toward an improved OS that did not reach statistical significance (41). These studies contributed to the establishment of taxane monotherapy as the standard second-line treatment following anthracyclines in MBC.

More recently, several studies have investigated the value of adding newer agents to a taxane backbone (Supplementary Table 4, available online). O'Shaughnessy et al. (12) randomly assigned 511 MBC patients who were previously treated with anthracyclines to either 3-weekly docetaxel singly or in combination with capecitabine (XT) (12). The XT combination was associated with an improved RR, TTP, and a 3-month prolongation in median OS (XT vs docetaxel alone: 14.5 vs 11.5 months, HR for death = 0.775, $P = .013$). No statistically significant difference in QoL was observed between the two groups. However, grade 3–4 toxicity was more frequent in the group treated with combination therapy (71% vs 49%), primarily due to increases in diarrhea, stomatitis, and hand-foot syndrome. In the XT group, 65% of patients required dose reduction during the course of treatment. An unplanned subset analysis of patients who underwent dose reduction to 950 mg/m^2 capecitabine and 55 mg/m^2 docetaxel showed no statistically significant difference in outcome when compared with patients who tolerated full XT dosing for the first four cycles (42). In this study, therapy in the event of progression was not prespecified. Fewer patients in the group that received docetaxel monotherapy received further chemotherapy on progression compared with the group that received combination therapy (63% vs 70%) and only 17% went on to receive capecitabine (12).

Subsequent studies have tried to address the relative benefits of sequential monotherapy and combination therapy with docetaxel and capecitabine. In a relatively small randomized phase II trial (43), 100 patients with previously treated MBC were randomly assigned to docetaxel monotherapy with single-agent capecitabine in the event of progression or the XT combination. Of patients who were initially treated with docetaxel monotherapy, 74% received capecitabine upon progression. A statistically significant benefit of the upfront XT combination treatment in terms of RR,

TTP, and OS (22.0 vs 19.0 months, P = .006) was observed. Similar to what was observed by O'Shaughnessy et al., more grade 3–4 diarrhea, stomatitis, and hand–foot syndrome were seen in the combination therapy group and 52% of patients required dose reduction. In a larger trial in Mexico (44), 368 MBC patients who had been treated with anthracycline were randomly assigned to upfront capecitabine monotherapy followed by a taxane on progression vs a combination of either capecitabine–paclitaxel (XP) or XT. In the capecitabine monotherapy arm, 64% of patients received taxane monotherapy on progression. Although higher RRs were observed in the combination therapy groups, no statistically significant improvements in TTP or OS were observed. Fewer patients reported grade 3–4 toxicity with the combination of XT or XP compared with previous studies.

Gemcitabine has also demonstrated activity in MBC patients previously treated with multiple chemotherapies, with an RR of up to 37% (45). Albain et al. (10) randomly assigned 529 women whose MBC had been treated with anthracyclines to the combination of 3-weekly paclitaxel–gemcitabine (GP) vs paclitaxel monotherapy. In this study, RR, TTP, and OS were improved by the addition of gemcitabine to paclitaxel to an extent similar to that obtained with the XT regimen in the study by O'Shaughnessy et al. Compared with XT, fewer patients reported grade 3–4 toxicity with the GP regimen, although more febrile neutropenia, thrombocytopenia, and fatigue were observed in the GP therapy group than in the paclitaxel monotherapy group. Patients who were treated with GP rated their QoL better than did patients who were treated with paclitaxel monotherapy. However, further therapy following progression in the paclitaxel monotherapy group was not prespecified. Overall, the delivery of additional chemotherapy following progression was similar between the two groups, but only 15.6% of patients in the paclitaxel monotherapy group crossed over to gemcitabine (10). No data comparing GP with paclitaxel followed by gemcitabine (P→G) are available. In a smaller study (47), 100 patients with MBC were randomly assigned to eight cycles of combination of gemcitabine and docetaxel (GT) or four sequential cycles of docetaxel followed by four cycles of gemcitabine (T→G). No difference in RR, TTP, and OS was observed (47).

Capecitabine Alone vs Combination Therapy

Single-agent capecitabine has impressive antitumor activity, with an RR up to 58% as first-line therapy for MBC (44). A large study in Australia (48) demonstrated that first-line capecitabine had a similar activity to CMF, with a favorable toxicity profile (Supplementary Table 5, available online). Capecitabine prolonged the median OS (22 vs 18 months, P = .02) in this head-to-head comparison. These results are similar to those of a previous and smaller randomized phase II trial in the United States with a similar design (49). Capecitabine is an oral agent with a favorable toxicity profile and thus an ideal control for evaluating combinations with novel agents. In a recent phase III study (50), 752 women with anthracycline- and taxane-pretreated MBC were randomly assigned to the combination of ixabepilone and capecitabine or capecitabine alone. Crossover to ixabepilone upon progression in the capecitabine monotherapy group was not mandated in the study protocol. The addition of ixabepilone improved RR (35% vs 14%, P < .001) and prolonged median progression-free interval

(5.8 vs 4.2 months, P < .001). Substantial increases in severe peripheral neuropathy, fatigue, and neutropenia were observed in the combination therapy group. Sufficient survival data were not available at the time of the initial publication. These data have led to the Food and Drug Administration approval of the combination of ixabepilone and capecitabine in anthracycline- and taxane-pretreated MBC (51).

Vinorelbine Alone vs Combination Therapy

Vinorelbine is a third-generation vinca alkaloid that improves TTF and OS, without compromising QoL, when compared with melphalan in anthracycline-pretreated MBC (52). In the GEICAM 9903 trial (53), 252 women with MBC pretreated with an anthracycline and a taxane were randomly assigned to the combination of gemcitabine and vinorelbine (GV) vs vinorelbine alone (Supplementary Table 6, available online). Although the addition of gemcitabine improved median progression-free interval (6.0 vs 4.0 months, P = .003), and there was a suggested improved RR in the GV group (36% vs 26%, P = .093), there was no difference in OS between the two regimens. More patients who were treated with single-agent vinorelbine were offered further systemic therapy following progression, including 35% who received gemcitabine. QoL was not formally assessed in this study. Overall, both regimens were well tolerated, although there was slightly more toxicity with the combination regimen, including febrile neutropenia, alkaline phosphatase elevation, nausea, and vomiting. An older trial comparing single-agent vinorelbine vs 5-FU/leucovorin (LV) with the combination of mitoxantrone and 5-FU/LV (54) did not show any difference in RR, TTP, or OS.

Single Agents No Longer Routinely Used vs Combination Therapy

Several studies compared single agents that are no longer routinely used in the management of MBC vs combination regimens. These trials are listed in Supplementary Table 7 (available online). Many of the studies were underpowered to show survival differences. The interpretation and relevance of these results is questionable now that modern agents with greater antitumor activity are used in the management of MBC.

Interpretive Summary

Although two meta-analyses have shown a slight improvement in OS with combination vs single-agent therapy in MBC (15,55), these overviews are heavily biased by the inclusion of clinical trials testing outdated chemotherapy regimens, many of which contained serious methodological flaws, failed to mandate crossover in the single-agent arm, and did not measure the impact of therapy on patients' QoL. Furthermore, it is possible that administration of additional lines of therapy upon progression may dilute the survival advantage of an upfront combination approach. Consequently, it is difficult to apply the conclusions of these meta-analyses to current clinical practice when deciding whether a combination or sequential approach should be used.

In the modern era, two well-conducted multi-institutional phase III clinical trials (12,10) have demonstrated that median OS is improved by approximately 3 months with a combination regimen

using a taxane backbone in patients pretreated with anthracyclines. These two studies showed that RR and TTP were improved by combination therapy, at the expense of greater toxicity. Unfortunately, very few patients in the single-agent therapy groups of these studies crossed over to the additional drug used in the combination regimen on progression. The failure to properly address the question of combination vs sequential monotherapy in these two studies limits the generalizability of the survival benefit reported.

To date, only eight randomized studies have addressed this important clinical question (Table 2). One large adequately powered study (21) demonstrated similar efficacy for upfront combination vs sequential anthracycline and taxane therapy, with greater toxicity in the combination arm. Similar results in terms of both efficacy and toxicity were reported by five other studies testing a variety of combination regimens (22,27,28,39,44,47). In a study in Scandinavia of patients who were previously treated with anthracyclines (39), single-agent docetaxel demonstrated a higher RR and TTP than methotrexate-5-fluorouracil therapy, although there was no difference in OS. Conversely, results from a small unpublished study (43) indicated that the combination of docetaxel and capecitabine improved RR, progression-free interval, and OS when compared with the sequential approach. The conclusions that can be drawn from these studies are limited by heterogeneity in trial design and conduct. The approach to sequential therapy varied greatly because many of the studies started treatment with a second agent following a predefined number of cycles of initial non–cross-resistant monotherapy (22,27,28,47) rather than pursuing the standard clinical practice of using symptomatic and/or radiographic progression as the trigger for shifting to second-line therapy.

It appears that combination therapy is associated with an improved RR and TTP compared with sequential therapy with greater expected treatment-related toxicity (Table 3). Unfortunately, it is difficult to draw definitive conclusions regarding the impact of combination therapy on OS and QoL; the latter, in part, because many trials do not report the incidence of low-grade toxic effects that may be most relevant to patients with metastatic disease. Because MBC is an incurable disease and the main aim of treatment is palliation, QoL and OS should be the ultimate endpoints against which any systemic therapy is evaluated. As a result, a properly conducted multi-institutional clinical trial with predefined therapy following progression in both the combination and sequential arms is needed. Prospective evaluation of treatment-related side effects and the impact on QoL using standardized patient-reported questionnaires and/or interviews is strongly recommended. Moreover, urgent research is required on the development and evaluation of supportive interventions that might

Table 2. Efficacy data from randomized studies with mandated crossover in the monotherapy arm*

First author, year (ref)	Comparison (No. of cycles if preplanned)	No. of patients	First-line therapy for MBC, %	Response rate, %	Median TTF, mo (95% CI)	Median OS, mo (95% CI)	Patients who received crossover in monotherapy arm, %
Alba,† 2004 (27)	A × 3 → Doc × 3	144	100	61 (50 to 72)	10.5 (NR)	22.3 (NR)	81‡
	A + Doc × 6			51 (39 to 63)	9.2 (NR)	21.8 (NR)	
Beslija,§ 2006 (43)	Doc → X	100	100	40 (NR)	7.7 (NR)	19.0 (NR)	74
	Doc + X			68 (NR)‖	9.3 (NR)§	22.0 (NR)‖	
Conte,† 2004 (22)	E × 4 → Pac × 4	202	100	58 (NR)	10.8 (7.9 to 13.6)¶	26.0 (18.1 to 33.8)	65‡
	E + Pac × 8			58 (NR)	11.0 (9.7 to 12.3)¶	20.0 (17.2 to 22.6)	
Koroleva,† 2001 (28)	Doc × 4 → A × 4	193	100	56 (NR)	6.9 (4.9 to 8.5)	13.8 (9.0 to 24.9)	NR
	A + Doc¶ × 8			49 (NR)	6.7 (5.2 to 8.2)	11.9 (10.6 to 15.4)	
	A + Doc† × 8			59 (NR)	8.3 (7.1 to 9.2)	14.5 (9.6 to 24.2)	
Sjöstrom,§ 1999 (39)	Doc → MF	238	85	42 (NR)‖	6.3 (NR)§	10.4 (NR)	50
	MF → Doc			21 (NR)	3.0 (NR)	11.1 (NR)	
Sledge,§ 2003 (21)	A → Pac	739	85	36 (NR)	5.8 (NR)#	18.9 (NR)	58
	Pac → A			34 (NR)	6.0 (NR)#	22.2 (NR)	59
	A + Pac			47 (NR)‖	8.0 (NR)‖,#	22.0 (NR)	
Soto,§ 2006 (44)	X → Pac or Doc	368	78	45 (NR)	8.4 (NR)¶	31.5 (NR)	64
	X + Pac			64 (NR)‖	6.7 (NR)¶	33.1 (NR)	
	X + Doc			75 (NR)‖	8.1 (NR)¶	28.5 (NR)	
Tomova,† 2008 (47)	Doc × 4 → G × 4	100	NR	28 (NR)	6.7 (4.7 to 9.0)#	15.9 (11.3 to reached)	63
	Doc + G × 8			31 (NR)	7.0 (5.5 to 8.2)#	15.5 (13.7 to 19.8)	

* A = doxorubicin; A + Doc† = doxorubicin 60 mg/m² and docetaxel 60 mg/m²; A + Doc¶ = doxorubicin 50 mg/m² and docetaxel 75 mg/m²; CI = confidence interval; Doc = docetaxel; E = epirubicin; G = gemcitabine; MBC = metastatic breast cancer; MF = methotrexate-5-fluorouracil; NR = not reported; OS = overall survival; Pac = paclitaxel; TTF = time to treatment failure; X = capecitabine.

† Trials with a preplanned number of monotherapy cycles before crossover.

‡ Percentage of patients randomly assigned to sequential therapy who completed all planned cycles of chemotherapy.

§ Trials in which the monotherapy treatment group crossed over on progression.

‖ Statistically significant ($P \leq .05$ using log-rank, Fisher exact, or χ^2 two-sided test; combination is compared with the single-agent group).

¶ Progression-free interval.

Time to disease progression.

Table 3. Selected toxicity data from randomized studies with mandated crossover in the monotherapy arm (% grade ≥3)*

First author, year (ref)	Comparison (No. of cycles if preplanned)	Febrile neutropenia, %	Mucositis, %	Diarrhea, %	Neurotoxicity, %
Alba, 2004 (27)	A × 3 → Doc × 3	29	12	3	4
	A + Doc × 6	48	7	10	4
Beslija, 2006 (43)	Doc → X	12	6	6	NR
	Doc + X	11	15	11	NR
Conte, 2004 (22)	E × 4 → Pac × 4	6	4	NR	13
	E + Pac × 8	7	8	NR	4
Koroleva, 2001 (28)	Doc × 4 → A × 4	10	7	2	5
	A + Doc* × 8	15	0	10	2
	A + Doc† × 8	10	2	3	0
Sjöstrom, 1999 (39)	Doc → MF	26†	9	10	5
	MF → Doc	6†	5	10	1
Sledge, 2003 (21)	A → Pac	4†	8	2	2
	Pac → A	8†	3	2	4
	A + Pac	13†	4	4	11
Soto, 2006 (44)	X → Pac or Doc	NR	6	5	NR
	X + Pac	NR	3	7	NR
	X + Doc	NR	4	7	NR
Tomova, 2008 (47)	Doc × 4 → G × 4	10	2	0	NR
	Doc + G × 8	4	4	4	NR

* A = doxorubicin; A + Doc* = doxorubicin 50 mg/m² and docetaxel 75 mg/m²; A + Doc† = doxorubicin 60 mg/m² and docetaxel 60 mg/m²; Doc = docetaxel; E = epirubicin; G = gemcitabine; MF = methotrexate-5-fluorouracil; NR = not reported; Pac = paclitaxel; X = capecitabine.

† Infection including febrile neutropenia.

ameliorate the toxic effects and side effects associated with the otherwise most efficacious chemotherapies. Consideration should also be given to well-defined translational research to better characterize the molecular determinants of response to MBC therapy. Similar studies have been successfully performed in other cancer types (56,57). Such a prospective trial is under discussion within the Breast International Group and the Breast Cancer Intergroup of North America networks.

In the absence of such evidence to guide daily clinical decision making in MBC, both combination and sequential single-agent chemotherapy are reasonable options as first-line systemic therapy. An important question for future research is the clear definition of patients who may benefit from a combination approach. Until such data are available, the ESO-MBC Task Force believes that sequential single-agent therapy should be the preferred choice for most MBC patients, in the absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control. These recommendations reflect consensus expert opinion and represent level 5 clinical evidence (58). Ultimately, the choice between combination and sequential systemic therapy for MBC must involve an open discussion of potential side effects and logistical requirements with patients, taking into consideration the cost and availability of chemotherapeutic agents in local clinical practice settings.

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Notes