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REVIEW

Combination of Cytotoxic Drugs for Patients with HER2-Negative Metastatic Breast Cancer

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ABSTRACT

In the last few decades the approach to metastatic breast cancer (MBC) treatment using chemotherapy, either as single or combination agents, has been largely studied and a wide spectrum of therapeutic options is now available. Anthracyclines and taxanes remain the cornerstone of treatment in this setting. The choice of combination chemotherapy versus monochemotherapy is still open to debate since results from clinical trials are, unfortunately, conflicting. Despite improvements in response and disease-free survival rates, there has been no overall survival benefit reported although toxicity is increased. Therefore, based on available data, clinical decision-making for a busy practitioner should consider not only patient/tumor characteristics and the potential benefits of treatments, but also their toxicity profiles and patient preferences. Novel cytotoxic compounds have been approved for clinical use and combination regimens incorporating these agents may bring new treatment opportunities for MBC patients. In this review, we summarize the main achievements and the currently available and future combinations of cytotoxic drugs for patients with HER2-negative MBC.

Keywords: Combination chemotherapy; HER2-negative; Metastatic breast cancer

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INTRODUCTION

Breast cancer is one of the most common female cancers and among the most frequent causes of cancer mortality among women worldwide. Most cases of breast cancer are early stage and operable at presentation, but approximately 15–20% of patients will relapse and ultimately die from metastatic disease [1]. The choice of

treatment for metastatic breast cancer (MBC) is strongly influenced by the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status of the tumor. However, almost all patients with metastatic disease receive chemotherapy during their clinical history.

When chemotherapy is indicated, anthracyclines and taxanes represent the most active agents, especially in previously unexposed patients. These drugs, as single agents, yield an objective response in 20–80% of patients with metastatic disease [2, 3]. Combination regimens involving anthracyclines and taxanes are valid treatment options for patients with MBC, providing overall response rates ranging from 47 to 77% and a significantly longer time to progression, ranging between 6.0 and 10.3 months, compared to other polychemotherapies [4–11]. However, whether combination chemotherapy offers an advantage over sequential therapy for the management of MBC is still an unresolved issue [12, 13]. This review focuses on the efficacy and toxicity profiles of taxane- and anthracycline-containing regimes that have been reported in the MBC setting. In addition, results of published and ongoing trials of combination treatments with novel microtubule-targeting agents approved for MBC are also described.

ANTHRACYCLINE-BASED COMBINATION TREATMENTS IN METASTATIC BREAST CANCER

Anthracycline-containing regimens have demonstrated significant disease-free and overall survival benefits in the adjuvant setting [1] and they also provide palliative benefit in metastatic disease. However, prolonged use of anthracyclines is limited by cumulative, dose-related cardiotoxicity, especially in metastatic patients who have been pretreated with anthracyclines in the adjuvant setting [10]. Many trials have compared single versus combination strategies using an anthracycline in MBC patients (Table 1). The French Epirubicin Study Group trial [14] showed that the addition of 5-fluorouracil (5-FU) and cyclophosphamide to epirubicin at two different doses [50 mg/m^2 (FEC50) and 75 mg/m^2 (FEC75)] was associated with an increase in response rate [30.6% for epirubicin alone (75 mg/m^2), 44.6% for FEC50, and 44.7% for FEC75; $P = 0.04$ for FEC50 vs. epirubicin alone and $P = 0.006$ for FEC75 vs. epirubicin alone]. Despite this, compared with epirubicin alone, the use of these combinations did not prolong progression-free interval or overall survival compared with epirubicin alone. A Finnish trial [15] compared 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 cyclophosphamide (500 mg/m^2), epirubicin (60 mg/m^2), and fluorouracil (500 mg/m^2) (CEF) three times per week received combination MMC–vinblastine (MV) following progression. An objective response was obtained in 55%, 48%, 16%, and 7% of patients treated with CEF, epirubicin, MMC, and MV, respectively [15]. A response to combination CEF tended to last longer than a response to single-agent epirubicin (median 12 vs. 10.5 months, respectively; $P = 0.07$) without statistical differences in time to progression or survival. This confirms that combination therapy improves disease response with no improvement in progression-free interval or

Table 1 Efficacy data and toxicity profiles from randomized studies with anthracycline-based and taxane-based combination therapies

First author (year)	Comparison	No. patients	Response rate (%)	Median TTF (months)	Median OS (months)	Febrile neutropenia (%)	Mucositis ≥G3 (%)	Diarrhea ≥G3 (%)	Neuropathy ≥G3 (%)
O'Shaughnessy [21]	D+X	511	42	6.1	14.5	16	17	14	NR
	D		30	4.2	11.5	21	5	5	NR
Albain [23]	G+P	529	41.4	6.14	NR	13	1	3	6
	P		26.2	3.98	NR	1	0.4	2	4
Sparano [22]	PLD+D	751	35	9.8	20.5	7	12	2	1
	D		26	7.0	20.6	7	1	1	1
Sledge [8]	A→P	739	36	5.8	18.9	4	8	2	2
	P→A		34	6.0	22.2	8	3	2	4
	A+P		47	8.0	22.0	13	4	4	11
Alba [18]	A→D	144	61	10.5	22.3	29	12	3	4
	A+D		51	9.2	21.8	48	7	10	4
Conte [17]	E→P	202	58	10.8	26.0	6	4	NR	13
	E+P		58	11.0	20.0	7	8	NR	4

A doxorubicin, *D* docetaxel, *E* epirubicin, *G* gemcitabine, *G3* grade 3, *NR* not reported, *OS* overall survival, *P* paclitaxel, *PLD* pegylated liposomal doxorubicin, *TTF* time to treatment failure, *X* capecitabine

overall survival, and does so at the expense of treatment-related toxicity and quality of life.

Because both anthracyclines and taxanes are among the most efficacious drugs in the treatment of breast cancer, the combination of the two drugs in first-line therapy of metastatic disease was a logical step. The choice of an optimal first-line combination incorporating anthracyclines and taxanes for anthracycline-naïve or minimally exposed MBC patients has been the focus of most trials. Among these, Jassem et al. [16] randomized patients with MBC to receive doxorubicin (A) (50 mg/m^2) followed 24 h later by paclitaxel (P) (220 mg/m^2) (AP) or 5-FU (500 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) (FAC). Combination therapy with AP showed a significant advantage in overall response rate (68% vs. 55%, respectively; $P = 0.032$], median time to progression (8.3 vs. 6.2 months, respectively; $P = 0.034$), and overall survival (23.3 vs. 18.3 months, respectively; $P = 0.013$)] rather than FAC with no unexpected toxicities. Bontenbal et al. [6] compared doxorubicin (50 mg/m^2) and docetaxel [(T) 75 mg/m^2) (AT) to a standard FAC regimen (5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2] as first-line chemotherapy for patients with MBC. Median time to progression and median overall survival were significantly longer for patients on AT compared with FAC (time to progression 8.0 vs. 6.6 months, respectively; $P = 0.004$; and overall survival 22.6 vs. 16.2 months, respectively; $P = 0.019$). In addition, the overall response rate was significantly higher in patients on AT compared with FAC (58% vs. 37%, respectively; $P = 0.003$) [6]. There were no significant differences in grade 3 or 4 neutropenia or cardiac toxicity, but neurotoxicity and neutropenic fever were significantly more common in the AT arm. The Eastern Cooperative Oncology Group (ECOG) 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 [8]. Combination therapy with AP achieved better results in terms of response rate (36% for doxorubicin, 34% for paclitaxel, and 47% for AP; $P = 0.84$ for doxorubicin vs. paclitaxel; $P = 0.007$ for doxorubicin vs. AP; and $P = 0.004$ for paclitaxel vs. AP) and median time to treatment failure (5.8 months for doxorubicin, 6.0 months for paclitaxel and 8.0 months for AP; $P = 0.68$ for doxorubicin vs. paclitaxel; $P = 0.003$ for doxorubicin vs. AP; and $P = 0.009$ for paclitaxel vs. AP), but there was no difference in term of median overall survival or quality of life. However, in two similar studies [17, 18] comparing single-agent anthracycline (epirubicin or doxorubicin) followed by single-agent taxane (paclitaxel or docetaxel) with combination regimens, no differences in response rate, progression-free interval, or overall survival were observed.

TAXANE-BASED COMBINATION TREATMENTS IN METASTATIC BREAST CANCER

The common use of anthracycline-based regimens in the adjuvant setting has increased the likelihood for patients with anthracycline-resistant tumors. Taxanes, such as paclitaxel and docetaxel, have emerged as the most active cytotoxic agents for breast cancer, either in early or advanced stages. In the metastatic setting, taxanes are active in anthracycline-resistant disease, and in phase III trials, single-agent taxanes were at least as active as, and sometimes more active than, single-agent anthracyclines [19, 20]. The clinical activity of taxane monotherapy against taxane

combination regimens has been extensively investigated in a variety of studies (Table 1). O'Shaughnessy et al. [21] reported significantly superior time to disease progression and overall survival with the addition of capecitabine to docetaxel in 511 patients progressing after anthracycline treatment either in the (neo-)adjuvant or the metastatic setting. Capecitabine plus docetaxel resulted in significantly superior efficacy in terms of time to progression (6.1 vs. 4.2 months, respectively; $P = 0.0001$), overall survival (14.5 vs. 11.5 months, respectively; $P = 0.0126$), and objective response rate (42% vs. 30%, respectively; $P = 0.006$) compared with docetaxel. Gastrointestinal side effects and hand–foot syndrome were more common with combination therapy, whereas myalgia, arthralgia, and neutropenic fever/sepsis were more common with single-agent docetaxel. More grade 3 adverse events occurred with combination therapy than docetaxel (71% vs. 49%, respectively), whereas grade 4 events were slightly more common with docetaxel than combination therapy (31% vs. 25%, respectively) [21]. Sparano et al. [22] enrolled 751 MBC patients previously treated with neoadjuvant–adjuvant anthracycline therapy to receive either docetaxel or pegylated liposomal doxorubicin (PLD) followed by docetaxel until disease progression or prohibitive toxicity. The primary endpoint was time to progression. Secondary endpoints were overall survival, objective response rate, cardiac toxicity, and safety. PLD–docetaxel significantly improved the median time to progression from 7.0 to 9.8 months ($P = 0.000001$) and the objective response rate from 26% to 35% ($P = 0.0085$)]. Overall survival was similar between the two groups. The PLD–docetaxel combination was more effective than docetaxel alone in women with MBC who had experienced relapse at least 1 year after prior adjuvant anthracycline therapy without increasing cardiac toxicity. The incidence of all grade 3 or 4 adverse events and serious adverse events were similar for the docetaxel arm (72% grade 3 or 4, 16% serious adverse events) and the PLD–docetaxel arm (78% grade 3 or 4, 18% serious adverse events), although a higher incidence of hand–foot syndrome and mucositis/stomatitis was observed in the PLD–docetaxel combination [22]. Albain et al. [23] reported an advantage in response rate, time to disease progression and overall survival by the addition of gemcitabine to paclitaxel in women with MBC who relapsed after adjuvant anthracyclines. Median survival on gemcitabine and paclitaxel combination was 18.6 months compared with 15.8 months on paclitaxel ($P = 0.0489$), with an adjusted Cox hazard ratio of 0.78 [95% confidence interval (CI) 0.64–0.96; $P = 0.0187$]. The time to progression was longer (6.14 vs. 3.98 months, respectively; $P = 0.0002$) and the response rate was better (41.4% vs. 26.2%, respectively; $P = 0.0002$) on gemcitabine than the paclitaxel combination. There was more grade 3 to 4 neutropenia on gemcitabine than the paclitaxel combination, and grade 2 to 4 fatigue and neuropathy were slightly more prevalent on gemcitabine than the paclitaxel combination [23].

NOVEL AGENT-BASED COMBINATION TREATMENTS IN METASTATIC BREAST CANCER

In an attempt to overcome chemotherapy resistance, new cytotoxic compounds have been developed for the treatment of patients with MBC. Ixabepilone, *nab*-paclitaxel and eribulin mesylate, all microtubule inhibitors, have been recently approved for clinical use.

These agents were shown to be active alone or in combination regimens, while other potential combination schemes are currently under evaluation in clinical trials (Table 2).

Ixabepilone

Epothilones are novel microtubule-stabilizing drugs that have a low susceptibility to common mechanisms conferring resistance to taxanes and other cytotoxic agents [24, 25]. Ixabepilone, a semi-synthetic derivative of natural epothilone B, is approved by the United States Food and Drug Administration (FDA) in combination with capecitabine for the treatment of patients with MBC resistant to anthracyclines and taxanes, and as monotherapy for MBC patients resistant or refractory to anthracyclines, taxanes, and capecitabine [26] Preclinical and clinical studies showed synergistic antitumor activity between ixabepilone and other chemotherapeutic drugs, including capecitabine [27–31]. Two large, randomized phase III studies showed that combination therapy with ixabepilone plus capecitabine was superior to capecitabine alone after the failure of anthracycline and taxane treatment in MBC. Thomas et al. [32] reported a significantly superior median progression-free survival (5.8 vs. 4.2 months, respectively; $P = 0.0003$) and objective response rate (35% vs. 14%, respectively; $P = 0.0001$) with the addition of ixabepilone to capecitabine compared with capecitabine alone in 752 patients with advanced or MBC progressing after anthracyclines. Progression occurred during treatment or within 3 months of the last dose in the metastatic setting, recurrence occurred within 6 months in the neoadjuvant or adjuvant settings, and resistance to taxanes occurred with disease recurrence documented within 4 months of the last dose in the metastatic setting or within 12 months in the adjuvant setting. Median overall survival was not significantly longer in the combination therapy group than the single-agent group (12.9 vs. 11.1 months, respectively; $P = 0.19$) [33]. Moreover, in a larger phase III trial that enrolled 1,221 MBC patients previously treated with, but not necessarily resistant to, anthracyclines and taxanes, the combination regimen with ixabepilone and capecitabine significantly improved median progression-free survival (6.2 vs. 4.2 months, respectively; $P = 0.0005$) and relative response (43% vs. 29%, respectively; $P = 0.0001$) compared with single-agent capecitabine [34]. In this study, anthracycline and taxane resistance was defined as tumor progression during treatment or within 3 months of the last dose in the metastatic setting, or recurrence within 6 months in the neoadjuvant or adjuvant settings [34]. However, a significant improvement in overall survival was not observed. The most common ixabepilone-related adverse event was peripheral neuropathy, which was primarily sensory and generally reversible with dose reduction or delay. Ixabepilone has also been evaluated in combination with other agents, such as anthracyclines. In a phase I trial, ixabepilone (16 mg/m^2 on days 1, 8, and 15) plus PLD (30 mg/m^2 on day 1 of a 4-week cycle) yielded objective responses in three of 13 patients (23%) with taxane-pretreated advanced breast cancer [35].

Nanoparticle Albumin-Bound Paclitaxel

Nanoparticle albumin-bound (*nab*-)paclitaxel is a new formulation of paclitaxel that does not require a solvent for delivery, reducing the risk of hypersensitivity reactions and eliminating

Table 2 Ongoing trials of novel agent-based combination therapies in metastatic breast cancer

Principal investigator, institution	Phase	Treatment	Population	Status	Primary endpoints	Clinical trials.gov identifier
Hope Rugo, University of California	Ib/II	Eribulin plus cyclophosphamide	Solid tumor malignancies	Recruiting	Maximum tolerated dose Clinical benefit rate	NCT01554371
H. Lee, Moffitt Cancer Center and Research Institute	I	Eribulin plus carboplatin	Metastatic breast cancer	Recruiting	Maximum tolerated dose Dose-limiting toxicity	NCT01795586
Claudio Savulsky Eisai Ltd	Ib/II	Eribulin plus capecitabine	Metastatic breast cancer	Active, not recruiting	Response rate Treatment-related toxicity	NCT01323530
Kimberly Blackwell, Duke University	II	*Nab*-paclitaxel plus carboplatin	Triple-negative metastatic breast cancer	Recruiting	Progression-free survival	NCT01207102
Jame Abraham, West Virginia University	I/II	*Nab*-paclitaxel plus doxorubicin HCl liposome injection (DOXIL®)[a]	Metastatic breast cancer	Completed	Maximum tolerated dose Dose-limiting toxicity Response rate	NCT00442260
Vivek Roy, Mayo Clinic Cancer Center	II	*Nab*-paclitaxel plus gemcitabine	Metastatic breast cancer	Completed	Response rate	NCT00110084
Xichun Hu, Fudan University	II	*Nab*-paclitaxel plus cisplatin	Metastatic breast cancer	Completed	Overall response rate	NCT01149798
Cynthia R Osborne, US Oncology	II	Ixabepilone plus carboplatin	Metastatic breast cancer	Active, not recruiting	Overall response rate	NCT01075100

Table 2 continued

Principal investigator, institution	Phase	Treatment	Population	Status	Primary endpoints	Clinical trials.gov identifier
Bristol-Myers Squibb	I	Ixabepilone plus capecitabine	Metastatic breast cancer	Completed	Maximum tolerated dose Dose-limiting toxicity	NCT00568022

[a] DOXIL®, Janssen Products, Horsham, PA, USA

the need for steroid and antihistamine premedication. Both the absence of solvents and the presence of albumin allow higher doses of paclitaxel to be delivered via *nab*-paclitaxel than with solvent-based paclitaxel. Indeed, drug transport into tumors is enhanced by albumin receptor (gp60)-mediated transcytosis across endothelial cells in preclinical models [36] and by association with the albumin-binding protein, SPARC (secreted protein, acidic and rich in cysteine) [37]. In preclinical and clinical studies [38–40], the equitoxic paclitaxel dose of *nab*-paclitaxel was approximately 50–70% higher than that of solvent-based paclitaxel. This higher doses afforded by *nab*-paclitaxel appears to translate into increased drug efficacy without an increase in toxicity. A large, randomized phase III trial demonstrated a higher response rate (33% vs. 19%, respectively; $P = 0.001$)], longer time to tumor progression (23.0 vs. 16.9 weeks, respectively), and progression-free survival (22.7 vs. 16.6 weeks, respectively) for *nab*-paclitaxel given every 3 weeks at 260 mg/m^2 when compared with polyoxyethylated castor oil-based paclitaxel at 175 mg/m^2 every 3 weeks in patients with MBC. Moreover, a statistically significant difference in median survival was observed in patients who received *nab*-paclitaxel compared with standard paclitaxel as second-line or greater therapy (56.4 vs. 46.7 weeks, respectively) [38]. In order to explore whether a weekly schedule might offer favorable clinical outcomes relative to the approved 3-weekly (Q3W) schedule, a phase II trial was conducted [40, 41]. Three hundred patients with previously untreated MBC were randomized to receive *nab*-paclitaxel at 100 mg/m^2 given weekly for 3 weeks followed by 1 week (QW) of rest, then 150 mg/m^2 QW and 300 mg/m^2 Q3W, and docetaxel 100 mg/m^2 Q3W. Weekly scheduled doses of

nab-paclitaxel were associated with a similar tolerability profile to Q3W dosing, with no new or unexpected toxicities reported. The incidence of important adverse events was similarly low across all three *nab*-paclitaxel groups, and was significantly higher in the docetaxel group. However, *nab*-paclitaxel 150 mg/m^2 QW appeared to be associated with a significantly greater overall response rate, longer progression-free survival and superior overall survival compared with the other groups, suggesting that this schedule may have a superior therapeutic index compared with Q3W dosing for first-line treatment of women with MBC [40, 41]. In the MBC setting, two phase II studies have investigated *nab*-paclitaxel chemotherapy doublets. The North Central Cancer Treatment Group (NCCTG) phase II trial prospectively evaluated *nab*-paclitaxel and gemcitabine for previously untreated patients [42]. *Nab*-paclitaxel (125 mg/m^2) and gemcitabine (1,000 mg/m^2) were administered on days 1 and 8 of a 21-day cycle until disease progression. Fifty patients were enrolled. Four (8%) and 21 (42%) patients had complete and partial responses, respectively, and median progression-free survival was 7.9 months (95% CI 5.4–10 months). Therapy was well tolerated: neutropenia was the most common toxicity (42% and 12%, grades 3 and 4 neutropenia, respectively), grade 3 fatigue (29%) and sensory neuropathy (6%). A phase II trial was designed to test the safety and efficacy of capecitabine and *nab*-paclitaxel in previously untreated MBC [43]. In this trial, 50 patients received capecitabine (825 mg/m^2 orally twice daily, on days 1–15) and *nab*-paclitaxel (125 mg/m^2 intravenously on days 1 and 8 of each cycle) every 3 weeks. The objective response rate was 61% (complete response 4%, partial response 57%), and seven patients had sustained (≥24-week) stable disease for a clinical benefit rate of 76.1%. Median progression-free survival was 10.6 months, and the median overall survival was 19.9 months. The most common adverse events of grade ≥3 were pain, hand–foot syndrome, and neutropenia [43].

Eribulin Mesylate

Eribulin, a synthetic analog of the marine macrolide halichondrin B, inhibits microtubule stability by blocking microtubule growth without affecting microtubule shortening, leading to the formation of abnormal mitotic spindles and, ultimately, apoptosis [44, 45]. Phase I and II studies indicated that eribulin has activity with acceptable toxicity in MBC, including patients pretreated with anthracyclines and taxanes. The phase III EMBRACE trial (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus **E7389**) compared eribulin with the physician's choice of treatment (most commonly, vinorelbine, gemcitabine, or capecitabine) in 762 patients with anthracycline- and taxane-pretreated, locally recurrent breast cancer or MBC [46]. Eribulin significantly improved median overall survival compared with the physician's choice of treatment (13.1 vs. 10.6 months, respectively; $P = 0.041$). Upon independent review, eribulin was also found to be associated with a higher relative response rate than the physician's choice of treatment (12 vs. 5%, respectively; $P = 0.002$) and showed a trend for improved progression-free survival (3.7 vs. 2.2 months, respectively; $P = 0.137$). Eribulin had a manageable tolerability profile, with grade 3/4 neutropenia reported in 45% of patients [46]. A phase Ib dose-escalation study evaluated eribulin mesylate in combination with capecitabine in patients with advanced/

metastatic cancer [47]. In total, 34 patients were recruited, five of whom had MBC. The combination of eribulin and capecitabine was generally well tolerated at all dose levels evaluated in the study and the most common grade 3/4 toxicity was neutropenia. The maximum tolerated dose for schedule 2 (1.4 mg/m^2 of eribulin mesylate in combination with capecitabine 1,000 mg/m^2 twice daily) was determined to provide superior drug exposure of eribulin than the maximum tolerated dose for schedule 1 (1.6 mg/m^2 of eribulin mesylate in combination with capecitabine 1,000 mg/m^2 twice daily), and this schedule is currently being evaluated in an ongoing phase II trial in patients with MBC.

CONCLUSION

Important therapeutic innovations within the last few decades have resulted in significant survival benefits for women with HER2-negative MBC. However, the ideal treatment strategies for specific subsets of patients have not been determined. The choice between combination and sequential cytotoxic chemotherapies is still controversial. Overall, combination regimens are frequently favored over single agents in an attempt to achieve superior tumor response rates. It is unclear, however, whether giving more intensive chemotherapy regimens results in improved health outcomes when both survival and toxicity are considered, and whether better response rates and duration of progression-free survival actually translate into better overall survival [48–52]. In general, survival gains with combination therapies have come at the expense of a significant increase in toxicity and a negative impact on quality of life. Therefore, based on the available data, there is consensus that combination therapy is the preferred choice, but only in the presence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control.

Several trials are underway to evaluate combination therapy involving novel antineoplastic agents, such as ixabepilone, eribulin or *nab*-paclitaxel, which may offer additional treatment options for MBC patients. However, an important issue for future research is to better define the molecular profiles of MBC to identify the patients who may benefit from a combination approach. In the absence of such evidence to guide daily clinical decision-making in the MBC setting, both combination and sequential single-agent chemotherapies are reasonable options. Patient- and disease-related factors and patient preferences should be used to guide the choice of the best chemotherapy regimen, taking into account that balancing the efficacy and safety is a key goal for delivering a positive risk-benefit profile for each patient.

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