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Oral chemotherapy in advanced breast cancer: expert perspectives on its role in clinical practice

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ABSTRACT

Metastatic breast cancer (MBC) is quite sensitive to chemotherapy, with patients often benefiting from multiple lines of treatment. Continuation of chemotherapy until disease progression, if tolerable, prolongs disease control and improves patient outcomes. Compared to combination regimens, sequential single-agent chemotherapy provides similar efficacy and improved tolerability and may represent the preferred option for most patients. Numerous agents are available, but there are few data to advise optimal sequencing. Oral chemotherapeutic agents, including capecitabine and vinorelbine, have demonstrated significant efficacy in patients with MBC. These drugs prolong disease control with good tolerability, especially when used as single agents. In addition, oral chemotherapy reduces the time and cost associated with treatment and usually is preferred by patients if compared with intravenous delivery. Metronomic administration of oral chemotherapy also represents a promising therapeutic approach for select patients with MBC, inhibiting tumor progression through multiple mechanisms of action. Ongoing clinical trials are exploring metronomic regimens as a strategy to prolong disease control with favorable tolerability. Key data on the role for oral chemotherapy in the therapeutic landscape for MBC will be reviewed and accompanied by expert perspectives on important considerations for the integration of oral chemotherapeutic agents into the treatment of patients with MBC.

Introduction

Despite substantial progress in the treatment of breast cancer, advanced disease is incurable and the goals of therapy consist of prolonging survival where possible but, most importantly, palliating symptoms and optimizing quality of life (QoL) [1–3]. Multiple parameters influence treatment choices for patients with metastatic breast cancer (MBC), including tumor biology, extent of disease, previous therapies, age, performance status, comorbidities, patient preference, and drug availability [1,2].

The role for oral chemotherapy in MBC was explored in two discussion forums held in San Antonio in December 2014 and December 2015. An expert faculty of breast medical oncology thought leaders and clinical experts from across Europe were invited to each interactive workshop to review the chemotherapy options for MBC and the potential role of oral cytotoxic agents in providing effective palliation. In addition to discussion around didactic state of the art presentations from the authors, the attendees discussed the management of case scenarios to help identify the place of oral chemotherapy in MBC. The following is a summary of these discussions and highlights important considerations in selecting oral chemotherapeutic agents for the management of patients with MBC. Support for both discussion forums and this manuscript was provided by an unrestricted educational grant from Pierre Fabre Medicament. The views expressed are those of the authors and were not influenced by the company.

Current therapeutic landscape for metastatic breast cancer

The ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2) recommend that treatment choice is driven by many factors, such as biology (hormonal receptor and HER2 expression), patient characteristics (age, comorbidities, menopausal status), and patient preferences, among others [1,2]. For triple-negative breast cancer (TNBC) lacking therapeutic targets, chemotherapy is the mainstay of treatment [1,2]. Decisions regarding

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optimal selection, sequencing, and duration of therapy for patients with advanced breast cancer continue to evolve. For those with HER2-positive disease, HER2 blockade is the backbone of treatment. Combination strategies with HER2-targeted agents are most often employed, such as combinations with IV or oral chemotherapy or endocrine therapy [1,2,4].

In patients with endocrine-sensitive, HER2-negative disease, endocrine therapy alone is preferred with increasing options for both sequential endocrine treatments alone and in combination with targeted agents such as everolimus [1,2] and (at the time of this discussion forum only in the United States) palbociclib [5]. However, endocrine resistance typically occurs and nearly all patients will receive chemotherapy during the disease course [1,2]. Resistance to endocrine therapy has lacked a clear definition, complicating treatment decisions in this patient subset. The ABC2 consensus guidelines define primary endocrine resistance as a relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within the first 6 months of first-line endocrine therapy for MBC while on endocrine therapy [1,2]. Secondary (acquired) endocrine resistance is defined as a relapse while on adjuvant endocrine therapy but after the first 2 years, or a relapse within 12 months of completing adjuvant endocrine therapy, or progressive disease at least 6 months after initiating endocrine therapy for MBC while still on endocrine therapy. Chemotherapy should be considered when there is concern regarding endocrine resistance and for those with immediately life-threatening and/or highly symptomatic disease. Numerous chemotherapeutic agents have demonstrated efficacy in patients with HER2-negative MBC, including oral agents and formulations [3].

Chemotherapy in metastatic breast cancer: considerations for therapy selection, sequencing, and duration

While the treatment of MBC is primarily palliative, strategies to optimize therapy and prolong survival remain important [1–3]. MBC is quite sensitive to chemotherapy, but with a large variation in the probability of response according to treatment factors and patient and disease features. Although duration of treatment and response often diminish as the number of lines of therapy increase, many patients will respond to multiple lines of chemotherapy well beyond the first-line regimen [6,7]. However, uncertainty remains regarding the best sequence of therapies as well as the optimal duration of therapy.

Meta-analyses and review of randomized clinical trial data demonstrate comparable efficacy, including overall survival (OS), for sequential versus combination chemotherapy [8,9]. In addition, sequential single-agent chemotherapy is associated with fewer adverse events, which can positively impact QoL. Based on similar efficacy, with better tolerability and QoL, current guidelines state that sequential single-agent chemotherapy is preferred over combination chemotherapy [1–3]. However, because combination regimens are associated with more rapid and higher probability of objective response, they may be needed for patients with rapidly progressing or life-threatening disease or highly symptomatic metastases.

Chemotherapy treatment selection should be based on previous chemotherapy exposure and response, side effect profile, comorbid conditions, and patient preference [1,2]. Chemotherapy selection is currently not tailored to tumor molecular profiles [1–3], with the possible exception of platinum agents for *BRCA*-associated cancers [1,2,10]. Numerous chemotherapeutic agents are available and have demonstrated efficacy in MBC, but there are few data from randomized clinical trials to advise on optimal sequencing of agents and this will be influenced by the use and type of adjuvant chemotherapy the patient has previously received, the treatment free interval and patient preferences [1–3]. Many patients will have received adjuvant anthracyclines with or without a taxane. Although patients with MBC may be rechallenged with an alternative anthracycline-based regimen if there is a long disease-free interval, different classes of agents are often preferred [1,2]. Taxanes remain an important first-line therapy for MBC in patients who are taxane-naïve or have disease progression more than 12 months after completion of adjuvant therapy with many clinicians using a different taxane or schedule to that used in the adjuvant setting.

Alternative choices for first-line therapies, and endorsed by the ABC2 guidelines [1,2], include single-agent capecitabine, vinorelbine, or eribulin. Specifically, eribulin demonstrated a survival benefit over the physicians' treatment of choice in heavily pretreated patients with MBC in the phase III EMBRACE trial (median OS 13.1 vs 10.6 months, hazard ratio [HR] 0.81; $P = 0.041$) [11]. A phase III study directly comparing eribulin to capecitabine as first-, second-, or third-line therapy in patients with anthracycline- and taxane-pretreated MBC did not show superiority for eribulin, with similar median OS (15.9 for eribulin vs 14.5 months for capecitabine, HR 0.88; $P = 0.056$) and progression-free survival (PFS: 4.1 vs 4.2 months, HR 1.08; $P = 0.30$) for both agents [12]. Gemcitabine, liposomal anthracyclines, *nab*-paclitaxel, platinum agents, ixabepilone, and clinical trial enrollment represent other treatment options for advanced disease, although ixabepilone is not available outside the United States [1–3].

Chemotherapy duration and the use of maintenance therapy remains an area of debate among clinicians. Continuation of chemotherapy until disease progression, if well tolerated, should be considered when prolonged disease control may be beneficial [1–3]. This is supported by data from a meta-analysis showing that a longer duration of first-line chemotherapy resulted in a significant PFS benefit (HR 0.64; $P < 0.001$) and OS (HR 0.91; $P = 0.046$) compared to shorter chemotherapy schedules [13]. However, given the modest improvement in OS, prolonged exposure to chemotherapy should be balanced against adverse events and QoL. Short breaks and flexibility in treatment schedule should also be considered for selected patients in remission [1–3]. Maintenance chemotherapy usually consists of continuing the same treatment dose and schedule until disease progression [14]. However, switch maintenance strategies are also under investigation and may improve OS and/or PFS, as demonstrated in the recent phase III IMELDA and TANIA trials of bevacizumab with or without chemotherapy [15,16]. For those with hormone receptor–positive breast cancer, maintenance endocrine therapy can be utilized after response to initial chemotherapy [17,18]. Ongoing studies are also exploring alternative dosing strategies, including metronomic dosing strategies, which are discussed in further detail below [19].

The role for oral chemotherapy in metastatic breast cancer

The concept that MBC is a treatable but still generally incurable disease reinforces the importance of balancing disease control with the detrimental effects that can be associated with prolonged chemotherapy exposure and very limited survival benefit [3]. Thus, it is important to discuss all treatment options with patients with MBC and evaluate the risk-to-benefit ratio, reflecting the treatment goals of improving both length and quality of life [1–3]. The needs of the patient and their personal preferences and expectations are important factors in treatment selection and acceptance of a therapeutic plan. Alternative dosing schedules and more convenient routes of administration, such as oral agents, should be considered, while ensuring that treatment is associated with low levels of cumulative toxicity. Numerous oral therapies are now available for the treatment of MBC, including chemotherapeutic agents and targeted agents. While oral targeted therapies such as lapatinib, everolimus, and palbociclib are improving patient outcomes, detailed discussion of these agents is beyond the scope

Table 1
Selected studies of capecitabine as a single agent in metastatic breast cancer [30–40]

Reference	Capecitabine schedule	*N*	Line of treatment	ORR, %	CBR, %	PFS/TTP, months	OS, months
O'Shaughnessy et al. Ann Oncol 2001 [30]	1255 mg/m² bid d1-14 q3w	61	1st	30	81	4.1	19.6
Stockler et al. J Clin Oncol 2011 [31]	1000 mg/m² bid d1-14 q3w or 650 mg/m² bid continuously	214	1st	21	49	6.0	22
Kaufmann et al. Eur J Cancer 2010 [32]	1000 mg/m² bid d1-14 q3w	161	1st	26.1	64	7.9	18.6
Robert et al. J Clin Oncol 2011 [33]	1000 mg/m² bid d1-14 q3w	206	1st	23.6	NR	5.7	NR
Sparano et al. J Clin Oncol 2010 [34]	1250 mg/m² bid d1-14 q3w	612	1st, 2nd, or 3rd, post anthrax and txn	28.8[a]	68.2[a]	4.4[b]	15.6
Talbot et al. Br J Cancer 2002 [35]	1255 mg/m² bid d1-14 q3w	22	2nd	36	59	3.0	7.6
Brufsky et al. J Clin Oncol 2011 [36]	1000 mg/m² bid d1-14 q3w	47	2nd	15.4	NR	4.1	NR
Miller et al. J Clin Oncol 2005 [37]	1250 mg/m² bid d1-14 q3w	230	2nd or 3rd, post anthrax and txn	9.1	NR	4.17	14.5
Reichardt et al. Ann Oncol 2003 [38]	1250 mg/m² bid d1-14 q3w	136	2nd or later, post anthrax and txn	15	62	3.5	10.1
Blum et al. J Clin Oncol 1999 [39]	1255 mg/m² bid d1-14 q3w	163	2nd or later, txn refractory	20	60	3.1	12.8
Blum et al. Cancer 2001 [40]	1255 mg/m² bid d1-14 q3w	75	2nd or later, txn refractory	26	57	3.2	12.2

[a]N = 462; [b]N = 480
Abbreviations: anthra, anthracycline; bid, twice daily; CBR, clinical benefit rate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; TTP, time to progression; txn, taxane

of this manuscript, which focuses specifically on the role for oral chemotherapies in MBC.

In comparison to standard intravenous (IV) chemotherapy, oral chemotherapy provides patients with more convenience and allows clinicians to more easily tailor therapy dosing if needed [20]. In addition, less time in the clinic is required, which translates into cost and staffing savings. Surveys demonstrate that most patients prefer oral therapy to IV treatments when equivalent efficacy is established [21,22]. However, oral chemotherapy is not free from potentially dangerous side-effects, and so it is essential from a safety perspective to have effective patient education and follow-up, as well as simple dosing schedules [20]. Dosing mistakes, such as patients forgetting the treatment breaks commonly used with some therapies (i.e., 2 weeks on, 1 week off for capecitabine) or taking the wrong number of pills can negatively affect both efficacy and tolerability. Adherence can be a concern and is influenced by multiple factors, including complex treatment regimens, requirement for substantial behavioral changes, inconvenient or inefficient clinics, poor communication by healthcare providers, gastrointestinal side-effects or abdominal pathology, and history of mental illness [23,24]. Improper handling or storage of oral medications can also be a problem, compromising the effectiveness of the medication [25]. Providing continuous patient education throughout the treatment course can help prevent these issues and improve efficacy, QoL, and compliance.

Both capecitabine and vinorelbine have demonstrated considerable efficacy and tolerability in MBC, particularly as second-line and third-line therapy after taxane failure. Capecitabine has demonstrated efficacy in multiple phase III trials, while the data supporting oral vinorelbine is currently limited to phase II studies [26,27]. A systematic review of over 2000 patients pretreated with anthracyclines and taxanes who received single-agent chemotherapy with capecitabine or IV vinorelbine supported the efficacy of these chemotherapeutic agents, producing mean disease control rates (overall response plus stable disease) of approximately 55% and 50%, respectively [28].

As a single-agent, capecitabine has yielded median PFS or time to progression (TTP) ranging from 3.0 months to 7.9 months in patients with MBC (Table 1) [29–40]. In a recent review of 31 studies of oral vinorelbine in over 1000 patients with MBC, this agent demonstrated good efficacy and tolerability, both as monotherapy and in combination with capecitabine or targeted therapy [27]. As a single-agent, oral vinorelbine was associated with a median PFS or TTP of 4.0 months to 8.2 months (Table 2) [27,41–46]. The combination of oral vinorelbine with capecitabine is also effective, yielding median PFS or TTP ranging from 3.4 to 10.5 months in patients with MBC (Table 3) [27,47–54]. There is no direct comparison between the use of these two agents in combination as opposed to in sequence. The combination is more complex, related to a significant incidence of side effects, and should be reserved for selected cases (e.g., highly symptomatic patients). Based on the available data, the current ABC2 guidelines identify single-agent capecitabine, vinorelbine, or eribulin as the preferred choices for patients who have previously received anthracyclines and taxanes and do not require combination chemotherapy [1,2].

In patients with HER2-positive MBC, both capecitabine and IV vinorelbine have demonstrated efficacy and tolerability in combination with HER2-targeted agents. Capecitabine is effective in combination with trastuzumab and lapatinib, with median TTP of 8.2 months and 6.2 months, respectively in patients with HER2-positive MBC after progression on first-line trastuzumab and chemotherapy [55,56]. Intravenous vinorelbine has also demonstrated efficacy in HER2-positive disease, demonstrating similar or better response rates and median TTP than taxanes when combined with trastuzumab as first-line chemotherapy in the phase III TRAVIOTA and HERNATA trials (Table 4) [57,58]. Additionally, in a retrospective comparison of two case series, oral vinorelbine in combination with trastuzumab appeared to be at least as effective as a standard taxane and trastuzumab combination [59]. The efficacy associated with vinorelbine plus trastuzumab, together with a good tolerability profile, makes this combination an important option for the treatment of HER2-positive MBC. Promising phase II data also exist for the safety and activity of the combination of vinorelbine with both trastuzumab and pertuzumab [60].

Metronomic chemotherapy in metastatic breast cancer

The tolerability and convenience of oral chemotherapy makes it an ideal formulation for metronomic dosing approaches. Metronomic chemotherapy consists of frequent administration of chemotherapy (often daily) at individual doses well below the maximum tolerated dose (MTD) without prolonged drug-free

Table 2
Oral vinorelbine as a single agent in metastatic breast cancer [27,41–46]

Reference	Oral vinorelbine schedule	*N*	Line of treatment	ORR, %	CBR, %	PFS/TTP, months	OS, months
Freyer et al. J Clin Oncol 2003 [41]	80 mg/m² weekly (after 3 administrations at 60 mg/m²)	58	1st	31	62	4.2	Not reached
Amadori et al. ECCO 2001 [27,42]	80 mg/m² weekly (after 3 administrations at 60 mg/m²)	63	1st	27	NR	4.6	21
Bartsch et al. ESMO 2008 [27,43]	60 mg/m² d1,8 q3w	100	1st - 4th Post anthra	25	51	7	17
Blancas et al. ASCO 2010 [27,44]	60 mg/m² weekly	45	1st or 2nd	29.5	59	4	NR
Mansour et al. ICACT 2010 [27,45]	80 mg/m² d1,8 q3w (after 1 cycle at 60 mg/m²)	26	1st Post anthrax and/or txn	42	NR	5	NR
Steger et al. ESMO 2014 [46]	80 mg/m² weekly (after 4 administrations at 60 mg/m²)	70	1st (bone mets)	NR	55.7	8.2	NR

Abbreviations: anthra, anthracycline; CBR, clinical benefit rate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; TTP, time to progression; txn, taxane

Table 3
Oral vinorelbine in combination with capecitabine in metastatic breast cancer [27,47–54]

References	Oral vinorelbine + capecitabine schedule	*N*	Line of treatment	ORR, %	CBR, %	PFS/TTP, months	OS, months
Tubiana-Mathieu et al. BJC 2009 [47]	OV 80 mg/m² d1,8 (after 1st cycle at 60 mg/m²) CAP 2000 mg/m²/d1-14, q3w	55	1st	51	63	8.4	29
Nolè et al. Cancer Chemother Pharmacol 2009[48]	OV 60 mg/m² d1,8,15 CAP 2000 mg/m²/d1-14, q3w	52	1st	44.2	73.1	8.4	25.8
Campone et al. Breast J 2013 [49]	OV 80 mg/m² d1,8 CAP 2000 mg/m²/d1-14, q3w	44	1st Post anthra	31.8	70.5	7.2	22.2
Tawfik et al. Cancer Chemother Pharmacol 2013 [50]	OV 60 mg/m² d1,8 CAP 2000 mg/m² d1-14, q3w	28	1st Post anthra and/or txn	57.1	76.5	8.6	27.2
Finek et al. Anticancer Res 2009 [51]	OV 60 mg/m² d1,8 CAP 2000 mg/m²/d1-14, q3w	115	1st or 2nd Post anthra	56.5	87.8	10.5	17.5
Delcambre et al. SABCS 2005 [52]	OV 60 mg/m² d1,8 CAP 2500 mg/m²/d1-14, q3w	31	1st: 90% 2nd: 10%	61	NR	NR	NR
Jones et al. Cancer Chemother Pharmacol 2010 [53]	OV 60 mg/m² d1,8,15 CAP 2000 mg/m²/d1-14, q3w	40	Post anthra and txn	20.0	62.5	3.4	11.3
Lorusso et al. Ann Oncol 2006 [54]	OV 60 mg/m² d1,8 CAP 2000 mg/m²/d2-7 and 9-16, q3w	38	Post anthra and txn	39.4	76.3	4.5	10.0

Abbreviations: anthra, anthracycline; CAP, capecitabine; CBR, clinical benefit rate; NR, not reported; ORR, overall response rate; OS, overall survival; OV, oral vinorelbine; PFS, progression-free survival; q3w, every 3 weeks; TTP, time to progression; txn, taxane

Table 4
Phase III TRAVIOTA and HERNATA trials of first-line vinorelbine with HER2-targeted therapy [57,58]

	TRAVIOTA [57]			HERNATA [58]		
	Taxane/Tras	VNR IV/Tras		Docetaxel/Tras	VNR IV/Tras	
N	40	41		143	141	
ORR, %	40	51	$P = 0.37$	59.3	59.3	$P = 1.00$
CBR, %	58	66	NR	75.6	75.4	NR
Median TTP, months	6.0	8.5	$P = 0.9$	12.4	15.3	HR 0.94; $P = 0.67$
Median TTF, months	4.7	5.8	$P = 0.15$	5.6	7.7	HR 0.50; $P < 0.0001$
Median OS, months	NR	NR	NR	35.7	38.8	HR 1.01; $P = 0.98$

Abbreviations: CBR, clinical benefit rate; HR, hazard ratio; NR, not reported; ORR, overall response rate; OS, overall survival; Tras, trastuzumab; TTF, time to treatment failure; TTP, time to progression; VNR IV, vinorelbine administered intravenously

breaks [61,62]. This approach offers several advantages, including low economic costs, oral administration, good tolerability, positive patient perception, and efficacy based on data from phase II and phase III clinical trials [63].

The mechanisms of action for metronomic chemotherapy are multi-targeted and remain to be fully elucidated. Possible mechanisms of action include inhibition of angiogenesis, stimulation of the immune system, and direct targeting of tumor cells (Figure 1) [61]. The antiangiogenic effects associated with metronomic chemotherapy are attributed to numerous mechanisms, such as direct targeting of tumor neovasculature, increased expression of the angiogenic inhibitor thrombospondin-1 [64], induction of apoptosis in circulating endothelial cells, and blockade of endothelial progenitor cell mobilization from the bone marrow [61,65–67]. Metronomic chemotherapy can also augment the anti-tumor immune response through a number of complex mechanisms. For instance, metronomic administration of chemotherapy stimulates apoptosis of immunogenic cells, depletion of regulatory T cells,

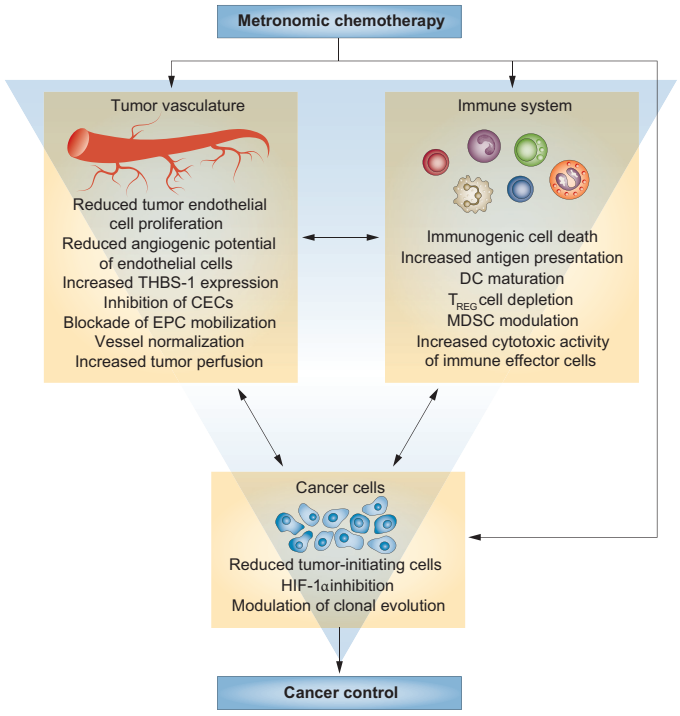

Fig. 1. Potential mechanisms of action of metronomic chemotherapy [61]. Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Clin Oncol 2014;11:413-31. Copyright 2014. Abbreviations: CECs, circulating endothelial cells; DC, dendritic cell; EPC, endothelial progenitor cell; HIF-1α, hypoxia inducible factor 1 alpha; MDSC, myeloid-derived suppressor cell; THBS-1, thrombospondin 1; T_{REG}, regulatory T cell.

and increased antigen presentation through maturation of dendritic cells. Data also suggest direct targeting of tumor initiating cells or cancer stem cells [61] and inhibition of hypoxia-inducible factor 1 (HIF-1α) [68] as additional mechanisms of action for metronomic chemotherapy, as reviewed elsewhere [63,69]. There is significant crosstalk between these various mechanisms of action, providing a rationale for combinations of metronomic chemotherapy with targeted agents or immunotherapies [61].

Interestingly, preclinical data suggest tumors that acquire resistance to metronomic chemotherapy, such as low-dose cyclophosphamide, retain their sensitivity to MTD cyclophosphamide [61,70]. This is important because it suggests metronomic chemotherapy and MTD chemotherapy could essentially be thought of as two distinct drugs and development of resistance to one may not preclude the use of the same drug using an alternative dosing schedule. Moreover, metronomic chemotherapy may prevent or delay development of chemotherapy resistance [61]. In mouse models of ovarian cancer, intermittent administration of docetaxel resulted in significant upregulation of genes involved in docetaxel resistance, while continuous dosing did not upregulate these genes [71]. Further clinical studies are needed to fully understand the impact of metronomic chemotherapy on drug resistance.

Numerous phase II clinical trials have demonstrated activity for oral chemotherapeutic agents as metronomic monotherapy in patients with MBC (Table 5) [31,63,72–75]. First-line capecitabine, administered at standard doses or continuously, improved OS (22 vs 18 months; HR 0.72; P = 0.02) and was better tolerated than classical cyclophosphamide, methotrexate, and fluorouracil (CMF) in women with MBC unsuitable for more intensive chemotherapy regimens [31]. Another phase II study of metronomic capecitabine (1500 mg once a day) demonstrated a clinical benefit rate (CBR) of 62%, including activity in patients with heavily pretreated disease and those who had previously received standard dose capecitabine [72]. Metronomic capecitabine was well tolerated, with minimal grade 3 and no grade 4 adverse events reported. However, another phase II randomized noninferiority trial was unable to demonstrate noninferiority for continuous dosing of capecitabine at 800 mg/m² bid daily compared to standard dosing (1250 mg/m² bid days 1 to 14 every 21 days) with regards to disease progression at 1 year [73].

Metronomic oral vinorelbine has demonstrated promising activity and safety as a single agent. Phase I trials established the recommended dose for metronomic oral vinorelbine as 50 mg 3 times per week for 3 weeks on, 1 week off [76,77]. In a clinical trial of 34 elderly patients with MBC, first-line metronomic oral vinorelbine dosed at 70 mg/m² resulted in an objective response in 38% of patients and was associated with a disease control rate of 68% [74]. Median PFS and OS were 7.7 months and 15.9 months, respectively. This active regimen was also well tolerated with no grade 4 adverse events and few grade 3 events, the most common of which were neutropenia (9%), anemia (9%), and febrile infection (6%). A second study of metronomic oral vinorelbine (30 mg, one day on and one day off) in elderly patients with MBC demonstrated a CBR ≥6 months of 50% and a disease control rate of 87.4% [75]. Excellent tolerability was observed, with improved QoL after 6 months of therapy and no grade 3/4 adverse events reported. The ongoing phase II randomized TEMPO-Breast 01 trial is comparing standard dose oral vinorelbine to metronomic oral vinorelbine as first-line therapy in patients with hormone receptor–positive, HER2-negative MBC [78]. Trial results are expected in 2017.

Combination metronomic regimens have also demonstrated activity and excellent tolerability in MBC (Table 6) [63,79–92]. The first metronomic combination to be explored in the metastatic setting was cyclophosphamide plus methotrexate (CM) [63]. A

Table 5
Selected trials of metronomic oral chemotherapy monotherapy in advanced breast cancer [31,72–75]

References	Agents and schedule	*N*	Line of treatment	ORR, %	CBR, %	PFS/TTP, months	OS, months
Stockler et al. J Clin Oncol 2011 [31]	Capecitabine (650 mg/m² bid continuously)	107	1st	20	50	6	NR
Fedele et al Eur J Cancer 2012 [72]	Capecitabine (1500 mg daily continuously)	58	2nd or later	24	62	7	17
Martin et al. Oncologist 2015 [73]	Capecitabine (800 mg/m² bid continuously)	97	1st – 3rd	32	71.2	6.8	23.3
Addeo et al. Clin Breast Can 2010 [74]	Oral vinorelbine (70 mg/m² weekly fractionated on days 1, 3, and 5 for 3 weeks on, 1 week off)	34	1st (elderly)	38	68	7.7	15.9
De Iuliis et al. Tumori 2015 [75]	Oral vinorelbine (30 mg one day on, one day off)	32	1st – 3rd (elderly)	68.7	87.4[a]	9.2	NR

[a]Disease control rate; CBR ≥6 months was 50%
Abbreviations: bid; twice daily; CBR, clinical benefit rate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression

Table 6
Selected trials of metronomic oral chemotherapy combinations in advanced breast cancer [79,81,83–92]

Reference	Agents and schedule	*N*	Line of treatment	ORR, %	CBR, %	PFS/TTP, months	OS, months
Combination oral chemotherapy regimens							
Colleoni et al. Ann Oncol 2002 [79]	Cyclophosphamide (50 mg/day continuously) + methotrexate (2.5 mg bid days 1 and 2 weekly)	63	1st or later	19.0	31.7	2.8	NR
Colleoni et al. Ann Oncol 2006 [81]	Cyclophosphamide (50 mg/day continuously) + methotrexate (2.5 mg bid days 1 and 4 weekly)	90	1st or later	20.9	41.5	3.8	18.2
VICTOR-1 Cazzaniga et al Int J Breast Cancer 2014 [83]	Vinorelbine (20-40 mg daily, d1,3,5 weekly) + capecitabine (500 mg tid continuously)	31	1st or later	16.1	58.1	NR	NR
VICTOR-2 Cazzaniga et al ABC3 2015 [84]	Vinorelbine (40 mg daily, d1,3,5 weekly) + capecitabine (500 mg tid continuously)	85	1st or later	NR	80	NR	NR
VEX trial Montagna et al Eur J Cancer 2015 [85]	Vinorelbine (40 mg daily, d1,3,5 weekly) + capecitabine (500 mg tid continuously) + cyclophosphamide (50 mg daily)	69	1st or later	30.4	78.3	22 for untreated patients; 14 for pretreated patients	NR
Addeo et al Cancer Chemother Pharmacol 2012 [86]	Vinorelbine (70 mg/m^2 daily, d1,3,5 weekly) + temozolomide (75 mg/m^2 d1-21 q4w)	36	1st or later, untreated brain mets	52	77	8	11
Wang et al Cancer Chemother Pharmacol 2012 [87]	Capecitabine (1000 mg/m^2 bid) + cyclophosphamide (65 mg/m^2 daily) days 1-14 q3w	66	1st – 5th	30.3	53.0	5.2	16.9
Yoshimoto et al Cancer Chemother Pharmacol 2012 [88]	Capecitabine (828 mg/m^2 bid) + cyclophosphamide (33 mg/m^2 bid) days 1-14 q3w	45	1st or 2nd	44.4	57.8	12.3	Not reached
Combinations with targeted agents							
Orlando BMC Cancer 2006 [89]	Cyclophosphamide (50 mg daily) + methotrexate (2.5 mg bid, days 1 and 4 weekly) + trastuzumab (6 mg/kg q3w)	22	1st or later	18	46	6	NR
Dellapasqua et al J Clin Oncol 2008 [90]	Capecitabine (500 mg tid continuously) + cyclophosphamide (50 mg daily) + bevacizumab (10 mg/kg q2w)	46	1st or later	48	68	10.5	NR
Garcia-Saenz et al J Chemother 2008 [91]	Cyclophosphamide (50 mg daily) + methotrexate (1 mg/kg q2w) + bevacizumab (10 mg/kg q2w)	22	2nd or later	31.8	63.6	7.5	13.6
Saloustros et al J BUON 2011 [92]	Vinorelbine (50 mg 3 times a week) + bevacizumab (10 mg/kg q2w)	13	1st or later	7.7	53.8	NR	NR

Abbreviations: bid; twice daily; CBR, clinical benefit rate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; tid, thrice daily; TTP, time to progression

study of metronomic CM in 63 patients with MBC demonstrated an ORR and CBR of 19% and 32%, respectively [79]. Longer follow-up of this combination in a larger group of patients with MBC (*N* = 153) demonstrated prolonged clinical benefit of 12 months or more in 16% of patients [80]. A trial of metronomic CM with or without thalidomide in 171 patients with MBC exhibited an ORR of 20.9% and CBR of 41.5% in the 90 patients who received CM [81]. No improvement was observed with the addition of thalidomide. Likewise, a retrospective trial that included 39 patients who received metronomic CM for MBC demonstrated an ORR of 20% and a tumor growth control rate of 51% [82].

The all-oral combination of metronomic vinorelbine and capecitabine has also demonstrated activity in MBC. The phase I/II VICTOR-1 trial examined vinorelbine (40 mg on days 1, 3, and 5 weekly) with capecitabine (500 mg thrice daily) in patients with MBC and demonstrated a response rate of 16.1% and a CBR of 58.1% [83]. The combination was well tolerated, with only 9 total grade 3/4 adverse events reported, consisting primarily of hematologic events, neuropathy, and hand-foot syndrome. The multicenter phase II VICTOR-2 study further examined the combination of metronomic oral vinorelbine and capecitabine in MBC, demonstrating a CBR of 80%, minimal grade 3/4 adverse events, and no deterioration of QoL [84].

In the phase II VEX trial, the combination of metronomic oral vinorelbine, cyclophosphamide, and capecitabine resulted in a CBR of 85% in previously untreated patients and 72% in pretreated patients with hormone receptor–positive MBC [85]. Only 4% of patients experienced a grade 3 adverse event (hand-foot syndrome, hematologic toxicity, and liver toxicity) and no grade 4 events were reported. Ongoing phase II and phase III clinical trials are exploring metronomic oral capecitabine or vinorelbine, including in the neoadjuvant setting with endocrine therapy and as first-line maintenance therapy in patients with response or stable disease following initial chemotherapy [63]. Studies are also demonstrating efficacy for metronomic oral chemotherapy in combination with targeted therapies such as antiangiogenic agents (Table 6) [63,89–92].

Conclusions

Balancing efficacy and QoL is essential for patients with MBC [1,2]. Selection of chemotherapy, endocrine therapy, and targeted agents should be based on current treatment recommendations, clinical trial data, careful assessment of patient and disease characteristics, and very importantly, patient preferences. Sequential monotherapy is the preferred choice for the vast majority of patients who require chemotherapy. Optimal strategies for sequencing therapy

are currently unknown. Chemotherapy should be continued until disease progression as long as it is well tolerated.

Within the landscape of treatment options, increased attention to patient preference and QoL favors the use of oral chemotherapy agents, such as capecitabine and oral vinorelbine [20]. These agents prolong disease control, provide good tolerability, and reduce the time and cost associated with treatment. However, patient education is fundamental to ensuring appropriate safe use of oral chemotherapeutic agents [20,23]. Oral chemotherapy is also a good option for maintenance treatment to prolong disease control. Metronomic chemotherapy provides multiple-targeted action against breast tumor progression [61]. The convenience and low cost of oral chemotherapeutic agents makes them ideal for metronomic dosing strategies [63]. Metronomic chemotherapy approaches, such as cyclophosphamide ± methotrexate, capecitabine, and oral vinorelbine, have demonstrated efficacy and excellent tolerability in phase II trials and can be considered for some patients with advanced disease [19,63]. Results from large, randomized clinical trials are needed to fully understand the optimal role and positioning for metronomic approaches in the management of patients with MBC.

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Conflict of interest statement

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