Capecitabine Monotherapy: Review of Studies in First-Line HER-2-Negative Metastatic Breast Cancer

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ABSTRACT

The goals of treatment for metastatic breast cancer (MBC) are to prolong overall survival (OS) while maximizing quality of life, palliating symptoms, and delaying tumor progression. For many years, anthracyclines and taxanes have been the mainstay of treatment for MBC, but these agents are now commonly administered earlier in the course of the disease. A recent meta-analysis revealed adverse effects on OS and overall response rates in patients with MBC receiving first-line anthracycline-based chemotherapy following relapse on adjuvant chemotherapy. Noncrossresistant cytotoxic agents and combinations that combine high clinical activity and acceptable tolerability while being convenient for patients are therefore needed for the first-line treatment of MBC patients. Capecitabine

has substantial antitumor activity in the first-line treatment of patients with MBC in prospective, randomized, phase II/III clinical trials as monotherapy and in combination with biologic and novel agents. First-line capecitabine monotherapy has a favorable safety profile, lacking myelosuppression and alopecia, and does not compromise the administration of further lines of chemotherapy. Capecitabine is suitable for long-term administration without the cumulative toxicity that can limit the prolonged use of other chemotherapy agents. Here, we review the available data on capecitabine as a single agent for first-line treatment of patients with human epidermal growth factor receptor 2-negative MBC. *The Oncologist* 2012;17:476–484

INTRODUCTION

Metastatic breast cancer (MBC) remains incurable, but the primary goals of treatment are to prolong the overall survival (OS) duration while maximizing quality of life (QoL), preventing or palliating symptoms, and delaying tumor progression. The choice of therapy is guided by a number of factors and is

made on an individual patient basis taking into account the hormone receptor status, human epidermal growth factor receptor (HER)-2 status, relapse-free interval, sites of metastasis, tumor-related symptoms, prior treatment, anticipated side effects, and patient choice [1]. Patients with rapidly progressing disease and/or symptomatic visceral metastases may gain the

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most benefit from a combination chemotherapy regimen, whereas patients with more slowly progressing disease, who have exhausted endocrine therapy options, may benefit from a less aggressive approach with single-agent chemotherapy [1–3].

Chemotherapy options for patients presenting with breast cancer are continually evolving. Anthracyclines and taxanes were the mainstay of treatment in the metastatic setting for many years. A role for these agents in the neoadjuvant [4, 5] and adjuvant [6, 7] treatment of breast cancer has been well established and is further supported by evidence-based guidelines [8–10]. Noncross-resistant cytotoxic agents and combinations that combine high clinical activity and acceptable tolerability while being convenient for patients are therefore needed for the first-line treatment of patients with MBC.

Capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland) is converted to 5-fluorouracil (5-FU) in a three-step enzymatic process, the final stage of which is mediated by thymidine phosphorylase (TP). Significantly higher TP activity ($p < .05$) has been recorded in a number of human tumor tissues (including colorectum, breast, stomach, cervix, uterus, ovary, kidney, bladder, and thyroid), compared with normal tissue adjacent to the tumor [11], allowing capecitabine to generate 5-FU preferentially at the tumor site. Capecitabine is indicated as monotherapy for the treatment of patients with locally advanced breast cancer (LABC) or MBC after failure of taxanes and an anthracycline-containing regimen and in patients for whom further anthracycline therapy is not indicated, and it has been extensively evaluated in both pretreated and first-line breast cancer patients. The dose of capecitabine approved by the U.S. Food and Drug Administration (FDA) for patients with LABC or MBC is 1,250 mg/m² twice daily (bid), given intermittently for 14 days on a 21-day cycle. Capecitabine has a favorable safety profile, with adverse events (AEs) readily managed by dose modification [12], and it offers the additional benefit of convenient oral dosing [13]. Capecitabine is suitable for long-term administration and generally lacks cumulative toxicity with prolonged use.

The objective of this review is to evaluate the available evidence for capecitabine as a single agent in the first-line treatment of patients with HER-2-negative MBC. Some of the studies discussed in this review enrolled patients with MBC unselected for HER-2 status; hence, data from patients with HER-2-positive MBC may have been included. Studies conducted purely in patients with HER-2-positive MBC were omitted, because capecitabine monotherapy is not an appropriate first-line treatment option in this setting. As a second-line therapy, capecitabine has demonstrated efficacy when combined with lapatinib [14, 15] and with trastuzumab [16] in randomized phase III trials in patients with HER-2-positive MBC progressing on prior trastuzumab.

LITERATURE SEARCH

We conducted a literature search using PubMed and key breast cancer congress abstracts from the American Society of Clinical Oncology, European Cancer Organization, European Society for Medical Oncology, and San Antonio Breast Cancer

Symposium for clinical trials of capecitabine monotherapy as first-line treatment for MBC patients. Search terms included: capecitabine, MBC, HER-2-negative, first-line, and chemo-naïve. Searches were limited to English language articles published within the last 10 years. Search results were filtered to identify: prospective, phase II/III trials of capecitabine as a single agent in the strict first-line MBC setting; trials in which capecitabine was the control monotherapy arm being compared with combinations of biologic or novel agents; and data from observational cohorts and retrospective analyses. Review articles and case studies were excluded.

FIRST-LINE CAPECITABINE MONOTHERAPY FOR MBC: EVIDENCE FROM PROSPECTIVE, PHASE II/III CLINICAL TRIALS

Data from two randomized, phase III studies and a large phase II study confirm the efficacy of capecitabine monotherapy in the first-line treatment of patients with MBC. Results of those trials are further supported by randomized, phase II/III studies in which capecitabine was combined with biologic or novel agents and selected as the reference monotherapy in the control arm.

Randomized, Phase III Studies of Capecitabine Monotherapy

The Australian New Zealand Breast Cancer Trials Group (ANZBCTG) ANZBCTG0001 multicenter, randomized, phase III study compared single-agent capecitabine with classical cyclophosphamide, 100 mg/m² on days 1–14, plus methotrexate, 40 mg/m², and 5-FU, 600 mg/m² on day 1 and day 8, every 28 days (the CMF regimen) as first-line treatment for women with MBC unselected for HER-2 status and unsuited for more intensive regimens ($n = 323$) [17]. Capecitabine was administered to the same total dose either intermittently (1,000 mg/m² bid, days 1–14, every 21 days) or as a continuous regimen (650 mg/m² bid, days 1–21, every 21 days). All patients had a relapse-free survival interval ≥ 6 months following adjuvant chemotherapy; 80% of patients had received adjuvant endocrine therapy. The progression-free survival (PFS) times, the primary endpoint, were similar in all treatment arms (median PFS interval, 6.0 months with either capecitabine regimen and 7.0 months with CMF; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.67–1.10), as was overall response rate (ORR) as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST): 22% for intermittent capecitabine, 20% for continuous capecitabine, and 18% for CMF (Table 1) [17–24]. The OS times were similar in patients receiving capecitabine intermittently and those receiving it continuously (HR, 0.86; 95% CI, 0.62–1.12; $p = .4$). However, a significantly longer OS duration was seen with capecitabine than with CMF (median OS time, 22.0 months for both capecitabine regimens combined and 18.0 months for CMF; HR, 0.72; 95% CI, 0.55–0.94; log-rank $p = .02$). Capecitabine-treated patients had a longer duration of therapy than those in the CMF arm (9.0 months versus 6.0 months, respectively), and they were significantly more likely to continue therapy beyond 6 months (40% versus 21%; $p = .001$) or 12 months (18% versus 6%; $p = .005$). Global quality of

Table 1. Randomized, phase II/III clinical trial evidence of the efficacy of capecitabine monotherapy as first-line treatment for metastatic breast cancer

Study	Regimen	Patients, <i>n</i>	Median overall survival, mos	Median time to progression/progression-free survival, mos	Overall response rate, %
Phase III					
Stockler et al. (2011) [17]	Cyclophosphamide, methotrexate, and 5-fluorouracil vs. capecitabine	109 vs. 214	18.0 vs. 22.0	7.0 vs. 6.0	18.0 vs. 21.0
Jäger (2010) [18]	Pegylated liposomal doxorubicin vs. capecitabine	105 vs. 105	22.4 vs. 29.4	6.2 vs. 7.1	22.9 vs. 24.4
Robert et al. (2011) [19]	Capecitabine + bevacizumab vs. capecitabine + placebo	409 vs. 206	29.0 vs. 21.2	8.6 vs. 5.7	35.4 vs. 23.6
Vahdat et al. (2009) ^a [20]	Capecitabine + ixabepilone vs. capecitabine	149 vs. 144	15.1 vs. 12.5	5.6 vs. 2.8	46.0 vs. 24.0
Phase II					
Kaufmann et al. (2010) [21]	Capecitabine	165	18.6	7.9	26.1
Baselga et al. (2009) ^b [22, 23]	Capecitabine + sorafenib vs. capecitabine + placebo	50 vs. 62	—	7.6 vs. 4.1	—
O'Shaughnessy et al. (2001) [24]	Cyclophosphamide, methotrexate, and 5-fluorouracil vs. capecitabine	33 vs. 62	17.2 vs. 19.6	3.0 vs. 4.1	16.0 vs. 30.0

^aPatients treated in the first-line setting with rapidly progressing disease after adjuvant anthracyclines and taxanes.

^bPatients treated in the first-line setting.

life (QoL) scale scores were similar across treatment arms, but several QoL scale scores were better with capecitabine than with CMF, particularly those related to hair loss.

An additional phase III study of first-line capecitabine in MBC patients is the randomized PEGylated LIposomal doxorubicin versus CApecitabiNe as first-line chemotherapy for metastatic breast cancer (PELICAN) study, which compared the efficacy of capecitabine (1,250 mg/m² bid, days 1–14, every 21 days) with that of pegylated liposomal doxorubicin (PLD) dosed at 50 mg/m² every 28 days (*n* = 210) [18]. A disease-free interval >12 months after completion of adjuvant anthracyclines was required. Approximately one third of patients in each arm had received adjuvant anthracyclines. A slightly higher percentage of patients in the capecitabine arm than in the PLD arm had both visceral and nonvisceral metastases (64% versus 56%, respectively). The primary end-point of time to progression (TTP) was similar with capecitabine and PLD (median TTP, 7.1 months versus 6.2 months, respectively; HR, 1.21; 95% CI, 0.84–1.75; *p* = .31) (Table 1). Capecitabine also had efficacy similar to that of PLD in terms of the secondary endpoints of OS (median OS time, 29.4 months versus 22.4 months, respectively; HR, 1.17; 95% CI, 0.79–1.74; *p* = .44), unconfirmed ORR (24.4% versus 22.9%, respectively; *p* = .86), and time to treatment failure (TTF) (median TTF, 3.6 months versus 4.6 months, respectively; HR, 1.27; 95% CI, 0.95–1.70; *p* = .10).

Prospective Phase II Evidence of the Efficacy of Capecitabine Monotherapy

The multicenter, single-arm, phase II Mono Efficacy of Capecitabine (MONICA) study investigated the efficacy and safety of

first-line capecitabine (1,000 mg/m² bid) in patients with HER-2-negative MBC across 35 sites in Germany (*n* = 165) [21]. Approximately 50% of patients had received chemotherapy in the adjuvant setting and 30% had received palliative endocrine therapy. A median TTP of 7.9 months (31.6 weeks; 95% CI, 26.9–36.3 weeks) was achieved with capecitabine monotherapy along with a median OS time of 18.6 months (74.2 weeks; 95% CI, 60.59–87.85 weeks), with an ORR of 26.1% (Table 1). A post hoc analysis revealed particular efficacy benefit in patients with versus without hand–foot syndrome (HFS) (TTP, *p* = .0542; OS time, *p* = .0209) and in those aged >65 years versus <65 years (TTP, *p* = 0.002; OS time, *p* = not significant). That trial represents the largest prospective, nonrandomized trial of single-agent capecitabine in the first-line setting.

Across the three first-line trials, the median PFS time and TTP were in the range of 6.0–7.9 months with first-line capecitabine monotherapy, and the median OS times were within the range of 18.6–29.4 months. Findings from an earlier randomized, phase II open-label study of capecitabine (1,255 mg/m² bid) versus CMF (cyclophosphamide, 600 mg/m²; methotrexate, 40 mg/m²; 5-FU, 600 mg/m²) every 21 days as first-line treatment for women aged ≥55 years with advanced breast cancer or MBC (*n* = 95) [24] are consistent with data from the phase III randomized trials and the single-arm phase II study described above (Table 1).

Capecitabine as the Reference Monotherapy Arm When Combined With Biologic or Novel Agents

In human breast cancer xenograft models, the combination of capecitabine and trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA) produced at least an additive effect

on tumor growth inhibition and delay [25]. Similarly, in a preclinical model of breast carcinoma, combined capecitabine and bevacizumab (Avastin®; Genentech Inc., South San Francisco, CA) had a synergistic effect on tumor growth inhibition [26]. Several recent, randomized trials evaluated these preclinical findings of capecitabine combined with novel agents.

The large, randomized, placebo-controlled, phase III Regimens In Bevacizumab for Breast ONcology-1 (RIBBON-1) trial examined the combination of bevacizumab with the investigator's choice of chemotherapy (capecitabine, 1,000 mg/m² bid, anthracyclines, or taxanes) as first-line treatment for patients with HER-2-negative LABC or MBC (*n* = 1,237) [19]. The capecitabine cohort and the anthracycline or taxane cohort were independently powered and analyzed in parallel. Within the capecitabine cohort (*n* = 615), a significantly longer median PFS interval, the primary endpoint, was seen with capecitabine plus bevacizumab than with capecitabine plus placebo (8.6 months versus 5.7 months, respectively; HR, 0.69; 95% CI, 0.56–0.84; *p* < .001; investigator assessment) (Table 1). This PFS benefit was confirmed by an independent review committee (9.8 months versus 6.2 months; HR, 0.68; 95% CI, 0.54–0.86; *p* = .0011) and was found to be independent of baseline patient risk factors, including age, disease-free interval, number of metastatic sites, prior adjuvant therapy, hormone receptor status, and triple-negative status. A significantly higher ORR was achieved in patients with measurable disease at baseline receiving capecitabine plus bevacizumab than in those receiving capecitabine plus placebo as evaluated using the RECIST (34.5% versus 23.6%, respectively; *p* = .0097). The median duration of response was also significantly longer in the bevacizumab-containing arm than in the capecitabine plus placebo arm (9.2 months versus 7.2 months; *p* = .033). The median OS times were 29.0 months with capecitabine plus bevacizumab and 21.2 months with capecitabine plus placebo (HR, 0.85; 95% CI, 0.63–1.14; *p* = .27), whereas the 1-year survival rates were 81.0% and 74.4%, respectively (*p* = .076). The trial was not powered to detect a difference in OS duration between the treatment arms.

The combined efficacy of the antiangiogenic inhibitor sorafenib (Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ) and capecitabine (1,000 mg/m² bid) was compared with that of capecitabine plus placebo in the randomized, double-blind, phase IIb SOLTI-0701 trial (*n* = 220) [22, 23]. Patients were required to have HER-2-negative LABC or MBC that had been treated with fewer than two chemotherapy regimens. A significantly longer PFS interval, the primary endpoint, was achieved in the capecitabine plus sorafenib arm than in the capecitabine plus placebo arm (median PFS time, 6.4 months versus 4.1 months, respectively; HR, 0.58; 95% CI, 0.41–0.81; *p* = .0006). The PFS benefit was maintained across all prespecified exploratory subgroups, including 112 patients treated in the first-line setting (median PFS time, 7.6 months versus 4.1 months, respectively; HR, 0.50; 95% CI, 0.41–1.04; *p* = .0022) (Table 1). The ORR was numerically higher with capecitabine plus sorafenib than with capecitabine plus placebo (38.3% versus 30.7%, respectively; *p* = .1229). An ongoing, randomized, placebo-controlled, phase III registration

trial will further assess the efficacy and safety of sorafenib in combination with capecitabine in patients with LABC or MBC (ClinicalTrials.gov identifier, NCT01234337).

Another randomized, double-blind, phase II trial looking at the efficacy of capecitabine in combination with a novel targeted agent, a small molecule urokinase-type plasminogen activator, in the first-line treatment of patients with HER-2-negative MBC recently completed recruitment (ClinicalTrials.gov identifier, NCT00615940) [27].

Two randomized, open-label, phase III trials have investigated the efficacy and safety of capecitabine (1,000 mg/m² bid) in combination with ixabepilone (Ixempra®; Bayer Oncology GmbH, Westfalen, Germany) compared with single-agent capecitabine (1,250 mg/m² bid) in patients with anthracycline- or taxane-pretreated MBC [28–30]. Because the two studies had similar designs, the data were pooled to achieve greater statistical power. In the pooled overall population (*n* = 1,973), combination therapy was superior to capecitabine monotherapy in terms of the PFS interval (median PFS time, 5.6 months versus 4.2 months, respectively; HR, 0.80; 95% CI, 0.73–0.88; *p* < .001). The ORRs were 42% in the combination therapy group and 25% in the single-arm capecitabine group; the median OS times were 14.6 months and 13.6 months, respectively (HR, 0.92; 95% CI, 0.83–1.01; *p* = .086) [20]. A proportion of patients received study treatment as their initial chemotherapy for metastatic disease.

Pooled data for 293 patients treated in the first-line MBC setting following disease progression within 1 year of adjuvant anthracyclines and taxanes were consistent with those for the pooled overall study population. Compared with single-agent capecitabine, the combination regimen produced significant PFS (median PFS time, 2.8 months versus 5.6 months, respectively; HR, 0.58; 95% CI, 0.45–0.76; *p* < .0001) and ORR (24% versus 46%, respectively) benefits. The median OS times were 12.5 months with combination therapy and 15.1 months with single-agent capecitabine (HR, 0.84; 95% CI, 0.65–1.10; *p* = .208) (Table 1) [20]. Because these are subgroup analyses of patients with aggressive, anthracycline- or taxane-refractory disease, the median PFS and OS times achieved with capecitabine monotherapy were lower than those reported in the randomized, phase III MBC monotherapy trials.

SAFETY OF FIRST-LINE CAPECITABINE MONOTHERAPY IN PROSPECTIVE, CLINICAL TRIALS

Across the phase II/III trials described, HFS and diarrhea were the most frequently reported grade 3 or 4 AEs (Table 2); alopecia and myelosuppression were rare. Information on specific capecitabine-related AEs was not captured by the RIBBON-1 study protocol. The safety profiles of the two capecitabine regimens in the ANZBCTG0001 study were comparable. Grade 3 HFS occurred at a significantly higher rate in capecitabine-treated patients (15.5%, versus 0% with CMF; *p* < .0001) whereas grade 3 or 4 neutropenia (1% versus 26%, respectively), febrile neutropenia (0% versus 10%, respectively), and stomatitis (0% versus 6%, respectively) were reported at a significantly higher rate in CMF-treated patients (*p* ≤ .0001, versus capecitabine) [17]. Patients in the PELICAN study

Table 2. Incidence of the most frequent grade 3 or 4 AEs in patients receiving first-line capecitabine monotherapy across randomized, phase II/III clinical trials

Study	Grade 3 or 4 AE, %				
	Hand-foot syndrome ^a	Diarrhea	Vomiting	Fatigue	Stomatitis
Phase III					
Stockler et al. (2011) [17]	16	7	3	3	0
Jäger et al. (2010) [18]	26	12	2	7	NR
Vahdat et al. (2009) ^b [20]	19	4	NR	2	<1
Phase II					
Kaufmann et al. (2010) [21]	8	4	1	NR	1
Baselga et al. (2009) ^c [22, 23]	13	5	NR	1	NR

^aGrade 3 only.^bPatients treated in the first-line setting with rapidly progressing disease after adjuvant anthracyclines/taxanes.^cPatients treated in the first-line setting.

Abbreviations: AEs, adverse events; NR, not reported.

receiving PLD experienced significantly lower rates of grade 3 or 4 diarrhea (0% versus 12%, respectively; $p = .0002$) and thromboembolic events (2% versus 10%, respectively; $p = .0186$) than those receiving capecitabine. Levels of grade 3 HFS (26% for capecitabine versus 36% for PLD; $p = 0.135$) and grade 3 or 4 cardiac events (0% for capecitabine versus 1% for PLD) were not significantly different between the treatment arms. In the MONICA study of single-agent capecitabine, the only grade 3 or 4 AE occurring in >5% of patients was HFS (grade 3, 7.5%). Two patients died during the study as a result of cerebral bleeding and myocardial infarction [21]. There was a low incidence of grade 3 or 4 AEs with the combination of capecitabine and sorafenib in the SOLTI-0701 trial, with the exception of HFS, which was reported in 45% of patients in the sorafenib arm and 13% of patients in the placebo arm. This high incidence of HFS has not previously been observed with capecitabine in combination with biologics and requires further investigation. In the two ixabepilone plus capecitabine studies, the most frequently reported grade 3 or 4 AE in the pooled single-agent capecitabine arm was HFS (grade 3, 19%), consistent with findings in the pooled overall study population.

OTHER CAPECITABINE MONOTHERAPY DATA FOR MBC

Two large, multicenter, prospective, observational studies in patients with MBC examined the use of first-line capecitabine monotherapy in routine clinical practice and found comparable results with those obtained from the randomized, interventional studies (Table 3). In the first study ($n = 876$), capecitabine was administered as first-line therapy to 35% of patients and as monotherapy to 64% of patients, including both first-line and later-line use [31]. In the second study ($n = 657$), patients with LABC or MBC received capecitabine according to the physician's chosen dose [32]. Overall, 94% of patients received capecitabine according to the standard intermittent schedule (14 days on of a 21-day cycle).

Supportive evidence for the effectiveness of first-line cape-

citabine monotherapy is also available from two French, retrospective analyses (Table 3). The first analysis included patients who received first-line capecitabine for slowly progressing MBC ($n = 226$), defined as the absence of life-threatening lesions [3]. Most patients (90% of the 161 patients aged <75 years) received additional chemotherapy following progression on capecitabine, indicating that first-line capecitabine does not compromise the use of further chemotherapy in this patient population. In the second analysis, the relative efficacy of various first-line chemotherapies was retrospectively examined in patients aged ≥ 75 years with MBC ($n = 117$) [33]. Capecitabine and vinorelbine (Navelbine®; Pierre Fabre Médicament, Boulogne, France) were the two most commonly prescribed first-line chemotherapies in 57% ($n = 67$) and 26% ($n = 31$) of patients, respectively. The median OS time, calculated from the initiation of chemotherapy, was 13.8 months (95% CI, 11.4–16.3 months) for the entire study population, and it was longer in patients receiving capecitabine than in those receiving other chemotherapies (Fig. 1). Similar findings were observed for the PFS interval (Table 3). The median PFS time was 6.2 months (95% CI, 4.1–8.1 months) for the overall population.

OTHER SINGLE-AGENT NONTAXANE CHEMOTHERAPIES FOR FIRST-LINE MBC

Limited data are available for other single cytotoxic agents in the first-line setting (Table 4) [17–24, 34–37]. In a phase III study in postmenopausal women aged ≥ 60 years with MBC, significantly greater efficacy was demonstrated with first-line epirubicin (Ellence®; Pfizer Inc., New York) at a dose of 35 mg/m² ($n = 199$) than with gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, IN) at a dose of 1,200 mg/m² ($n = 198$). The median TTP were 6.1 months versus 3.4 months, respectively ($p = .0001$), whereas the median OS times were 19.1 months versus 11.8 months, respectively ($p = .0004$) and the ORRs were 40.3% versus 16.4%, respectively ($p < .001$) [34]. Grade 3 or 4 neutropenia (25.3% with gemcitabine versus 17.9% with epirubicin) and leukopenia (14.3% with gemcit-

Table 3. Capecitabine monotherapy as first-line treatment for metastatic breast cancer: evidence from observational cohorts and retrospective analyses

Study	Regimen	Patients, <i>n</i>	Median overall survival, mos	Median progression-free survival, mos	Overall response rate, %
Observational cohorts					
Siedentopf et al. (2009) [31]	Capecitabine (median starting dose, 1,070 mg/m ² bid; median overall dose, 962 mg/m ² bid)	561 ^a	NR	7.4 ^a	37.0 ^a
Dalivoust et al. (2010) [32]	Capecitabine (56% of patients received a starting dose of 781–1,093 mg/m ² bid)	183 ^b	24.1 ^b	7.9 ^b	NR
Retrospective analyses					
Debled et al. (2009) [3]	Capecitabine (mean starting dose, 1,000 mg/m ² bid)	226	23.6	8.8 ^c	NR
Debled et al. (2011) [33]	Capecitabine (median starting dose, 1,000 mg/m ² bid) vs. other chemotherapy (vinorelbine, anthracyclines, or taxanes)	117	17.1 vs. 9.9 ^d	8.1 vs. 5.1 ^e	NR

^aPatients receiving capecitabine monotherapy (including both first-line and later-line use).
^bPatients treated in the first-line setting.
^cTime to treatment failure.
^d*p* = not significant.
^e*p* = .015. All capecitabine doses are according to the standard intermittent schedule (14 days on of a 21-day cycle).
Abbreviations: bid, twice daily; NR, not reported.

Figure 1. Kaplan–Meier plot of OS with first-line capecitabine versus other chemotherapies in patients with MBC aged >75 years: retrospective analysis [33].

Abbreviations: CI, confidence interval; MBC, metastatic breast cancer; OS, overall survival.

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abine versus 19.3% with epirubicin) were the most frequently reported AEs. Good efficacy was achieved with ixabepilone in a phase II study (*n* = 65), with an ORR of 41.5% (95% CI, 29.4%–54.4%), a median OS duration of 22.0 months (95% CI, 15.6–27.0 months), and a median TTP of 4.8 months (95% CI, 4.2–7.6 months) [35]. The most frequently occurring grade 3 or 4 ixabepilone-related AEs were neutropenia (58%) and leukopenia (50%). Similar activity was reported in a phase II study of single-agent vinorelbine at a dose of 30 mg/m²/week (*n* = 145). The ORR was 41%, median OS time was 18.0 months, and median TTP was 6.0 months [36]. Grade 3 or 4 granulocytopenia was reported in 72% of patients. Available data for single-agent capecitabine as first-line treatment for patients with MBC, including subgroup analyses of randomized trials, are comparable with these findings. The median PFS interval and TTP were in the range of 2.8–7.9 months, the median OS time was in the range of 12.5–29.4 months, and the ORR was in the range of 21.0%–26.1% (Table 4).

SUMMARY

Capecitabine monotherapy has substantial antitumor activity in the first-line treatment of patients with MBC. Across a number of randomized, phase II/III studies, the median PFS time and TTP were in the range of 6.0–7.9 months with single-agent capecitabine and the median OS time was within the range of 18.6–29.4 months. These findings are further supported by trials in which first-line capecitabine was used as the reference monotherapy arm when combined with biologic or novel agents, as well as from observational cohorts and retrospective

Table 4. Overview of the efficacy of first-line, single-agent nontaxane chemotherapies in randomized, phase II/III clinical trials

Agent	Patients, <i>n</i>	Median overall survival, mos	Median time to progression/time to treatment failure, mos	Overall response rate, %
Gemcitabine, 1,200 mg/m ² [34]	198	11.8	3.4	16.4
Vinorelbine, 30 mg/m ² [36]	145	18.0	6.0	41.0
Vinorelbine, 30 mg/m ² [37]	63	11.7	3.0	44.0
Ixabepilone, 40 mg/m ² [35]	65	22.0	4.8	41.5
Capecitabine, 1,000–1,250 mg/m ² twice a day [17–24]	958	18.6–29.4	6.0–7.9	21.0–26.1

analyses. In the absence of randomized, head-to-head trials, the antitumor activity of single-agent capecitabine appears comparable with that of other cytotoxic agents in the first-line treatment of MBC patients.

Across the randomized studies, HFS and diarrhea were the most frequently reported grade 3 or 4 AEs associated with capecitabine, whereas alopecia and myelosuppression were rare. In a survey of breast cancer survivors, nurses, and physicians, chemotherapy-induced alopecia was among the top five issues for patients [38] and consistently ranked as the most troublesome side effect in a literature review focusing on the impact of alopecia on QoL [39]. When combining therapies, in particular with biologics, the overlapping side effects of the individual agents must be considered, doses need to be adjusted accordingly, and proactive toxicity management must be performed. So far, however, the only unexpected capecitabine-related AE in the trials of novel or biologic agents was a higher incidence of grade 3 or 4 HFS with sorafenib plus capecitabine. Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/minute), and a lower starting dose of 950 mg/m² bid is recommended in patients with moderate renal impairment (baseline CrCl, 30–50 mL/minute). Because age determines the calculated CrCl, patients aged >65 years should also receive the lower dose of capecitabine.

Many of the trials in this review used a starting dose of capecitabine lower than that approved by the FDA (1,250 mg/m² bid), most often 1,000 mg/m² bid (14 days on of a 21-day cycle), which has been shown to lead to better tolerability of the drug without compromising its efficacy [12]. Dose modification of capecitabine also allows for extended treatment, which can improve outcomes for patients without cumulative toxicity. In the ANZBCTG0001 study, capecitabine-treated patients were significantly more likely to continue therapy beyond 6 months ($p = .001$) and 12 months ($p = .005$) than CMF-treated patients, which most likely accounted for the significantly longer OS time ($p = 0.02$) seen with capecitabine than with CMF in that trial. A number of studies are also investigating novel dosing schedules of capecitabine, including administering the drug for 7 days followed by a 7-day rest period, a 28-day intermittent dosing cycle, and continuous dosing. Two phase II trials in patients with MBC reported modest efficacy when capecitabine (1,000 mg/m² bid) was administered on a 7-days-on–7-days-off schedule in combi-

nation with bevacizumab [40] and with lapatinib [41]. The safety profile of this dosing schedule was acceptable, with minimal gastrointestinal toxicity observed in both studies. High clinical activity was shown with a 28-day intermittent dosing schedule in Japanese patients with MBC, in whom capecitabine (825 mg/m² bid) was administered on days 1–21 every 28 days [42, 43]. Safety was comparable with that of the standard 21-day intermittent regimen. In a randomized phase II study comparing continuous (800 mg/m² bid, days 1–21, every 21 days) and intermittent (1,250 mg/m², days 1–14, every 21 days) capecitabine dosing, patients treated with the continuous regimen appeared to have a lower incidence of related AEs than patients treated with the standard intermittent regimen [44]. Noninferiority (TTP at 1 year) of the continuous arm to the intermittent arm could not be demonstrated despite similar dose intensities and cumulative doses.

In the RIBBON-1 trial, the efficacy benefit seen with combined capecitabine and bevacizumab, in terms of the PFS interval, was achieved in all patient groups, irrespective of age, disease-free interval, number of metastatic sites, prior adjuvant therapy, hormone receptor status, and triple-negative status [19]. A recent retrospective cohort study explored response, survival, and prognostic factors in 75 patients with HER-2-negative MBC receiving capecitabine monotherapy following anthracycline and taxane failure [45]. In the overall study population, the ORR was 29.3% (95% CI, 20%–40%); the ORRs were 37.0% (95% CI, 26%–50%) for patients with hormone receptor–positive disease and 0% (95% CI, 0%–19%) for patients with hormone receptor–negative disease ($p = .003$). A hormone receptor–negative status was the strongest prognostic factor for the PFS time on univariate analysis (HR, 2.09; 95% CI, 1.14–3.87; $p = .015$) and was associated with a shorter PFS time in a multivariate analysis (HR, 2.24; 95% CI, 0.15–4.36; $p = .01$). Similar findings were obtained in exploratory subgroup analyses of a randomized, open-label trial of adjuvant capecitabine-containing chemotherapy, with greater recurrence-free survival benefits seen in patients with estrogen receptor–positive disease (HR, 0.60; 95% CI, 0.37–0.96) than in those with estrogen receptor–negative disease (HR, 0.77; 95% CI, 0.46–1.27) [46]. However, in preplanned subgroup analyses of a randomized phase III trial in patients with high-risk early breast cancer receiving adjuvant capecitabine-containing chemotherapy, contrasting results were found—

patients with hormone receptor–negative disease appeared to achieve a longer disease-free survival interval (HR, 0.76; 95% CI, 0.55–1.05) than those with hormone receptor–positive disease (HR, 0.90; 95% CI, 0.66–1.23) [47]. Newer breast cancer trials will focus on determining the specific subgroups of patients most likely to benefit from capecitabine therapy and provide clarity on this issue.

CONCLUSIONS

First-line treatment options for patients with HER-2-negative MBC are evolving, with greater use of capecitabine in this setting and a decline in the use of anthracyclines [48]. Single-agent capecitabine, often given at a dose of 1,000 mg/m² bid, for 14 days of a 21-day cycle, has proven efficacy in the first-line setting. Furthermore, first-line capecitabine monotherapy has a manageable toxicity profile, lacking myelosuppression and alopecia, which allows for prolonged administration, generally without cumulative toxicity.

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