Critical Reviews in Oncology/Hematology 100 (2016) 74–87

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Cytotoxic chemotherapy: Still the mainstay of clinical practice for all subtypes metastatic breast cancer

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ARTICLE INFO

Article history:
Received 13 October 2015
Received in revised form
24 December 2015
Accepted 20 January 2016

Keywords:
Metastatic breast cancer
Anthracycline
Taxane
Capecitabine
Eribulin
Etirinotecan pegol

ABSTRACT

Cytotoxic chemotherapy remains central to the treatment of all subtypes of metastatic breast cancer (MBC). We review evidence-based chemotherapy options for women with MBC after an anthracycline and a taxane including re-challenge with anthracycline or taxane, capecitabine, eribulin and ixabepilone as a single agent or combination with capecitabine (not approved in the EU); and the vinca alkaloid vinflunine as single agent or combined with either capecitabine/gemcitabine (also not approved EU or USA). Etirinotecan pegol, comprising irinotecan bound to polyethylene glycol by a biodegradable linker, is a new cytotoxic agent for patients with MBC that has achieved encouraging response rates in phase II studies; it has been further evaluated in the phase III BEACON trial. New cytotoxics should address novel targets or modes of delivery, achieve meaningful improvements in outcomes and seek to identify predictive biomarker(s).

Abbreviations: 5FU, 5-fluorouracil; A, anthracycline; BEACON, BrEAst Cancer Outcomes with NKTR-102; BRCA, breast cancer gene; CALGB, cancer and leukemia Group B; CTCs, circulating tumor cells; CI, confidence interval; CHF, congestive heart failure; DFI, disease-free interval; EMBRACE, Eisai Metastatic BReast Cancer study Assessing physician's Choice vs E7389; EPR, enhanced permeability and retention; NKTR-102, etirinotecan pegol; EMA, European Medicines Agency; EU, European Union; q21d, every 3 weeks; FDA, Food and Drug Administration; 1L, first-line; HFS, hand–foot syndrome; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat; MBC, metastatic breast cancer; nab-P, nab-paclitaxel; NPLD, non-pegylated doxorubicin; NR, not reported; NS, not statistically significant; ORR, overall response rate; OS, overall survival; PPE, palmer-plantar erythrodysesthesia; PLD, pegylated liposomal doxorubicin; PN, peripheral neuropathy; PFS, progression free survival; QOL, quality of life; T, taxanes; TTP, time to tumor progression; TOP1, topoisomerase I; T-DM1, trastuzumab emtansine; TPC, treatment of physicians' choice; TNBC, triple-negative breast cancers; US, United States.

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http://dx.doi.org/10.1016/j.critrevonc.2016.01.021

1. Introduction

Despite advances in the diagnosis and treatment of women with early breast cancer, globally more than 500,000 women die annually from the disease, reflecting the ongoing need for better treatment for women with metastatic breast cancer (MBC) (World Health Organization, 2014). Increasingly, we appreciate the heterogeneity of MBC in terms of its biology, but when making systemic treatment decisions, there are four main subgroups: hormone receptor (HR)-positive (≥65% of invasive breast cancers), which comprise luminal A cancers that are human epidermal growth factor receptor 2 (HER2)-negative and low Ki 67 and luminal B cancers that are HER2-positive or high Ki 67; HER2-positive (15–20%); and HR- and HER2-negative or triple-negative breast cancers (TNBC; 15–20%) (Lakhani et al., 2012). The median survival of patients with MBC is approximately 24 months, but is better in patients with HR-positive and HER2-positive tumors than those with TNBC (André and Zielinski, 2012; Kennecke et al., 2010; Bonotto et al., 2014).

While there are major differences in the treatment of patients with MBC, chemotherapy remains fundamental to the management of women with all molecular subtypes. For those with TNBC, chemotherapy offers the only systemic treatment option, but they are not the only group in whom chemotherapy is important. Patients with HR-positive disease, the biggest MBC subgroup, usually receive successive lines of endocrine therapy as long as they respond (Fedele et al., 2012). Everolimus appears to delay endocrine resistance (Baselga et al., 2012); palbociclib also enhances the efficacy of endocrine therapy (letrozole or fulvestrant) (Finn et al., 2014). Ultimately, when endocrine options have been exhausted, or the patient develops more aggressive disease, chemotherapy becomes relevant. Similarly, patients with HER2-positive MBC receive targeted therapies (*e.g.*, trastuzumab, pertuzumab, lapatinib) usually in combination with chemotherapy; trastuzumab emtansine (T-DM1) is given as monotherapy, but is a conjugate that includes the cytotoxic agent maytansine (Krop et al., 2014). Independent of the molecular phenotype, chemotherapy will, therefore, be an option at some point for most patients with MBC. Early reports of immunotherapy targeting PD-1/PD-L1 and antiandrogens are encouraging in subsets of TNBC, but these are not ready to replace chemotherapy (Emens et al., 2015; Traina et al., 2015).

Improving overall survival (OS) and/or quality of life (QOL) are key aims in treating patients with MBC. A perception may exist when considering chemotherapy: that the choice is between efficacy with treatment or better QOL without treatment. This misconception ignores the complications of the underlying disease on QOL. Our aim should, therefore, be to improve both quantity and quality of life for women with MBC.

Another guiding principle in treating patients with MBC is that single-agent sequential treatment is usually preferable to combination treatments (Fedele et al., 2012). The latter frequently achieves higher response rates, but at the cost of increased toxicity and little impact on OS. Although single-agent sequential treatment is accepted as "standard," the evidence from randomized trials regarding which drug to use following anthracycline and taxane has been surprisingly limited, especially for "old" agents such as vinorelbine and gemcitabine (Oostendorp et al., 2011). As a result, guidelines do not specify the sequence in which drugs should be given.

In contrast to the use of endocrine and HER2 targeted therapies, where biomarkers predictive of efficacy (*e.g.*, ER, HER2 status) are integral to treatment decisions, similar biomarkers are not well defined in the context of specific chemotherapy. The data are arguably strongest for patients with BRCA-mutated MBC in whom carboplatin was substantially more effective and better tolerated than docetaxel as first-line treatment (Tutt et al., 2014a). The ability to "personalize" the choice of cytotoxic to the individual patient and her cancer more widely would represent a major paradigm shift.

Drug resistance is, without doubt, the primary impediment to successful treatment of patients with MBC (Perez, 2009). With the increased use of anthracyclines (although with less cumulative doses) and taxanes in the (neo) adjuvant setting, a growing proportion of patients with MBC have pretreated and/or drug-resistant disease (Perez, 2009). Usual practice after an anthracycline and taxane has been to favor agents from a class not previously administered, with the expectation that the cancer is less likely to be cross-resistant to such treatment. The need remains, therefore, for new and better chemotherapy for women with MBC, almost half (43%) of whom receive >3 lines of chemotherapy (Ribeiro et al., 2012). New agents should preferably belong to a novel class, or have a novel mechanism of action, improve OS while maintaining or improving QOL when given as monotherapy, and be well tolerated and supported by sound evidence that would ideally include a predictive biomarker.

This article does not attempt to be a comprehensive review of chemotherapy in MBC. Rather, we focus on single-agent treatment following an anthracycline and a taxane, limiting ourselves to the most widely used drugs and emerging chemotherapy options.

2. Current therapeutic options for anthracycline- and taxane pretreated MBC

Until recently, therapeutic options after failure of anthracycline and taxane were limited (André and Zielinski, 2012). Currently, widely approved monotherapies for later-line treatment of MBC include capecitabine, eribulin, nanoparticle albumin-bound (*nab*)-paclitaxel, and ixabepilone (in the U.S.); vinorelbine is approved after an anthracycline (but not specifically a taxane) in Europe. Pegylated liposomal doxorubicin (PLD) and single agents such as gemcitabine, platinum agents, and irinotecan are also used (Table 1). There is no agreement regarding the preferred agents and their sequence; a recent consensus report recognized that evidence is strongest for eribulin and capecitabine (Partridge et al., 2014). Likewise, carboplatin/cisplatin chemotherapy seems to be especially active in patients with BRCA 1/2 mutations or for TNBC with DNA repair deficiency (Isakoff et al., 2015). The TNT randomized phase III trial compared carboplatin with docetaxel in 376 patients with metastatic/locally recurrent advanced TNBC and/or BRCA1/2 positive tumors (Tutt et al., 2014b). In the 43 BRCA positive patients the ORR was 68% *vs* 33% and PFS of 6.8 *vs* 3.2 months in the carboplatin vs docetaxel arms, respectively. Such differences were not, however, seen in the overall population (ORR of 31.4 vs 35.6% and PFS of 3.1vs 4.5 months in the carboplatin vs docetaxel arms, respectively). Indeed, many of the current options after anthracycline and taxane have not been compared in randomized clinical trials, and cross-trial comparisons can be difficult. Consequently, treatment decisions are frequently based on personal experience, prior therapy, adverse event profiles, and patient preference (Ribeiro et al., 2012).

2.1. Rechallenge with, or reformulation of, an anthracyclines or taxane

There is a paucity of evidence documenting the efficacy of rechallenge with a conventional anthracycline or taxane in patients with MBC (Ribeiro et al., 2012; Partridge et al., 2014; Isakoff et al., 2015; Tutt et al., 2014b; Venturini et al., 1996). Although responses have been described, most studies are single-center cohorts, small phase II trials, or retrospective analyses of phase III studies; such trials often do not specify previous adjuvant chemotherapy, and patients with anthracycline- and taxane-resistant or refractory dis-