Treatment Options in Anthracycline and/or Taxane Pretreated Patients with Metastatic Breast Cancer

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In developed countries nearly 30% of women with early stage breast cancer will eventually develop metastatic breast cancer (MBC), however, recent reports have demonstrated improvements in median survival mainly due to progresses made in treatment options [1, 2]. The therapeutic management of these women is multifaceted, encompassing many issues including tumor factors (i.e., aggression of disease, tumor burden, sites of disease, estrogen receptor, and HER2 status), previous treatment factors (i.e., use of and responsiveness to prior therapies, and associated toxicities) and last but not least patient factors (i.e., menopausal status, performance status, comorbidities, psychological concerns, and patient preferences).

The phase II trial of mitomycin (MMC) and vinorelbine in patients with MBC pretreated with anthracycline and/or taxane, which appears in this month's issue of ONKOLOGIE [3], successfully focuses attention on the need for effective second and third-line regimens once anthracyclines and taxanes fail. The concept of anthracycline/taxane resistance is complicated by an assortment of patient populations and definitions in the clinical literature. Thus, Pivot et al. [4] put forward a series of definitions for anthracycline resistance applicable to other chemotherapeutics. These are associated with a statistically significant difference in survival from the date of progression with the median overall survival (OS) being 5 months for primary and secondary resistance, 9 months for progressive disease (PD) within 6 months after the last dose of anthracycline and 11 months for PD between 6 and 12 months after the last dose of anthracycline, clearly signaling the need for clarity of definitions in clinical trials of this nature.

Therapeutically, in this setting, capecitabine is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and was endorsed by the 1st international consensus guidelines for advanced breast cancer (ABC1) [5]. It thus represents the international standard of care. A systematic review of 28 single-agent capecitabine trials revealed a median overall response rate (ORR) of 28%

(range 9–53%) with a median OS of 11.0 months (range 5.3–18.1 months). The advantages of capecitabine are well documented and include good efficacy, tolerability with minimal grade 3–4 toxicity, oral preparation, maintaining quality of life, and cost effectiveness [6].

Another commonly employed option is vinorelbine, which in anthracycline and taxane pretreated patients, yields response rates (RR) of 10–35% as a single agent and 25–61% in combinations with non-taxanes in anthracycline pretreated patients [7–17].

Newer agents, such as eribulin, have gained approval by the FDA and EMA in patients with prior anthracycline and taxane exposure. The Embrace trial (Eribulin to best physicians choice) in heavily pre-treated locally advanced or MBC patients revealed an ORR of 12.2 versus 4.7% ($p = 0.002$), a progression free survival (PFS) of 3.7 versus 2.2 months (hazard ratio (HR) = 0.87, 95% confidence interval (CI) = 0.71–1.05, $p = 0.137$) and an OS of 13.1 versus 10.6 months (HR 0.81, 95% CI = 0.61–0.99, $p = 0.041$) with a tolerable toxicity profile [18].

Additional agents include nab-paclitaxel, which in phase II trials produced RR of 15% in anthracycline and taxane pretreated patients and ixabepilone in combination with capecitabine [19, 20].

A further alternative may arise from the ongoing BEACON trial, a phase III, open-label, randomized, multicenter study of pegylated irinotecan versus physician's choice in 840 MBC patients pre-treated with anthracycline, taxane, and capecitabine in the adjuvant or metastatic setting [21].

In the current study of MMC and vinorelbine, 65% of patients were pre-treated with anthracyclines and taxanes, but it is unclear how these patients are positioned within the Pivot et al. classifications. This notwithstanding, the ORR was 26% with a median PFS of 5.0 months (95% CI = 3.6–6.8), comparable to other agents approved for this setting. We assume HER2 negativity though this is not described in the text, but alluded to in the conclusion.

This trial emphasizes the controversial discussion of single agent versus combination chemotherapy for MBC patients. Evidence for both arguments exists in this well debated issue with a Cochrane review establishing a higher RR (OR for response = 1.28, 95% CI = 1.15–1.42, $p < 0.001$), longer time to progression (HR = 0.78, 95% CI = 0.73–0.83, $p < 0.001$) and longer OS (HR for death = 0.88, 95% CI = 0.83–0.94, $p < 0.001$) for combination chemotherapy [22]. However, not all patients will derive benefits from combination therapy in MBC.

Conversely, these marginal benefits are offset by the toxicity associated with combination treatment. Additionally, these results are confounded by several factors blunting the effect of either arm. International guidelines identify single sequential chemotherapy and combination options as reasonable first-line choices [23]. In second or third-line settings, combination therapy is more contentious.

In the current study of MMC plus vinorelbine we observe rates of patient discontinuation (14%) due to the well-established but rare dyspnea syndrome with MMC and vinorelbine, hematological toxicity and asthenia. This is comparable to rates with capecitabine (7–13%), vinorelbine (5%) and eribulin (17%) [15, 18, 20, 24, 25]. The most significant effect of treatment is hematological toxicity with grade 3 or 4 neutropenia of 37% significantly higher than seen with capecitabine (1%) [6]. Other combination strategies in this setting (e.g., gemcitabine/vinorelbine, ixabepilone/capecitabine) yield similar hematological toxicity, highlighting the consequences of combination treatment in pre-treated MBC [15, 20].

MMC has been used in combination with vinblastine or vinorelbine in MBC. In the present study, the authors choose a non-standard administration of MMC (3-h infusion) to minimize thrombocytopenia rates. Unfortunately, the rates of thrombocytopenia and the distribution by grade reported in trials using MMC + vinorelbine/vinblastine bolus are comparable to rates of the current trial [26–29]. Even administration as a 5-day infusion with 5-fluorouracil results in thrombocytopenia rates of approximately 20%, likely reflecting the natural toxicity profile of MMC rather than an administration effect [29].

The present article highlights that MBC patients are unique amongst metastatic cancer patients due to the multitude of agents that are active in breast cancer. While the toxicity profile of MMC plus vinorelbine indicates that this regimen may not be the first preference in anthracycline and taxane pretreated patients, older agents and their combinations should not be forgotten as potential therapeutic options in the enthusiasm for new agents. Also, the selection of patients to be treated with combination chemotherapy in the metastatic setting remains fundamental and should be agreed during the multidisciplinary team discussion.

Disclosure Statement

The authors declare no conflict of interests.

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