Management of advanced breast cancer: how to integrate scientific data and clinical judgment

23rd International Congress on Anti Cancer Treatment

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Recent epidemiological data have shown a significant decline in breast cancer mortality over the past 15 years, as a result of screening programs, better education, and the introduction of more effective adjuvant treatments[1]. However, about 20-30% of the patients eventually relapse while approximately 5-7% of cases present with metastatic disease at diagnosis[2]. Metastatic breast cancer is still largely incurable: the median survival time is generally in the range of 2 to 4 years[3].

In the metastatic setting, treatment goals can be quite different depending on patient and tumor characteristics. There are patients for whom the main objective is symptom control to improve or maintain quality of life, cases with life-threatening disease for whom a rapid tumor shrinkage is required, asymptomatic patients with slowly growing disease for whom a prolonged progression-free survival (PFS) duration is the desirable target; finally, some patients can obtain an important survival prolongation and a few of them might be cured[4]. The selection of treatment depends on several factors, including patient characteristics, aggressiveness of the disease, response to previous therapies, time since last exposure, agents used in the past and cumulative doses. Availability and

regulatory approval of various anticancer agents further diversify treatment patterns in different part of the world.

A rapidly growing pool of effective treatment options for advanced breast cancer has increased response rates and outcome. First, many new cytotoxic drugs are in development or have recently been approved in this setting, such as ixabepilone, eribulin and nab-paclitaxel. For instance, in the phase III trial EMBRACE, eribulin mesylate improved overall survival (median 13.1 months, 95% CI 11.8-14.3), compared to treatment of physician's choice (median 10.6 months, CI 9.3-12.5; HR 0.81 95% CI 0.66-0.99, p=0.041), in patient who had received two to five prior chemotherapy regimens, including an anthracycline and a taxane for advanced breast cancer.[5] In clinical studies, 3-weekly nab-paclitaxel has been shown to increase both the safety and the efficacy of 3-weekly paclitaxel in patients with advanced breast cancer (median time to progression 23 vs 16.9 weeks, hazard ratio 0.75, p=0.006).[6] Weekly nab-paclitaxel produced meaningful results even in taxanes pre-treated patients (ORR 14% and 16% in the 100 and 125 mg/sqm cohorts, respectively; median PFS of 3 and 3.5 months, respectively).[7] At the same time, research efforts are directed to implement the pool of targeted therapies, in order to offer more individualized options to breast cancer patients. In fact, the molecular breast cancer subtype is a fundamental determinant of treatment choice both in early and advanced setting. Breast cancer consists of at least three different diseases: hormone-sensitive breast cancer, the human epidermal growth factor receptor (HER2)-positive subtype, and triple-negative disease. Each molecular subtype

has distinct biological features and a distinct clinical course: hormone receptor–positive (HR+) disease is generally characterized by a more indolent course, with a long disease-free interval (DFI) and a tendency to relapse in the bone or soft tissues; amplification of the HER-2 gene confers a more aggressive clinical behavior to the HR+ subgroup, with a higher propensity for visceral relapses. Both triple-negative breast cancer and hormone receptor–negative (HR-)/HER-2+ breast cancer are aggressive subtypes, with early visceral or central nervous system metastases.

Each molecular subtype requires distinct therapeutic approaches.

In HR+ tumors, endocrine manipulation is the cornerstone of therapy. Treatment choice depends on many factors such as menopausal status and disease-free interval. For postmenopausal women many agents are available: non-steroidal and steroidal aromatase inhibitors (AI), tamoxifen and fulvestrant; however no definitive recommendation for the optimal cascade can be given. For premenopausal patients, the data on aromatase inhibitors or fulvestrant are more scanty[8]. In case of life-threatening and rapidly-growing disease, or in case of failure of various endocrine agents, chemotherapy has to be considered. Yet, recent studies have shown that HR+ positive tumors do also derive benefit from additional targeted agents: data from the BOLERO-2 trial showed an impressive improvement in progression free-survival with the addition of everolimus to exemestane vs exemestane alone as first- or second-line treatment for HR+ advanced breast cancer patients, after failure of a non-steroidal AI in the adjuvant or metastatic setting (median PFS 10.6 vs 4.1 months according to central assessment,

HR 0.36;95% CI 0.27-0.47, p<0.001)[9]. Thus, overcoming endocrine resistance by combined targeting of redundancy pathways will be one of the key issues in the near future. In this context, even the association of trastuzumab or lapatinib to endocrine agents is an important option for HR+/HER2+ patients. Targeting HER2 in HR+ breast cancer has been explored as a means of improving endocrine responsiveness. The randomized phase II TAnDEM trial included 207 patients with known ER+/HER2+ metastatic breast cancer and reported a doubling of progression-free survival with the addition of trastuzumab over anastrozole alone (hazard ratio 0.63; 95% CI, 0.47 to 0.84; median PFS, 4.8 *v* 2.4 months; p =0016)[10]. Finally, results from a phase III trial of 1,286 patients with metastatic ER+ breast cancer who were randomized to receive either letrozole alone or letrozole combined with lapatinib have been published. In patients with known ER+/HER2+ tumors (n=219), the addition of lapatinib to letrozole significantly reduced the risk of progression as compared to letrozole alone: median PFS was 8.2 *v* 3.0 months, respectively (HR 0.71; 95% CI, 0.53 to 0.96; p=0.019)[11].

In HR-/HER2+ tumors, the incorporation of trastuzumab has substantially reversed the negative prognostic impact of HER-2 overexpression/amplification[12]. However, due to the approval of trastuzumab as standard adjuvant therapy for early HER2+ breast cancer and the emergency of resistance to this drug, the need of new anti-HER2 agents has emerged, as well as the need to clarify the role of continuing trastuzumab beyond progression, with different cytotoxic agents. Lapatinib, combined with capecitabine, has been approved for the treatment of HER2+ metastatic breast cancer patients, previously

treated with trastuzumab. Many other anti-HER2 agents are being developed such as T-DM1, neratinib and pertuzumab. In T-DM1 trastuzumab is conjugated with an antimicrotubule drug maytansinoid. Activation of cytotoxicity of this conjugate requires internalization into the cell after binding to HER2. A single-arm, phase II trial (n = 112 MBC patients whose disease progressed on trastuzumab) showed at a follow-up of ≥12 months a median PFS of 4.6 months (95% CI, 3.9 to 8.6) and an overall response rate of 26%. Hypokalemia, thrombocytopenia, and fatigue were the most common observed adverse events. No dose-limiting cardiotoxicity was reported[13]. T-DM1 is undergoing further testing in the context of several other studies. An open-label, phase III randomized trial (EMILIA) is comparing single-agent T-DM1 with the combination of capecitabine and lapatinib in patients whose HER2-positive disease has progressed on trastuzumab. In another phase III trial MARIANNE, T-DM1 monotherapy is being compared to trastuzumab plus a taxane. Neratinib/HKI-272 is an oral, irreversible, small molecule inhibitor of EGFR/HER1, HER2, and HER4. In an open-label, phase II study, patients with advanced HER2-positive BC with and without prior trastuzumab treatment received neratinib. The 16-week PFS was 59% for patients with prior trastuzumab (n = 63) and 78% for those without (n = 64); median PFS were 22.3 and 39.6 weeks, respectively. The most frequent AEs were diarrhea, nausea, vomiting, and fatigue. Grade 3 or 4 diarrhea occurred in 30% of patients with prior trastuzumab therapy, leading to neratinib dose reduction in 29% of this cohort[14]. A phase III randomized study of paclitaxel with either neratinib or trastuzumab in MBC is ongoing, as is a randomized

phase II study of neratinib alone versus the combination of capecitabine and lapatinib. Pertuzumab is a first-in-class recombinant, humanized monoclonal antibody that binds to domain II of the HER2 receptor, thus inhibiting HER2 heterodimerization with HER1, HER3, and HER4. Recent data from a randomized phase III trial showed that the combination of trastuzumab, pertuzumab and docetaxel as first-line treatment for HER2+ advanced breast cancer patients, significantly improves progression-free survival, with a gain of 6 months in median progression-free survival, as compared to the combination of trastuzumab and docetaxel (PFS 18.5 vs 12.4 months, HR 0.62; 95% CI, 0.51 to 0.75; P<0.001)[15]. These results contribute to increase the interest in dual HER2 blockade that derived from early breast cancer trials. In this context, the combination of trastuzumab and lapatinib in trastuzumab-pretreated patients resulted in a more prolonged PFS as compared to lapatinib alone (HR 0.73; 95%CI 0.57-0.93, p=0.008)[16].

Lastly, chemotherapy is the only available option so far for the triple-negative (TNBC) subtype, which is characterized by the absence of hormone receptors and HER-2 negativity. At this time, there are no targeted agents that are specifically approved for the treatment of this breast cancer subtype. Bevacizumab appears to prolong progression-free survival when added to chemotherapy for patients with TNBC (as it does for those with HR+/HER2- disease), but does not enhance survival[17]. Moreover, neoadjuvant trials provide conflicting results on the role of bevacizumab for TNBC[18,19]. Although there was great enthusiasm based on phase II data for the combination of

carboplatin, gemcitabine and the PARP-inhibitor iniparib, the phase III results did not support the preliminary data[20]. A variety of other targeted therapies, including the PI3K inhibitors and a number of agents that inhibit DNA repair are under active investigation.

Nowadays, more patients are likely to be diagnosed with oligo-metastatic disease, asymptomatic and in good performance status, due to the use of more sophisticated imaging techniques and the information derived from serum-markers dosage; therefore more selective therapeutic strategies that include a multimodality approach and local therapies are becoming more and more important. A substantial improvement in multimodality treatments, including, but not limited to, stereotactic radiosurgery, percutaneous radiofrequency ablation, and minimally invasive surgery, has increased the chance for disease control in selected patients with limited and indolent metastatic disease. In this context, surgery on primary tumor in case of oligometastatic disease has been suggested to improve survival, but further data are needed and a randomized trial addressing this issue is ongoing.

Furthermore, an interesting field of research is the molecular characterization of metastatic disease. Biopsies of recurrent sites are not routinely performed and treatment decision for metastatic disease is mainly based on the receptor status of the primary tumor. However, discordance rates in HR and/or HER2 status between primary and recurrent tumors have been reported in the range of 10% to 35%[21]. Reasons for discordance may include: test artifacts, tumor heterogeneity, genetic drift during progression, selective pressure of adjuvant therapies. Nevertheless, recent reports

suggest that the change in the receptor status during tumor progression may have also a prognostic impact[22].

It is therefore critical to incorporate all disease and patient information to assure the best treatment strategy for a given patient. The choice of the best treatment for metastatic disease has become even more difficult because the more efficacious agents have been progressively incorporated into the management of earlier stages. As a consequence, even if the number of patients who experience disease recurrence is gradually decreasing, treatment options for recurring patients are more and more influenced by prior exposure to adjuvant therapy. Unfortunately, most trials conducted in advanced breast cancer do not take into account all these factors that are necessary for an appropriate decision-making process.

A deeper insight into tumor biology and mechanisms of resistance to established therapies will allow to develop new cytotoxic or targeted drugs or new combinations of available drugs for the treatment of metastatic disease. Key preclinical studies are needed, in order to guide the choice of which combination or single-agent deserve to be tested in early phase clinical trials. Moreover, well-designed trials that take into account the critical issues that frequently present in clinical routine are needed, in order to allow for a better translation of scientific results into daily practice.

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