Editorial

Implementing clinical practice guidelines for breast cancer management: searching for homogeneity in real-life heterogeneity

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Breast cancer is one of the most common solid tumors in the world and a major cause of premature mortality among women (1). Despite the notable progresses and the high efficacy of diagnostic tools and multimodal treatment strategies (surgery, radiotherapy and medical treatments) in early disease, up to a third of breast cancer patients still recur and die (2). Breast cancer encompasses a broad spectrum of different situations and various clinical challenges, depending on the specific cancer histology, tumor grade, disease stage and definition of the molecular subtype (luminal A, B, Triple-negative/basal-like, HER2-enriched). Obviously, the clinical context can also change according to the characteristics of the patient, such as age, menopausal state, comorbidities, without neglecting specific clinical conditions as male breast cancer, concomitant pregnancy, or the presence of genetic anomalies of cancer predisposition (namely BRCA 1 and 2 mutations).

Moreover, breast cancer represents a crucial commitment for healthcare institutions (governmental organizations, scientific societies), to ensure adequate information, clear management indications and, sometimes, "reassurance" towards health workers, patients and their families, but also public opinion. Their need for information, as clear and concise as possible, requires an explanation about the quality of evidence and the expression of the strength of recommendations, easily exploitable.

Clinical practice guidelines are statements that include practical resolutions and management proposals intended to optimize patient care outcomes and efficiencies, but also to minimize disparities. They are structured according to a systematic review of evidence-based knowledge, assessing the benefits and harms of alternative care options and taking into account the actual availability of suggested choices, in the specific context of application.

Increasing evidence showed that adherence to guidelines is associated with improved outcomes in patient care, as well as prolonged survival and better quality of life (3).

However, in recent years, concrete availability of real life medical resources has become a major concern in clinical practice guidelines, and this is particularly important for developing countries or socioeconomically diverse communities.

China is one of the most important developing countries, with a large territory and uneven economic and academic developments.

Conceiving and implementing a consensus document on diagnosis and treatment of breast cancer, applicable to different territorial realities and capable of summarizing the perspective of the Chinese Society of Clinical Oncology (CSCO), is a truly ambitious challenge. Indeed, the CSCO guidelines must consider differences in regional development, namely with regard to the availability of medical compounds and diagnostic tools, without forgetting the social value of cancer treatment. Moreover, since a vast amount of data and knowledge revealed the genomic bases of breast cancer heterogeneity, it is important to take into account the advances in precision medicine, as the genomic "revolution" gradually translates into clinical practice (4). The publication of the updated CSCO guidance on diagnosis and management of breast cancer in 2020 could

revive the debate on this controversial topic (5). Indeed, clinical practice guidelines systematically synthesize composite and sometimes conflicting multi-disciplinary and multi-level learnings into a cogent advice to guide practical decisions. However, a question remains unanswered: are guidelines really effective and applicable?

More globally, we can consider meta-analyses, systematic reviews and clinical practice guidelines as part of the same effort to implement the uniformity of knowledge, where clinical situations and real-life practice tend to create heterogeneity of judgment, interpretation and attitudes. This, however, does not mean absolute and blind homogeneity in decision-making, neither that some variation in care, reflecting local circumstances and patient specificities, are not opportune. Indeed, specifically with respect to guidelines, the greatest challenge implementing their diffusion and use is not related to uncertainty in regards to clinical "independence" in patient care but rather the challenge of preventing "sterile" proposals, not applicable in the existing environment, almost like Cervantes' Don Quixote, engaged in a battle against windmills. In this sense, there are two crucial aspects in a clinical practice guideline, to ensure that feasible and effective regulations are created: (I) its educational role; (II) its consistency with other similar reference texts.

As regards the first aspect, in their capacity as rapidly and easily using tool in everyday practice, clinical guidelines play a very specific formative role in ensuring that their users fit into a multidisciplinary perspective, as an academic discipline in interdisciplinary dialogue with others. As in the case of other influential guidelines, considered as a reference text in the management of breast cancer diagnosis and treatment, namely in US and Europe, the working group that drafted CSCO guidelines includes different scientific areas, like surgery, medical oncology, radiotherapy, histopathology, radiology, molecular biology (5-7). Thus, through a multi-professional and multi-disciplinary approach, an attempt was made to generate rigorous, yet simple, operational, clear and accessible clinical recommendations, through a systematic literature review process, with the aim of helping patients, clinical and non-clinical operators to decide the most appropriate assistance modalities in different clinical situations.

Regarding the second aspect mentioned, concerning the contents of the document and its consistency with major international guidelines, it is noteworthy to underline in CSCO guidelines three overall recommendations, which are able to summarize, depending on molecular breast cancer subtype, the current shared approach in the management of corresponding disease phenotypes, at major incidence and high clinical relevance (5).

Advanced luminal breast cancers

In luminal A or B advanced breast cancer (estrogen receptor positive, HER2-negative tumors), the preferred treatment should be endocrine therapy, namely considering combination with new targeted therapies (i.e., CDK4/6 inhibitors) (5-7). The disease control rate and progression-free survival (PFS) of endocrine therapy plus targeted therapy is not inferior to those of chemotherapy, with better quality of life and greater acceptance for the patients (5-7). Moreover, women with breast cancer who respond to an endocrine-based treatment with clinical benefit should receive additional endocrine therapy at disease progression, as all the major international guidelines recommend the use of several lines of hormone therapy before using chemotherapy, unless no response is achieved (5-7). In these cases, when chemotherapy is needed, both combination chemotherapy and sequential single-agent treatment are reasonable options (5-7). Based on the available data, compared with single-agent chemotherapy, combination chemotherapy usually has a higher objective response rate and longer PFS (5-7). However, no overall survival (OS) benefit is demonstrated. Moreover, combination chemotherapy is more toxic. Thus, combination chemotherapy should be considered for patients with rapid clinical progression, life-threatening visceral metastases or the need for rapid symptom and/or disease control (5-7).

In summary, handling luminal tumors, similar indications should be recognized for prescribing combination chemotherapy rather sequential single agent treatment or chemotherapy rather endocrine therapy. They are related to the need of a rapid onset of response, as in the case of highly symptomatic patients requiring symptoms relieve within a short period of time (the so-called visceral crisis). However, visceral crisis is not the mere presence of visceral metastases but implies important organ dysfunction, as defined by signs and symptoms, laboratory studies and radiological evidences, leading to a clinical indication for the most rapidly efficacious treatment (7). Noteworthy, it is quite rare, occurring only in 10–15% of patients as initial clinical presentation (7).

HER2-enriched early breast cancer

New questions arise concerning different aspects of HER2-

enriched (HER2-positive, estrogen receptor positive or negative) breast cancer treatment and new challenges emerge, namely in the management of localized disease, among the suggestion of de-escalated treatment strategies for low-risk patients and the need of escalated therapies for patients at high risk of relapse.

In spite of appearances, this is not a contradiction: in fact, these two different therapeutic approaches are simply the most appropriate answer to adapt treatment strategies according to the biological and clinical features of each patient.

On this basis, reasons for pursuing a therapeutic de-escalation in the treatment of localized HER2-positive disease are different and all relevant. On the one hand, it must be considered that the use of trastuzumab has been validated only in combination with chemotherapy. However, the overall toxicity of this association, namely in low-risk patients, seems disproportionate to the benefit. On the other hand, it should also be stressed the risk of cardiac toxicity, due to anthracyclines but also to trastuzumab. Finally, we cannot forget the problems linked to the costs of treatments.

Thus, a first way to optimize (neo) adjuvant treatment of HER2-positive early disease is achievable through a therapeutic de-escalation of chemotherapy. Different strategies are evaluable, for example omitting anthracyclines (i.e., TCbH regimen: docetaxel, carboplatin and trastuzumab) or reducing the overall duration of chemotherapy (i.e., wTH regimen, weekly paclitaxel and trastuzumab), namely in the adjuvant setting of HER2-positive small tumors (≤3 cm), at low risk of relapse (pN0) (5,6). In these cases, 1-year trastuzumab remains the standard adjuvant treatment (5,6). However, a large number of clinical trials tested a short (namely 6 months) therapy: even if the non-inferiority of this treatment cannot be universally established, the likelihood of a significant benefit with 1-year trastuzumab compared to 6 months is limited (8,9). Undoubtedly, a shorter duration of trastuzumab may be suitable for some patients with low-risk disease, especially if an increased risk of cardiotoxicity is present.

Even if therapeutic de-escalation is an important objective, clinical and biological characteristics of high-risk disease (high-grade, advanced stage, poor response to neoadjuvant treatments, metastatic lymph node involvement) require, on the contrary, a therapeutic intensification compared to standard therapy. To this end, the most appropriate therapeutic options universally validated are two: either the reinforcement of the (neo) adjuvant treatment via a dual anti-HER2 blockade (namely trastuzumab and pertuzumab), instead of trastuzumab alone, or the selective treatment intensification in non-pathological complete responders (nonpCR) after neoadjuvant therapies, via the use of the drug-conjugated antibody trastuzumab emtansine (T-DM1), in the adjuvant setting (5,6).

Advanced triple-negative breast cancer

Triple-negative breast cancer (estrogen and progesterone receptor negative, HER2-negative tumors) has a poorer prognosis compared with other breast cancer subtypes (10). About 75% to 85% of triple-negative tumors express basal markers and 15% to 20% are associated with a BRCA mutation (10). Triple-negative tumors relapses occur more frequently and earlier than those of other breast cancer subtypes (10). Few advances are available in the treatment of metastatic triple negative tumors. For most patients with triple-negative advanced breast cancer, chemotherapy remains the only non-investigational systemic treatment, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds, namely for patients with BRCA-mutated triple-negative tumors (5-7). However, in this sad scenario, two approaches emerge as an interesting and promising option, guided by molecular selection (11-13).

For patients with a germline BRCA mutation, single-agent PARP inhibitor is a preferred treatment option for those with triple-negative advanced breast cancer (11). Single-agent PARP inhibitors (olaparib, talazoparib) are associated with a PFS benefit, improvement in quality of life and a favorable toxicity profile (5-7).

As shown in the Impassion 130 study, the combination of the PD-L1 antibody atezolizumab with albumin paclitaxel as first-line treatment of metastatic or unresectable locally advanced triple-negative breast cancer could significantly prolong PFS (12). In particular, it achieved OS benefit in patients with positive PD-L1 expression (PD-L1 ≥1% in immune cells) (13). Unfortunately, as recently reported, phase 3 Impassion 131 study, evaluating the combination of atezolizumab with paclitaxel, did not meet its primary end-point of PFS in patients with metastatic triple-negative breast cancer (14).

Therefore, due to variable availability of medical compounds (namely for PARP inhibitors) and/or uncertain results of clinical studies (namely for PD-L1 antibodies), active participation in clinical trials on immune checkpoint inhibitors or PARP inhibitors is currently strongly

recommended in all guidelines (5-7).

In fact, evidence-based guidelines can be valuable tools, but only if their content is up-to-date and able to recognize the present limits of knowledge. Implementing a clinical approach to ensure that guidelines maintain their relevance in real-life practice is crucial for improving a correct and reliable perception of new developments, thus allowing clinicians and patients to make informed decisions, optimizing outcomes and efficiencies.

For this goal, efforts must persist not only in research but also in public policy and healthcare to guarantee homogenous access to multidisciplinary and qualified care and full implementation of these guidelines. However, it is important to remember that clinical decisions on the individual patient require, in addition to an exact knowledge of scientific evidences, respect for the values and ethics of medical profession.

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