Editorial

CSCO breast cancer management guidelines 2022: Australian perspective

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We applaud the astronomical efforts of the authors in publishing the Chinese Society of Clinical Oncology (CSCO) guidelines on breast cancer management encompassing both early and advanced disease (1). The guidelines are well written and include clear recommendations for each disease setting as well as literature review behind each recommendation. We would like to add a few comments to highlight some differences in practice between Australia and CSCO.

The CSCO guidelines have recommended neoadjuvant dual human epidermal growth factor receptor 2 (HER-2) therapy for early HER-2 positive breast cancer. This is supported by the NeoSphere study, demonstrating higher pathological complete response (pCR) with the addition of pertuzumab to trastuzumab and chemotherapy backbone (2). Although pertuzumab is approved by the Therapeutic Goods Administration (TGA) in Australia, it is currently not listed on the Pharmaceutical Benefits Scheme (PBS) for this indication. Thus, large majority of Australian patients are treated with Trastuzumab alone, in combination with neoadjuvant chemotherapy.

Neoadjuvant anthracycline-containing chemotherapy has been listed as level II recommendation for early HER-2 positive breast cancer. The role of neoadjuvant anthracycline is supported by the 2012 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, which has demonstrated better outcomes including overall mortality for anthracycline-containing chemotherapy over non-anthracycline regimen (3). Moreover, the large majority of patients recruited in the landmark APHINITY and KATHERINE adjuvant trials received anthracycline-based chemotherapy (4,5). We acknowledge the results from the Breast Cancer International Research Group 006 (BCIRG 006) (6). This study has shown similar disease-free survival outcomes for anthracycline-taxane and anthracycline-free (taxane-carboplatin) regimen, thus suggesting treatment de-escalation with non-anthracycline regimen as an alternative regimen. However, this trial is not powered to demonstrate equivalence between both regimens. Thus, anthracycline-taxane combination is commonly used in the neoadjuvant setting for early HER-2 positive breast cancer in Australia. The use of taxane-carboplatin is considered when anthracyclines are contra-indicated.

The CSCO recommendation for adjuvant trastuzumab emtansine (TDM-1) in non-pathological responders post neoadjuvant therapy is consistent with our practice in Australia based on the KATHERINE study. We note that the majority of patients recruited received neoadjuvant Trastuzumab in combination with chemotherapy (5). Therefore, the role and benefit of adjuvant TDM-1 in patients who have received dual HER-2 blockade remains unclear at this stage. Otherwise, extended anti-HER-2 therapy with adjuvant Neratinib has been recommended following completion of neoadjuvant treatment in non-pathological complete responders. The benefit offered by Neratinib is mainly limited to the hormone receptor positive subgroup and is associated with high incidence of diarrhoea (7). Considering the availability of adjuvant endocrine therapy, Neratinib is not routinely used in Australia and is not PBS-listed for this indication.

In early triple negative breast cancer, pooled analysis from 12 international trials has confirmed the association between pCR and long-term outcomes following pre-operative chemotherapy (8). Similar findings were shown in a prospective analysis demonstrating worse prognosis in patients with residual disease following neoadjuvant chemotherapy (9). Existing data from randomised trials has demonstrated improved pCR (and possibly, long term outcomes) with the addition of pre-operative carboplatin to taxane- and anthracycline-containing neoadjuvant regimen (10,11). Thus, treatment intensification with addition of neoadjuvant carboplatin is commonly used in Australia. As expected, this approach is associated with higher rates of haematological toxicities and may require treatment delay, dose reduction or granulocyte colony-stimulating factor (G-CSF) as supportive measures. Carboplatin was also used in the KEYNOTE 522 trial which looked at the addition of programmed cell death protein-1 (PD-1) inhibitor, pembrolizumab in the peri-operative setting (12). This trial has shown an improved pCR rate regardless of programmed death-ligand 1 (PD-L1) expression and event free survival in the pembrolizumab experimental arm, leading to its approval in United States and Europe (13,14). The optimal adjuvant treatment strategy in patients with residual disease following neoadjuvant Pembrolizumab remains unclear and there are no data to support the use of concurrent pembrolizumab and capecitabine, or olaparib (in the presence of BRCA mutation). At this stage, peri-operative pembrolizumab is not PBS-listed in Australia.

For early hormone-positive breast cancers, adjuvant rather than neoadjuvant treatment approach is generally used in Australia considering low pCR rate after neoadjuvant chemotherapy in this patient cohort (15). Patient selection for adjuvant chemotherapy in luminal-like early breast cancer requires thorough risk assessment including tumour burden, tumour biology, host factors such as co-morbidities, and patient preference. Risk calculators including the National Health Service (NHS) PREDICT tool can be used to provide an estimate on recurrence risks and potential benefit from adjuvant treatment (16). Gene expression profiling may be considered in intermediate-risk patients such as one to three lymph node involvement or node-negative with high grade disease to improve patient selection and avoid over-treatment with chemotherapy. However, there is no Medicare rebate for this testing and its significant expense would mean that it remains out of reach for many Australians. Combination of anthracycline- and taxane-containing adjuvant chemotherapy is commonly used especially in high-risk disease with high nodal burden. Anthracycline-free chemotherapy regimen such as docetaxel/cyclophosphamide (TC) can be considered as an alternative especially in intermediate risk, early breast cancer. This is supported by ABC trial and PlanB/SUCCESS C pooled analysis demonstrating lack of meaningful outcomes with anthracycline based regimen in lower risk, less than four positive lymph node, hormone receptor positive breast cancer (17,18).

As presented by the authors, there are emerging data to support the role of adjuvant cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor in high risk, hormone receptor positive, node positive breast cancer. The monarchE study has shown three-year improvement in invasive disease-free survival with the addition of abemaciclib for two years (19). These findings are in contrast to the PALLAS and Penelope B trials which failed to demonstrate benefit with palbociclib (20,21). Approximately 60% of patients recruited in monarchE trial had at least four lymph nodes involved, suggesting that the benefit of adjuvant CDK 4/6 inhibitor may be limited to high-risk patients (19). Accessing adjuvant abemaciclib in Australia is difficult for majority of patients as it is not PBS-listed for this indication.

Adjuvant bisphosphonates are generally recommended for post-menopausal women with intermediate- and high-risk early breast cancer in Australia. The EBCTCG meta-analysis has found significant benefit for adjuvant bisphosphonates in post-menopausal breast cancer patients with reduction in bone recurrence, breast cancer mortality and overall survival (22). Bone health protection is another incentive for adjuvant bisphosphonates considering post-menopausal women on endocrine therapy are associated with higher risks of osteoporosis (23).

Overall, the recommended treatment strategies in the advanced setting are also consistent with our practice in Australia. Combination chemotherapy and dual anti-HER-2 blockade is standard first line treatment for advanced HER-2 positive breast cancer in Australia. Sequential single agent chemotherapy or in combination (in selected situations) are acceptable treatment options in advanced triple negative breast cancer. Immunotherapy is currently not approved for use in Australia for this patient cohort. More recently, sacituzumab govitecan has been listed on PBS for patients with advanced triple negative breast cancer progressing on prior therapy, providing another treatment option for this population (24).

Finally, the authors also described potential role of artificial intelligence (AI) in assisting diagnosis and

treatment decision-making in breast cancer. This is an intriguing field which may serve as an effective tool to assist radiologists and pathologists in improving accuracy in diagnosis. There are no long-term clinical trials assessing the role of AI to the best of our knowledge and we look forward to more data from the CSCO group.

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