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Summary of Session 2

Navigating human epidermal growth factor 2-positive (HER2+) early breast cancer (eBC) treatment

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(Neo-)adjuvant trastuzumab is the standard of care for HER2+ eBC

Adjuvant therapy targeting human epidermal growth factor receptor 2 (HER2) with trastuzumab improves 5-year disease-free survival (DFS) by 9% compared with chemotherapy (hazard ratio [HR], 0.63; p<0.001),[1] yet approximately 25% of women with eBC experience recurrence or death within 10 years.[2]

In the neoadjuvant setting, dual anti-HER2 therapy with pertuzumab and trastuzumab plus chemotherapy significantly improves pathological complete response rates in women with advanced or HER2+ eBC (45.8% vs 29.0%; p=0.0141) without significantly affecting tolerability.[3] Therefore, dual anti-HER2 therapy plus chemotherapy is a recommended neoadjuvant treatment option for women with HER2+ eBC and for facilitating a breast-sparing management approach.[4]

De-escalating and escalating treatment with trastuzumab in eBC

Treatment de-escalation may be feasible for women with low-risk eBC, or to avoid chemotherapy-related toxicity, while treatment escalation may be necessary for woman with higher-risk disease.[4-6] Dr Angus Leung reviewed current international guidelines regarding the treatment of HER2+ eBC, the utility of which were emphasized by Dr Roland Leung during the panel discussion following the presentation[4-6]:

- De-escalating adjuvant treatment to paclitaxel and trastuzumab (APT regimen) is associated with favourable long-term outcomes for patients with low-risk disease (eg, small, node-negative tumours; <2% risk of cancer recurrence at 3 years).[7]
- Dual (neo-)adjuvant anti-HER2 therapy plus chemotherapy should be administered to women with high-risk eBC, especially those with high numbers of positive nodes or hormone receptor-negative (HR-) disease.[3,8] The APHINITY regimen is preferred for neoadjuvant treatment,[8] but pertuzumab is not yet approved in the adjuvant setting in Hong Kong.
- Extended HER2 inhibition with neratinib may be considered in women with higher-risk disease who have previously completed adjuvant trastuzumab plus chemotherapy, especially for patients with HR+ disease.[9,10]

Updates from the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting regarding shorter durations of trastuzumab treatment

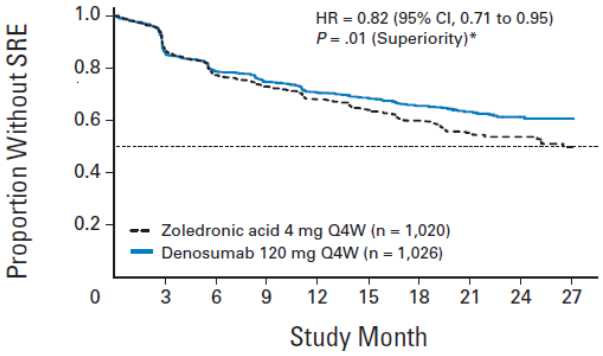
Dr Thomas Yau added to Dr Angus Leung's presentation by introducing the preliminary findings from the PERSEPHONE study indicating that a 6-month course of trastuzumab is non-inferior to a 12-month course in women with HER2+ eBC.[11] Nevertheless, Dr Angus Leung noted that de-escalating

chemotherapy may still be preferred in some patients and additional research is required to identify subgroups in which the 6-month trastuzumab regimen is most suitable.

Denosumab limits skeletal-related events (SREs) and extends DFS for patients with breast cancer

Metastatic bone disease accounts for 65–75% of breast cancer metastases and can cause localized, irreversible damage to bones.[12] In a randomized phase III study of women with advanced breast cancer and ≥1 bone metastasis, denosumab delayed the time to the first SRE by 18% compared with zoledronic acid (Figure 1).[13] Notably, <50% of patients receiving denosumab experienced an SRE over 27 months, and treatment was generally well tolerated, with the rates of adverse events being similar between treatment groups.[13] Denosumab also reduced the risk of SREs in a pooled analysis of three phase III studies, including patients with breast, prostate, and other solid tumours or multiple myelomas, extending the time to first SRE by 17% compared with zoledronic acid (27.7 months vs 19.5 months, respectively; HR, 0.83; 95% confidence interval [CI], 0.76–0.90; p<0.001).[14]

Figure 1. Time to first SRE in women with breast cancer and ≥1 bone metastasis[13]

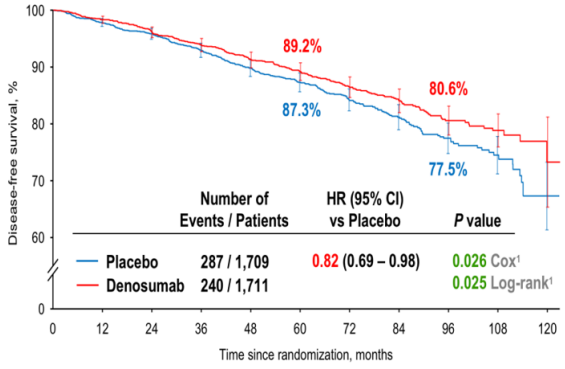


CI, confidence interval; HR, hazard ratio; Q4W, once every 4 weeks; SRE, skeletal-related event

Updates from the 2018 ASCO Annual Meeting regarding denosumab in postmenopausal women with hormone receptor-positive (HR+) eBC

Dr Thomas Yau provided updated data on the use of denosumab in patients with HR+ eBC from the ABCSG-18 study , which indicated that adding denosumab 60 mg once every 6 months to adjuvant aromatase inhibitor therapy improved DFS by 18% versus placebo after 8 years of follow-up in postmenopausal women with HR+ eBC (80.6% vs 77.5%; HR, 0.82; 95% CI, 0.69–0.98; Figure 2) and was generally well-tolerated over 10-years of treatment.[15] Furthermore, the Kaplan-Meier curves appear to be diverging with time.[15]

Figure 2. DFS in postmenopausal women with HR+ eBC receiving aromatase inhibitor therapy with or without denosumab Q6M[15]



CI, confidence interval; DFS, disease-free survival; eBC, early breast cancer; HR, hazard ratio; HR+; hormone receptor-positive; Q6M, once every 6 months

Case study from Dr Sharon Chan

A 45-year-old patient presented to Dr Chan who had previously been diagnosed with $cT_2N_2M_0$ breast cancer. Physical examination revealed a 4x3 cm tumour and a subsequent mammogram demonstrated 3.2 cm spiculated density with pleomorphic microcalcification. In addition, an ultrasound identified a R10H lobulated hypoechoic lesion (4.31x2.91x3.7 cm) with multiple enlarged lymph nodes. Biopsy showed invasive ductal carcinoma (HR+ and HER2+). Positron emission tomography (PET) scan revealed no distant metastases.

The patient was administered neoadjuvant doxorubicin–cyclophosphamide (4 cycles), docetaxel–carboplatin (4 cycles) and a surgical clip was inserted. A post-chemotherapy mammogram revealed that the spiculated density had disappeared and the lesion had shrunk to 2.27 cm on ultrasound. However, a significant amount of microcalcification was still present, so a hook wire-guided wide local excision with axillary dissection was performed and pathological examination returned a ypT_0N_0 result. No disease recurrence has been identified 4 years after surgery.

This case study highlights the limitations of imaging for guiding surgical treatment options in the neoadjuvant setting, given the modest accuracy of physical examination, ultrasound and mammograms in identifying the extent of disease.[4,16] In particular, there is a risk of both under- or overestimation of tumour size, which can affect treatment decisions (eg, overestimation resulting in an unnecessary mastectomy).[17] While magnetic resonance imaging (MRI) is believed to be a superior method of imaging, a meta-analysis showed that the sensitivity of MRI for predicting a pathological complete response (pCR) is only 63%.[18] Studies have also shown that the accuracy of imaging differs by tumour subtype. For example, MRI has a higher specificity and sensitivity in patients with HER2+ disease compared with other subtypes.[19] In conclusion, there is no standard imaging protocol in the neoadjuvant setting. Therefore, prior to making surgical decisions in the neoadjuvant setting, it is important to carefully evaluate patients with breast cancer using both a physical examination and imaging, while remaining aware of the limitations of each technique.

Case study from Dr Ng Ting Ying

A 71-year-old patient presented to Dr Ng with diabetes mellitus, hypertension and hyperlipidaemia who had previously been diagnosed with left-sided breast cancer. The patient had undergone a mastectomy with concomitant sentinel lymph node biopsy approximately 18 months previously.

Following the earlier mastectomy, a $pT_{1a}N_0M_0$ HR-/HER2+ multifocal invasive ductal carcinoma was diagnosed. Adjuvant therapy was not administered following surgery because of the patient's age and comorbidities, and 7 months after surgery the patient presented with left axillary swelling. A biopsy revealed disease recurrence with similar histology to the primary tumour with a Ki-67 score of 50%. A PET-computed tomography scan also revealed multiple bulky metastatic nodes in the left axilla (levels I–II with a maximum size of 3.7 cm).

As complete resection of the left axillary lymph nodes was not possible due to matting, neoadjuvant chemotherapy with paclitaxel–carboplatin–pertuzumab–trastuzumab was administered. The patient completed 6 cycles of treatment in total, which was well-tolerated. Left axillary dissection subsequently revealed that all 13 left axillary lymph nodes were negative for disease. Treatment with 18 cycles of trastuzumab and loco-regional radiotherapy continued following axillary dissection.

Summary

Treatment of eBC should be highly individualized with patient risk factors and diagnostic imaging determining whether to escalate or de-escalate treatment.[4] Trastuzumab has demonstrated consistent benefits as adjuvant and neoadjuvant treatment and should be regarded as the standard of care for women with HER2+ eBC.[4-6] Denosumab may also offer additional benefits by reducing the risk of SREs, and extending DFS, especially for women with metastatic disease or postmenopausal HR+ eBC.[13,15]

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