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Summary of Session 5

Management of HER2+ Early Breast Cancer

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Adjuvant systemic treatment - a risk-adapted approach

Adjuvant trastuzumab reduces the risk of death by at least 20-30% compared with chemotherapy alone,[1] and is given for 1 year based on the results of HERA study.[2] Although trastuzumab improves survival in the adjuvant setting, combined therapy with anthracycline-based regimens has been associated with cardiac toxicity. To circumvent cardiac toxicity associated with anthracycline, a non-anthracycline based regimen, docetaxel, carboplatin and trastuzumab (TCH), was compared with doxorubicin plus cyclophosphamide followed by docetaxel (AC-T) and AC-T plus trastuzumab (AC-TH) in BCIRG 006 study.[3] After 10.3 years of follow up, 10-year disease-free survival was 74.6% with AC-TH (P<0.0001), 73.0% with TCH (P=0.0011), and 67.9% with AC-T. In a subset analysis of node-positive patients, disease-free survival rates (DFS) were lower compared with the overall population, with 69.6% for AC-TH (P < .001), 68.4% for TCH (P=0.0018), and 62.2% for AC-T. Therefore, nodal status is an important risk factor for disease recurrence.[4]

For escalation and de-escalation of trastuzumab treatment, a risk-adapted approach based on nodal status can be used. If a patient is with T1a/T1b/T1c and node-negative breast cancer, de-escalation of treatment can be adopted; if a patient has node-positive, locally advanced or inflammatory breast cancer, escalation can be exercised.

a. De-escalation

APT (Tolaney) was a single-arm trial which recruited 406 breast cancer patients with HER2+, ER+ or ER- and node- tumour of size ≤3cm. They received paclitaxel (80mg/m^2) and trastuzumab (2mg/kg) once per week for 12 weeks, followed by trastuzumab (6mg/kg) every 3 weeks for 13 cycles. Adjuvant weekly paclitaxel and trastuzumab demonstrated favourable long-term outcomes, with 7-year DFS of 93%.[5] In addition, there were several trials investigating the efficacy of short-term use of trastuzumab. The two largest trials, PHARE and PERSEPHONE, compared the efficacy of trastuzumab 6-month regimen with 1-year regimen.[6,7] The hazard ratio of PHARE and PERSPHONE were 1.08 (95% CI 0.93-1.25, P=0.39) and 1.07 (90% CI 0.93-1.24, P=0.011) respectively. Given the contradictory results, it is still controversial to use short duration trastuzumab.

b. Escalation

APHINITY trial studied whether the addition of pertuzumab to trastuzumab and chemotherapy could improve outcomes among patients with HER2+ early breast cancer after surgery.[8] At 3.8-year median

follow-up, in terms of invasive disease-free survival (IDFS), even though pertuzumab combination reduced the risk of recurrence by 19% compared with trasuzumab plus chemotherapy (HR 0.81, 95% CI 0.66 – 1.00, P = 0.0446), the magnitude of benefit was small, with +1.7% only. However, the absolute benefit of pertuzumab could be improved in selected patients, for instance, +3.2% for node-positive and +2.3% for HR- breast cancer.

In order to investigate whether any biomarkers can predict the benefit of dual-HER2 blockade, a comprehensive genomic and immune-marker based analysis of APHINITY trial was conducted, including DNA analysis, RNA-Seq analysis, tumour-infiltrating lymphocytes analysis and HER2 IHC/FISH.[9] The biomarker analyses showed that PI3K pathway alterations, MYC amplification, ZNF703 amplification and lack of TOP2A amplification were associated with poor prognosis, but none of the above markers were able to predict the benefit of pertuzumab. High tumour-infiltrating lymphocyte counts appeared to be associated with favourable outcomes and greater pertuzumab benefit,[9] which supports an immune-mediated mechanism of action for pertuzumab.[10] In addition, HER2 gene copy ≥6 was associated with better prognosis and greater pertuzumab benefit.[9] The above two markers can potentially serve as biomarkers to predict the outcome of pertuzumab-based therapy.

c. Post-adjuvant neratinib after trastuzumab-based adjuvant therapy

The ExteNET study evaluated the safety and efficacy of 1-year post-adjuvant neratinib after adjuvant trastuzumab plus chemotherapy in early HER2+ breast cancer.[11] 5-year IDFS was improved in the neratinib arm compared with placebo (90.2% vs 87.7%, HR 0.73, P = 0.0083), but the magnitude of improvement was small (+2.5%). The benefit of neratinib was greater in patients with HR+ tumors (+4.4%; HR 0.60, 95% CI 0.43-0.83), and in HR+ patients who started treatment within 1 year of completing trastuzumab without a pathological complete response (pCR) after neoadjuvant thearpy (+7.4%, HR 0.60, 95% CI 0.33-1.07).

Neoadjuvant therapy – current practice and potential in de-escalation

The goals of neoadjuvant therapy are to eradicate micro-metastases early, downstage tumour for breast conserving therapy, observe in-vivo tumour response, improve prognostication by pCR status, and to guide subsequent treatment decisions.

a. 1st generation neoadjuvant trial - chemotherapy with/without trastuzumab

NOAH trial showed that the addition of trastuzumab to chemotherapy as neoadjuvant therapy significantly improved event-free survival (HR 0.59, P = 0.013) and pCR rates in breast and axillary nodes (38% vs 19%) compared with chemotherapy alone.[12]

b. 2nd generation neoadjuvant trials - combination of trastuzumab with other HER2 targeted agents

Three trials, namely neoALTTO, CHER-LOB and USON, showed that dual targeting with neoadjuvant trastuzumab plus lapatinib improved pCR rates compared with either agent alone.[13-15] In NeoSphere trial, the combination of docetaxel, trastuzumab and pertuzumab demonstrated the highest total pCR rate vs docetaxel plus trastuzumab, trastuzumab plus pertuzumab, and docetaxel plus

pertuzumab in chemotherapy-naive patients with primary tumours >2 cm (45.8% vs 29.0% vs 16.8% vs 24.0%).[16] Notably, achieving total pCR (tpCR) was associated with longer progression-free survival (HR 0.54, 95% CI 0.19-1.00).[17] In TRYPHAENA trial, the combination of pertuzumab-trastuzumab with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens achieved respectable pCR rates (55-66%) in HER2+ early breast cancer.[18] Improved DFS was also seen in patients who achieved tpCR (HR 0.27 95% CI 0.11-0.64).[19]

c. 3rd generation neoadjuvant trials - TDM1 plus dual targeting

KRISTINE was a phase 3, open-label trial which randomly assigned patients with early HER2+ breast cancer (1:1) to receive either TDM1 plus pertuzumab (TDM1+P), or docetaxel, carboplatin, trastuzumab and pertuzumab (TCH+P) as neoadjuvant therapy.[20] After 6 cycles of neoadjuvant therapy and surgery, patients in the TDM1+P arm would continue to receive the regimen, with adjuvant chemotherapy permitted for those with residual disease in lymph node(s) or in the breast (>1cm), whereas patients in TCH+P arm would receive trastuzumab plus pertuzumab for additional 12 cycles. Traditional neoadjuvant chemotherapy plus dual HER2-targeted blockade achieved higher pCR rates than TDM1+P (56% vs 44%, P = 0.0155), though it was found that TDM1+P arm achieved a more favourable safety profile during neoadjuvant treatment. At a median follow-up of 36 months, TCH+P achieved higher 3-year event-free survival (EFS) rate (94.2% vs 85.3%; HR 2.61, 95% CI 1.36-4.98).[21] It was observed that the two EFS curves separated early at the time of surgery and remained parallel to each other after surgery. The EFS events in TDM1+P arm were mainly contributed by locoregional progression before surgery, resulting in a poorer EFS. Further investigation within TDM1+P arm found that the group of patients who had locoregional progression during neoadjuvant therapy had lower HER2 mRNA expression, higher proportion of patients with HER2 IHC2+, and higher proportion of patients who had heterogenous expression of HER2. Focusing at the time point after surgery, the IDFS curves of the two treatment arms overlapped with each other (HR 1.11, 95% CI 0.52-2.40). It was observed that patients achieving pCR had better IDFS, again demonstrating that pCR is an important prognostic factor. The advantage of using TDM1+P over chemotherapy-based treatment was the lower incidence of grade ≥3 adverse events.[21]

PREDIX HER2, a phase 2 open-label trial, randomized patients to 6 cycles of TDM1 or docetaxel, trasztuzumab and pertuzumab (DTP) as neoadjuvant therapies.[22] All received postoperative epirubicin plus cyclophosphamide, with the TDM1 arm receiving 4 courses and the DTP arm receiving 2 courses, and both arms also received adjuvant trastuzumab for 11 courses. There was no significant difference in pCR rates between the two arms (45% vs 47%, P = 0.359), but higher pCR rates were observed in patients with HR- tumours in both arms. The pCR rates were independent of tumour size for both regimens. All adverse events, with the exception of liver toxicity, occurred more frequently in the DTP arm.

d. Key messages

In general, dual HER2 blockade can enhance pCR rate. Non-pCR is associated with worse prognosis. Neoadjuvant TDM1 with pertuzumab (KRISTINE) or TDM1 (PREDIX HER2) was better tolerated than cytotoxic-based neoadjuvant therapy. TDM1 with or without pertuzumab may be considered for

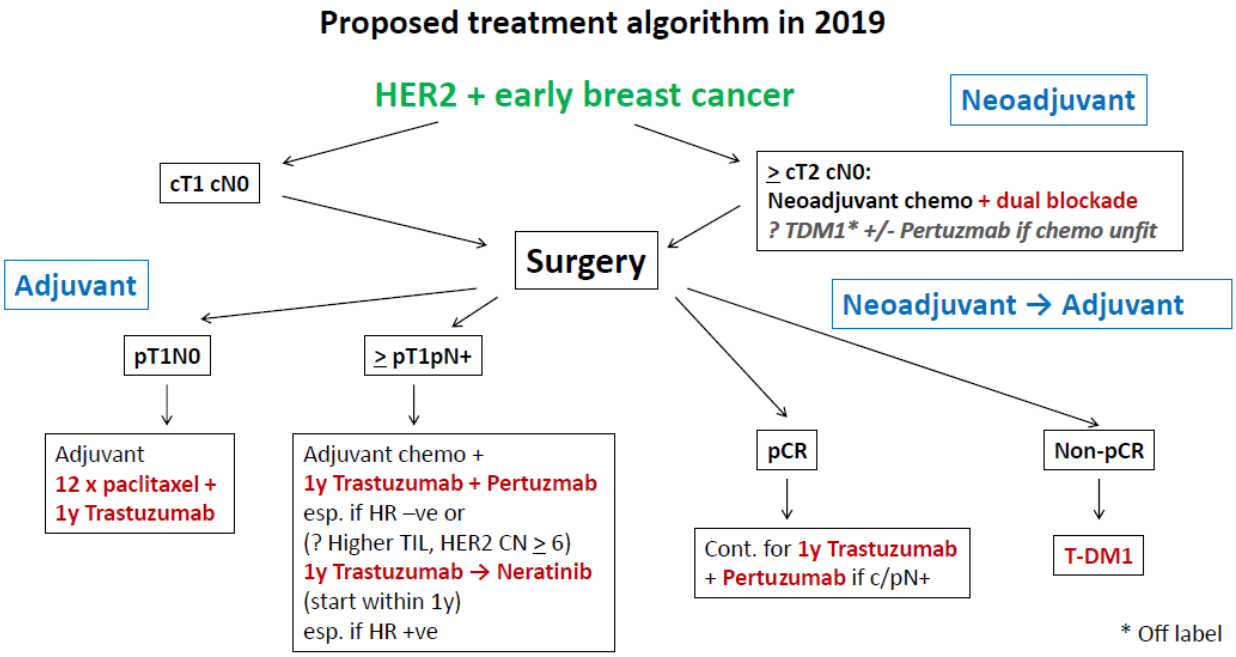
patients who are not suitable for chemotherapy or refuse chemotherapy, especially for those showing strong and homogenous HER2 expression.

Bridging neoadjuvant and adjuvant therapies

KATHERINE, a phase 3, open-label trial, compared the use of TDM1 with trastuzumab as adjuvant therapy in patients with HER2+ early-stage breast cancer with residual invasive disease in breast or axillary lymph nodes after receiving neoadjuvant therapy consisting of chemotherapy plus trastuzumab (dual HER2-targeted agents allowed).[23] Patients were randomly assigned to receive adjuvant TDM1 or trastuzumab for 14 cycles, and allowed to receive radiation and endocrine therapy. Adjuvant TDM1 demonstrated both statistically significant and clinically meaningful improvement in IDFS compared with trastuzumab (unstratified HR = 0.50, 95% CI 0.39 – 0.64, P <0.0001). The 3-year IDFS rate improved from 77.0% with trastuzumab to 88.3% with TDM1. Benefit of TDM1 was consistent across all key subgroups including HR status, extent of residual invasive disease, and single or dual HER2-targeted neoadjuvant therapy, except that TDM1 was not as favourable in patients with central HER2 IHC2+. The safety data were consistent with the previous studies of TDM1, and the adverse events of TDM1 were generally tolerable and manageable. Further follow-up on OS data is necessary. On May 3rd 2019, FDA approved TDM1 for the adjuvant treatment for patients with non-pCR after neoadjuvant taxane and trastuzumab-based treatment.

Conclusion

Based on the results of the trials discussed, Dr Sze has proposed a treatment algorithm for HER2+ early breast cancers as below:



Presented by Dr Henry Sze in 2019 HKBCF ASM

Case Study from *Dr. Chang Tien Yee, Amy*
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A 39-year-old female with past history of hypertension and compression fracture at T7 presented with dizziness for a few days. Physical examination showed a 5x4cm mass in her right breast with no skin changes. CT scan in September 2018 showed hydrocephalus with cerebral edema, brainstem compressed with early coning features, a 5.5 x 1.4 x 5cm occipital mass, features worrisome for C4-6 bone metastases with collapsed C4, multiple enlarged neck lymph nodes at bilateral level 2 and right level 5, and no cord compression. MRI in October 2018 showed diffuse marrow infiltration alone C spine compatible with metastases, collapsed C4 and epidural soft tissue causing mild impingement of cord at C4-5, and paravertebral soft tissue obliterating left C3/4 and bilateral C4/5 neural foramina.

Brain tumor excision and posterior spinal fusion were performed in October 2018. The patient was diagnosed with ER+, PR+ and HER2+ metastatic carcinoma. PET-CT post-op showed diffuse bone metastases at skull, bilateral scapulae, bilateral clavicles, right sided rib cage, most levels of spine and bilateral ilium. Pathological collapse at C4-6, T8 and L3 was observed. Multiple nodular lesions at right breast were consistent with multifocal tumour, largest over R9-10H with 4.5cm diameter and the tumour was not fixed to chest wall. Metastatic right axillary lymph node, mediastinal lymph node, right supraclavicular lymph node and bilateral neck lymph node were involved. Breast biopsy was not taken at that time.

The patient was advised for stereotactic radiosurgery (SRS) and fractionated RT (SRT) to post-op brain tumour bed. She received palliative radiotherapy to C4-6 and T6-8. SRT 9Gy per fraction to cerebellar region for 3 times and 4Gy per fraction to C4-6 and T6-8 for 5 times were completed at the end of October 2018. Subsequent treatment with dual anti-HER2 therapy combined with chemotherapy was initiated. She received pertuzumab, trastuzumab and docetaxel every 3 weeks for 6 cycles from November 2018 to April 2019, and then continued dual HER2-targeted therapy.

The latest PET-CT in April 2019 showed reduction in size and metabolic activity in right breast R10H lesion. Other smaller lesions in right breast and all other metastatic lesions were resolved. Bone marrow diffuse uptake was likely due to reactive marrow changes related to recent chemotherapy. MRI of the brain was performed in May 2019 and no recurrence was noted.

The next step of treatment was worth discussing. Whether mastectomy, post-op adjuvant treatment or radiotherapy shall be performed depends on clinical needs and patient's conditions.

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