June 29th 2019
HONG KONG BREAST CANCER FOUNDATION ANNUAL SCIENTIFIC MEETING 2019

Summary of Session 6

Triple Negative Breast Cancer

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Triple-negative breast cancer is a very aggressive disease, with a median overall survival of only 9-12 months.[1] Treatments currently available include traditional systemic chemotherapy (e.g. anthracycline, cyclophosphamide, taxane, platinum, eribulin), targeted therapy (e.g. olaparib, talazoparib) and immunotherapy (e.g. nivolumab, pembrolizumab, atezolizumab). Yet, as shown in KEYNOTE-086, overall response rates (ORR) with pembrolizumab were low, only about 5% in previously treated patients irrespective of PD-L1 expression, but higher in first-line patients (23.1% in previously untreated PD-L1+ disease).[2,3] Thus, PD-L1 can be a biomarker in triple-negative breast cancer, though not a perfect one. Similar to KEYNOTE-086, a phase-1 study also showed the ORR for atezolizumab in metastatic triple-negative breast cancer was 26% in first-line setting, but poor in second- and third-line settings (5%-10%).[4]

Immunotherapy combination

To improve treatment outcomes for triple-negative breast cancer patients, combining chemotherapy with immunotherapy, or using targeted therapy are potential options.

Immunotherapy + chemotherapy

IMpassion130 was a phase 3, double-blind, placebo-controlled trial which randomly assigned (1:1) patients with metastatic or inoperable, locally advanced triple-negative breast cancer without prior therapy for advanced triple-negative breast cancer to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel.[5] In the intention-to-treat (ITT) population, the two progression-free survival (PFS) curves almost overlapped with each other (HR 0.80, 95% CI 0.69-0.92, P = 0.002). In the subgroup with PD-L1+ tumours, significantly greater improvement in PFS was seen in the atezolizumab arm (median PFS, 7.5 months vs 5.0 months; HR 0.62, 95% CI 0.49-0.78, P <0.001).[5] As a result, atezolizumab plus nab-paclitaxel received accelerated approval by the FDA in March 2019 as a first-line treatment in patients with PD-L1 IC+ metastatic triple-negative breast cancer. Updated overall survival (OS) results showed that there was no statistically significant improvement in the lTT population (21.0 months vs 18.7 months, P = 0.0777), but median OS improvement from 18.0 to 25.0 months was observed in the PD-L1+ population (HR 0.71, 95% CI 0.54-0.93).[6] Atezolizumab in combination with nab-paclitaxel were well-tolerated, with no cumulative toxicities and no new- or

late-onset safety signals.[5] The combination sets a new benchmark as the first therapy to cross the 2-year landmark OS benefit in first-line therapy for PD-L1+ metastatic triple-negative breast cancer.

Other ongoing research to enhance efficacy of immunotherapy

The MEK pathway is active in triple-negative breast cancer. Activation of the MEK pathway suppresses inflammatory response to T cells, leading to reduced antigen presentation and PD-L1 expression. Combining a MEK inhibitor with an anti-PD-L1 inhibitor may improve antigen presentation while blocking PD-L1-mediated suppression.[7] In the multi-stage, multi-cohort Phase II COLET study, patients with metastatic triple-negative breast cancer were randomized (1:1) to receive first-line treatment with paclitaxel or nab-paclitaxel, while all patients received atezolizumab and cobimetinib.[8] ORRs were similar between the paclitaxel arm (34%) and the nab-paclitaxel arm (29%). Numerically longer median PFS were observed in patients with PD-L1+ disease (paclitaxel arm: PD-L1-: 3.7 months, PD-L1+: 9.0 months; nab-paclitaxel: PD-L1-: 5.6 months, PD-L1+: 7.0 months).

Breast cancer is low in the spectrum of somatic mutation preference in general and breast cancer with high tumour mutation burden being immunogenic is questionable. The TAPUR study is a phase 2 basket study that evaluated the anti-tumor activity of commercially available targeted agents in patients advanced cancers with specific genomic alterations.[9] Result of a small cohort of 28 patients with metastatic breast cancer with high tumour mutation burden (defined as ≥9 mutations/megabase) treated with single-agent pembrolizumab were reported. HR status was not known and no control group was involved in the trial. ORR was 21% and most of the responders were HER2-negative patients. Median progression-free survival was 10.6 weeks and some patients could even derive progression-free survival longer than 1 year.

Clinically targetable pathways

Over 90% of triple-negative breast cancer patients have an aberration in at least one of these pathways.[10] In addition to immune checkpoint blockade, there are many potential targetable pathways in triple-negative breast cancer as well, for example, PI3K/mTOR, BRCA in DNA Repair pathway, and Ras/MAPK.

Conclusion

New therapies for triple-negative breast cancer include atezolizumab for PD-L1 IC+ patients and PARP inhibitors for patients with germline BRCA mutation. Nowadays, PD-L1 status is tested in all triple-negative breast cancer cases. Testing of germline BRCA should also be incorporated into clinical practice especially in young patients or patients with relevant family history. With the emergence of new treatment strategies, there may be a need to restructure the classification system of triple-negative breast cancer based on clinical and intrinsic factors as well as immune and mutation profiles.

Case Study from *Dr. Chan Wong Lok, Wendy*
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The case involved a 48-year-old premenopausal woman with triple-negative breast cancer. Modified radical mastectomy was performed on her right breast in August 2017. Her pathology reports showed T2N1, invasive ductal carcinoma, grade 3, 3.3-cm mass, 2 of 12 lymph nodes being involved, ER = 0, PR = 0, HER2 = 0 and Ki-67 = 30%. The patient received adjuvant chemotherapy, including dose-dense anthracycline for 4 cycles and dose-dense paclitaxel for 4 cycles, and completed adjuvant treatment in January 2018. Adjuvant locoregional radiotherapy was completed in mid-March 2018.

After 9 months, the patient complained of pelvic pain. MRI of the pelvis was performed in December 2018 and showed multifocal metastasis, with the largest lesion at the right iliac crest with cortical destruction and suspicious muscular infiltration. PET-CT was also performed in January 2019 and showed multiple bone metastasis at bilateral ilium, pubis, L1 and L5.

The patient started on atezolizumab 1200mg IV D1 Q4W plus nab-paclitaxel 100mg/m^2 IV D1, 8, 15 Q4W since mid-January 2019. After 3 cycles, reassessment PET-CT was performed in April 2019. Most of the bone lesions were improved and no new lesion was found. After 6 cycles of atezolizumab and nab-paclitaxel treatment, the patient did not experience major side effects. She recently had mild bradycardia and needed cardiac work-up which might be associated with nab-paclitaxel. All blood tests including thyroid function test and cortisol were normal.

Although 840mg atezolizumab is not available in Hong Kong, physicians still have the dosing choices such as 1200mg Q4W and 1200mg Q3W. Efficacy may not be related to the dose of atezolizumab based on this case.

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