TRIPLE NEGATIVE BREAST CANCER: METASTATIC TREATMENT

ESMO PRECEPTORSHIP ON BREAST CANCER

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Prof Georgia Demetriou
Division of Medical Oncology
Wits Donald Gordon Medical Center
& Charlotte Maxeke Johannesburg Academic Hospital
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Speaker fees
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  Merck Serano
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Data in Panel A are from Cheang et al.
Data in Panel B are from Dent et al.

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In the setting of metastatic breast cancer the subtype of TNBC, is relatively higher and accounting for a larger number of breast cancer deaths due to its highly aggressive nature.

For those patients presenting with metastatic disease, anthracycline based chemotherapy with or without a taxane would be an appropriate first line approach.

There is no protocol for the first line metastatic treatment in previously treated TNBC patients who have subsequently presented with metastatic disease.

The use of multidrug regimens in the treatment of patients with metastatic breast cancer is controversial.

Sequential monotherapy for advanced breast cancer is appropriate were there is no evidence of a visceral crisis, certainly patient- and disease-related factors should to be used to best identify patients who may benefit from combination treatment.

ESMO has recommended the use of combination treatment in patients with extensive visceral disease.

Therefore, given the often-aggressive nature of TNBC in the setting of extensive visceral disease the use of a combination of drugs rather than a single agent can be advocated.
ANTHRACYCLINE RECHALLENGE

- A single prospective Phase III trial looked at re-challenging with an anthracycline.
- In the study patients with advanced breast cancer previously treated with neoadjuvant or adjuvant anthracycline, were randomly assigned to receive either docetaxel or pegylated liposomal doxorubicin (PLD) followed by docetaxel.
- Treatment with PLD–docetaxel significantly improved time to progression (median 10 versus 7 months) and overall response rate (ORR  35% versus 26%).
- The clinical significance of this re-challenge approach needs to be treated with reserve as the cumulative doses of non-pegylated anthracyclines need to be closely monitored due to the potential for cardio-toxicity remembering that PLD has a different pharmacology.
PLATINUM BASED TREATMENT

- Platinum-based treatments have in recent years received more attention for the treatment of TNBC, especially where there is a link to germ-line mutations in BRCA1 gene.
- Approximately 10% of TNBC tumors have BRCA1 mutations (and 90% of BRCA1-mutated tumors are TNBC).
- In a retrospective study, a regimen of cisplatin and gemcitabine in combination improved the outcome for patients with TNBC patients regardless of whether a BRCA1 mutation was present or not, despite these patients still having an overall poor prognosis.
- Vinorelbine with cisplatin has shown benefit similar to gemcitabine and cisplatin and is a viable option. Single agent vinorelbine is also an option
The Triple-Negative Breast Cancer Trial (TNT) has provided important insights into the role of platinum- and taxane-based chemotherapy. The trial enrolled 376 patients with either a known deleterious BRCA1/2 germline mutation (and any metastatic breast cancer phenotype) or metastatic TNBC.

Although no significant difference was seen in the overall TNT population, a significantly better objective response rate of 68% to carboplatin versus 33% to docetaxel was found amongst the 43 patients with a germline BRCA1/2 mutation.

- PFS benefit favouring carboplatin (median PFS of 6.8 versus 4.4 months) was found without a corresponding OS benefit.
- Benefit was not reflected in the overall TNT population, where there was no significant PFS or OS advantage to either agent.
PARP INHIBITORS

- The OlympiAD clinical trial randomly assigned patients with advanced HER2-negative breast cancer and a germline BRCA mutation to a PARP inhibitor, olaparib (300 mg twice daily), or standard physician’s choice chemotherapy. The significant progression-free survival (PFS) favoured olaparib.
  - with a median PFS of 7.2 months versus 4.2 months.
  - Subgroup analysis of PFS for randomised stratification factors revealed an outstanding HR for progression of 0.39 (95% CI 0.27–0.57) amongst the TNBC subset, which made up nearly 50% of the treatment cohorts in both arms.
PARP INHIBITORS

• The EMBRACA clinical trial compared the PARP inhibitor talazoparib (1 mg daily) with protocol-specified standard therapy (capecitabine, eribulin, gemcitabine or vinorelbine) and found a favourable median PFS
  ‒ PFS of 8.6 versus 5.6 months in the standard therapy group (HR for progression or death 0.54, 95% CI 0.41–0.71) with a trend towards an OS benefit, but the data are immature.
  ‒ Although rates of adverse events were similar in the two treatment arms, patients randomly assigned to talazoparib reported superior quality-of-life outcomes with a significant delay in the onset of a clinically meaningful deterioration in global health status.

• The addition of iniparib to gemcitabine and carboplatin has shown promising results for all patients with metastatic TNBC regardless of their BRCA mutation status. A randomised phase 2 clinical trial showed that the addition of iniparib prolonged the median PFS
  ‒ PFS from 3.6 to 5.9 months (HR for progression, 0.59; \(P=0.01\)) and the median OS from 7.7 to 12.3 months (HR for death, 0.57; \(P = 0.01\)).
  ‒ The phase 3 clinical trial did not meet the pre-specified co-primary end points, PFS and OS, but did report an efficacy signal for patients randomly assigned to second- or third-line PARP inhibitor therapy.
ERIBULIN TREATMENT

- Eribulin has been investigated and approved for advanced or metastatic breast cancer in patients who have progressed after prior anthracycline and taxane regimens where suitable.
- Phase III EMBRACE study assessing treatment of the physician’s choice versus eribulin, showed a significant increase in overall survival for the eribulin arm
  - Median overall survival 13 versus 11 months.
  - Of the patients enrolled 19% had TNBC, and eribulin was most effective in hormone receptor-negative patients who had a 34% decreased risk of death compared with the control arm.
**IXABEPILONE TREATMENT**

- Ixabepilone is an epothilone anti-microtubule agent, in an open-label Phase III trial ixabepilone plus capecitabine was compared with capecitabine alone in patients with anthracycline-pretreated or -resistant, and taxane-resistant locally advanced or metastatic breast cancer.

- Patients treated with ixabepilone plus capecitabine had a 25% reduction in estimated risk of progression (HR = 0.75, 95% CI 0.64–0.88) compared those who received capecitabine alone.
  - The overall response rate was also greater for the ixabepilone-treated group (35% versus 14%).
  - A subset analysis of TNBC patients has reported statistically superior progression free survival for the combination arm (4.2 versus 1.7 months), however no increase in overall survival was shown.
  - Ixabepilone treated patients did have more grade 3 or 4 adverse events especially neuropathy (21% versus 0%) and neutropenia (68% versus 11%), which may limit the drugs clinical use when the side effect profile is weighed up with against its benefit and the patients quality of life in the setting of metastatic disease.
The anti-Vascular Endothelial Growth Factor (VEGF) monoclonal antibody bevacizumab has shown benefit in some TNBC subgroups if combined with taxanes and other agents.

In a meta-analysis of three Phase III trials of bevacizumab as first-line treatment in a pooled subset of 621 patients with TNBC, the median progression free survival was longer in patients treated with bevacizumab plus chemotherapy than in those treated with chemotherapy alone (8.1 versus 5.4 months), but no difference in overall survival was seen.

Similar results were seen in a subgroup analysis of the RIBBON-2 trial, which investigated various chemotherapies with and without bevacizumab as second-line treatment of metastatic breast cancer. In patients with TNBC (n = 159), progression free survival with bevacizumab was improved (median 6.0 versus 2.7 months P = 0.0006) and again while a trend towards improved overall survival was seen (HR = 0.624), it failed to reach statistical significance (P = 0.0534).

This agent is no longer approved for use in metastatic breast cancer by the FDA however it is still approved by EMA for the treatment of metastatic breast cancer. Due to the lack of overall survival benefit it is not recommended for standard use.
Epidermal Growth Factor Receptor (EGFR) is overexpressed in 60% of basal like cancers.

The EGFR monoclonal antibody cetuximab was investigated in a trial, BALI-1 which looked at cetuximab in combination with cisplatin (N = 173) for the treatment of metastatic TNBC versus cisplatin alone.

An overall response rate of 20% versus 10% was seen with a progression free survival of 3.7 versus 1.5 months.

The use of cetuximab is as yet not registered for use in metastatic TNBC and cannot be recommended.
IMMUNOTHERAPY

- TNBC has the highest tumour mutational burden among all breast cancer subtypes.
- More mutations can lead to the synthesis of more abnormal proteins, which may function as ‘neoantigens’ to be recognised by the antigen-presenting cells that can ultimately start an antitumour immune response.
- Supporting this hypothesis, tumour-infiltrating lymphocytes (TILs) are frequently present in TNBC samples, and increased levels of TILs are associated with a good prognosis.
- TNBC is considered an interesting subset for the development of immunotherapy.
Atezolizumab is a PD-L1–blocking monoclonal antibody that binds to PD-L1 and inhibits its interactions with PD-1 (programmed cell death protein 1) and B7.1 receptors. This action releases the PD-L1/PD-1–mediated inhibition of immune response, including activation of an antitumor immune response without inducing antibody-dependent cellular cytotoxicity. PD-L1 may be expressed on tumor cells or tumor-infiltrating immune cells and can contribute to inhibition of an antitumor immune response in the tumor microenvironment. Binding of PD-L1 to PD-1 and B7.1 receptors on T cells and antigen-presenting cells results in suppression of cytotoxic T-cell activity, T-cell proliferation, and cytokine production.
IMMUNOTHERAPY

• In the Impassion 130 phase III study, 902 patients with metastatic TNBC with no previous treatment for metastatic disease were randomised 1:1 to receive nab-paclitaxel (100 mg/m² on days 1, 8 and 15 every 28 days) combined with atezolizumab (840 mg intravenously on days 1 and 15 every 28 days) or placebo until disease progression or limiting toxicities.

• In the overall population, the addition of atezolizumab to nab-paclitaxel increased the median PFS (7.2 months with atezolizumab-nab-paclitaxel vs 5.5 months with placebo-nab-paclitaxel; HR 0.80; 95% CI 0.69 to 0.92; p=0.002), although it did not significantly improve overall survival: 21.3 months with atezolizumab-nab-paclitaxel arm vs 17.6 months with the placebo-nab-paclitaxel (HR 0.84; 95% CI 0.69 to 1.02; p=0.08).

• In the subgroup of PD-L1-positive patients (defined as PD-L1 expression on tumour-infiltrating immune cells ≥1% of the tumour area), the median PFS (7.5 months vs 5.0 months; HR 0.62; 95% CI 0.49 to 0.78; p<0.001) and OS (25 months vs 15.5 months; HR 0.62; 95% CI 0.45 to 0.86) were improved with atezolizumab-nab-paclitaxel in comparison to placebo-nab-paclitaxel.
The frequency of grade ≥3 adverse events was 48.7% in the atezolizumab-nab-paclitaxel group and 42.2% in the placebo-nab-paclitaxel group, with the most common events in both groups being neutropaenia, peripheral neuropathy, fatigue and anaemia. Grade ≥3 potentially immune-related toxicities occurred in 7.5% of the patients in the atezolizumab-nab-paclitaxel group and in 4.3% of the patients in the placebo-nab-paclitaxel group.

The combination of nab-paclitaxel and atezolizumab was granted accelerated approval in combination with nab-paclitaxel in the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express programmed cell death ligand 1 (PD-L1–stained tumor-infiltrating immune cells of any intensity covering ≥ 1% of the tumor area), by the U.S. Food and Drug Administration (FDA) it is a promising strategy to be considered for PD-L1-positive patients with metastatic TNBC.
**Treatment of advanced TNBC**

**Diagnosis of advanced TNBC**
- Genetic counselling and *BRCA* mutation status testing should be discussed with patient

**Combination ChT (patients with rapid progression, visceral crisis, need for rapid symptom/disease control)**
- Preferred regimens: Carboplatin + gemcitabine OR Cisplatin + 5-FU or capecitabine

**Sequential single-agent ChT**
- Previously untreated with anthracycline or taxanes
  - Anthracycline or taxanes
- Previously treated with anthracycline and/or taxanes

**BRCA mutation**
- PARPi
- Carboplatin
- Capecitabine

**BRCA wild-type**
- Eribulin
- Vinorelbine

*Note: Include in clinical trials when available*
In the setting of metastatic breast cancer the subtype of TNBC, is relatively higher and accounting for a larger number of breast cancer deaths due to its highly aggressive nature.

For those patients presenting with metastatic disease, anthracycline based chemotherapy with or without a taxane would be an appropriate first line approach.

There is no protocol for the first line metastatic treatment in previously treated TNBC patients who have subsequently presented with metastatic disease, sequential monotherapy where there is no visceral crisis is appropriate.

Combination therapy in patients with visceral crisis is recommended.

Platinum based treatments in TNBC with or without BRAC mutation is useful

PARP inhibitors offer a novel mechanism of action in BRAC mutated patients

Immunotherapy is an option in TNBC with PD-L1 expression of >1%

Anti-VGEF and Anti-EGFR therapy is not standard of care
THANK YOU