review

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ASCO 2019: highlights in HER2-positive metastatic breast cancer

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Summary At the 2019 ASCO (American Society of Clinical Oncology) Annual Meeting, several interesting trial results were presented in the field of HER2-positive metastatic breast cancer. The end-of-study analysis of the pivotal CLEOPATRA trial indicated an overall survival of 57.1 months in patients receiving pertuzumab in addition to trastuzumab and docetaxel in the first-line setting. SOPHIA was the first phase III trial comparing the Fc-engineered antibody margetuximab plus chemotherapy by physician's choice with trastuzumab plus chemotherapy in heavily pretreated patients; the novel antibody yielded a statistically significant albeit short prolongation of progression-free survival (PFS) over standard treatment. The phase III NALA trial compared the second-generation tyrosine-kinase inhibitors neratinib with lapatinib; both drugs were combined with capecitabine. In this study a clinically meaningful prolongation of PFS by 2.2 months was observed. In addition, the time to intervention for brain metastases was prolonged in the neratinib group and the cumulative incidence of brain metastases was lower as well. On the downside a high rate of grade 2 and 3 diarrhoea was observed.

Keywords ASCO Annual Meeting 2019 · HER2-positive disease · Highlights · Metastatic breast cancer · Review · Update

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Take-home message

The end-of-study analysis of the CLEOPATRA trial highlighted the excellent OS achievable in HER2-positive MBC today with the addition of pertuzumab to the former first-line treatment standard of trastuzumab and docetaxel. While the phase III trial SOPHIA suggested margetuximab may be superior to trastuzumab in pretreated patients, the PFS benefit was small in absolute numbers and OS data need to be awaited. The NALA trial revealed a clear benefit for neratinib over lapatinib in terms of PFS; in addition, time-to-intervention for BM was longer in the neratinib arm as well suggesting a clinically relevant effect.

Introduction

Results of several interesting studies were presented at this year's ASCO (American Society of Clinica Oncology) Annual Meeting in the field of HER2-positive metastatic breast cancer (MBC), among them the end-of-study analysis of the pivotal CLEOPATRA trial, first phase III results with the novel monoclonal HER2-directed antibody margetuximab and the phase III NALA trial comparing the second-generation tyrosine kinase inhibitor (TKI) neratinib plus capecitabine with lapatinib plus capecitabine. This article is intended as a short overview of these and further data.

CLEOPATRA end-of-study analysis

The CLEOPATRA trial lead to the approval of pertuzumab in combination with docetaxel and trastuzumab as first-line therapy in patients with metastatic and locally advanced, inoperable HER2-positive breast cancer. In this phase III trial ($n = 808$), the addition of pertuzumab to standard therapy yielded a statistically

significant and clinically relevant prolongation of progression-free survival (PFS) from 12.4 to 18.5 months (hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.51–0.75; $p<0.001$) [1]; overall survival (OS) was also significantly prolonged. At the 2019 ASCO Annual Meeting, the end-of-study analysis was presented. Final OS results were 40.8 months in the placebo group and 57.1 months in patients receiving pertuzumab (HR 0.69; 95% CI 0.58–0.82) for an absolute difference of 16.3 months [2]. At the 8-year landmark OS analysis, 37% of all patients in the pertuzumab group were still alive as opposed to 23% of patients in the control arm. These data therefore highlighted the success of HER2-targeted therapy in changing the natural history of this disease subtype and first-line therapy consisting of a taxane, trastuzumab and pertuzumab remains the standard-of-care in the first-line treatment of HER2-positive MBC.

SOPHIA

As outlined above, chemotherapy plus trastuzumab and pertuzumab is the first-line standard in HER2-positive MBC; the antibody–drug conjugate (ADC) T-DM1 is used in the second-line setting and as first-line treatment in patients with early relapse [3]. Further treatment options include the EGFR/HER2 TKI lapatinib and different combinations of chemotherapy and trastuzumab. While sequential administration of these options may achieve prolonged disease control, patients with HER2-positive MBC will eventually progress indicating an urgent need for novel drugs.

The prospective randomized phase III trial SOPHIA randomized heavily pretreated patients with HER2-positive MBC to margetuximab plus chemotherapy by physician's choice or trastuzumab plus chemotherapy [4]. Margetuximab is a chimeric monoclonal antibody; similarly to trastuzumab, it targets the extracellular domain ECD4 of HER2. In contrast to trastuzumab, however, it has an altered Fc domain designed to have a higher affinity for the activating Fcγ-receptor IIIA (CD16A) and a lower affinity for the inhibitory Fcγ-receptor IIB (CD32B), resulting in improved immunologic properties such as increased antibody dependent cellular cytotoxicity (ADCC) and an increased HER2-specific T-cell response [5]. In a previously published phase I trial conducted in 66 patients with different HER2-positive solid cancers, single-agent margetuximab yielded a promising response rate of 17% in the MBC cohort [6].

Overall, 536 pretreated patients were accrued to the SOPHIA study. Potential chemotherapy combination partners included capecitabine, eribulin, gemcitabine and vinorelbine with the majority of patients receiving vinorelbine (35%), capecitabine (27%) and eribulin (25%). Of note, patients were heavily pretreated with 100% in both arms having already received prior trastuzumab and pertuzumab and >90% T-DM1 as well, reflecting a real-life population treated according to the most recent standards. PFS by central blinded analysis was defined as the primary study endpoint; in the intention-to-treat population, PFS in the margetuximab arm was 5.6 months compared 4.9 months in the standard arm (HR 0.76; 95% 0.59–0.98; $p=0.033$); in a preplanned exploratory subgroup analysis, the benefit of margetuximab seemed to be larger in patients harbouring the low affinity *CD16A-158F* allele of the Fcγ-receptor (median PFS 6.9 vs. 5.1 months; HR 0.68; 95% CI 0.52–0.90; $p=0.005$). In 524 patients with baseline measurable disease, overall response rate (ORR) was numerically higher with margetuximab as compared to trastuzumab as well (22% vs. 16%). Regarding toxicity, the rate of grade 3/4 adverse events was numerically higher in the experimental arm but the rate of serious adverse events (SAEs) was numerically lower (14.8% vs. 17.4%). The only major difference between the two antibodies was the rate of infusion-related reactions, which were observed in 14.4% of patients receiving margetuximab as compared with 3.8% in the trastuzumab arm; these, however, were easily controlled with appropriate premedication.

The SOPHIA trial therefore suggests that Fc-engineering results in improved immunological properties that may in turn lead to increased clinical activity. While the PFS HR of 0.76 appears promising, the absolute PFS benefit of 0.9 months in a heavily pretreated population is somewhat disappointing. Therefore, OS results must be awaited before a final conclusion regarding the potential role of margetuximab can be drawn; in addition, the results must be put in context with emerging data from other novel HER2-directed drugs such as the ADC trastuzumab-deruxtecan.

NALA

Neratinib is a second-generation (irreversible) pan-HER TKI inhibiting the tyrosine kinase domains of EGFR, HER2 and HER4. The drug has been approved by EMA based upon results of the ExteNET trial as extended adjuvant treatment in patients with HER2/hormone-receptor (HR) co-expressing tumours with a high recurrence risk after one year of trastuzumab-based adjuvant therapy [7, 8]. In MBC, activity of neratinib plus paclitaxel was comparable with trastuzumab plus paclitaxel as first-line treatment of HER2-positive MBC [9]; recently, clinically relevant activity of neratinib plus capecitabine was reported in patients with pretreated brain metastases [10]. As expected with a pan-HER2 TKI, diarrhoea was the main toxicity.

The prospective randomized phase III NALA trial randomized 621 pretreated patients with HER2-positive to neratinib in combination with capecitabine or lapatinib plus capecitabine [11]. Patients were required to have received a least two lines of prior HER2-directed treatment for MBC. Approximately 30% had

received ≥3 prior treatment lines. In contrast to the SOPHIA trials, however, only one third of all patients had received prior treatment with trastuzumab, pertuzumab and T-DM1.

Centrally confirmed PFS was defined as the primary study endpoint and progression risk was reduced by 24% in the neratinib group (HR 0.76; 95% CI 0.63–0.93; $p=0.0059$) PFS numbers in the restricted means analysis were 6.6 months for patients receiving lapatinib and 8.8 months for patients receiving neratinib, respectively. OS—a co-primary endpoint—was numerically improved by 1.7 months (HR 0.88; 95% CI 0.72–1.07; n.s.). ORR in patients with measurable disease at screening was also slightly higher in patients receiving neratinib (32.8% vs. 26.7%; n.s.), as was clinical benefit rate (44.5% vs. 35.6%; $p=0.0328$) and duration of response (HR 0.50; 95% CI 0.33–0.74; $p=0.0004$).

Brain metastases (BM) are frequently encountered in patients with HER2-positive MBC. In a competing risk model, time-to-intervention for BM was longer in the neratinib arm and the cumulative incidence of CNS interventions was lower as well (29.2% vs. 22.8%; $p=0.043$, Gray's test) suggesting a clinically relevant effect on the progression of BM.

Diarrhoea was the most frequent side effect in the NALA trial in both arms, but a higher rate was observed in patients in the neratinib group (any grade diarrhoea 83% vs. 66%; grade 3/4 diarrhoea 24% vs. 13%). Onset of diarrhoea occurred within the first two weeks of neratinib exposure. For clinical routine use, this problem requires appropriate patient education, close monitoring and dose modifications if indicated. In addition, prophylactic use of loperamide should be considered. Despite this drawback, NALA defined neratinib as the new standard when combination therapy consisting of a TKI and capecitabine is being considered.

Clinical practice

A retrospective analysis conducted in Canadian patients receiving HER2-directed treatment for HER2-positive MBC regardless of treatment line evaluated the prognostic role of achieving a complete remission (CR) [12]. Even in patients with a median duration of response ≥2-fold higher than observed in the pivotal phase II/III trials, patients achieving CR had a significantly longer PFS and OS indicating the excellent prognosis of MBC patients with a favourable response to HER2-directed treatment. The probability of achieving a CR was higher in patients with age <50, premenopausal status and a limited number of metastatic sites.

Two retrospective analysis from the US National Cancer Database evaluated treatment patterns and outcome in 6215 patients with HR and HER2 co-expressing tumours [13, 14]. OS was significantly shorter in elderly patients and in patients with poor socioeconomic status. A relatively high rate of patients (37%) received first-line endocrine therapy without anti-HER2 drugs. In a second analysis, OS was evaluated according to first-line therapy. Median OS in patients with first-line endocrine therapy was 42.3 months (range 39.5–45.6 months). In patients receiving first-line chemotherapy, median OS was 38.4 months (range 33.8–43.0 months) as compared with 46.8 months (range 44.9 months–NA) with first-line chemotherapy in combination with HR2-directed treatment; finally, in patients receiving a combination of endocrine therapy and HER2-directed treatment, median OS was 56.0 months (range 45.1 months–NA). While these OS data clearly reflect a selection bias, results do still suggest that in carefully selected patients with luminal B/HER2-positive disease, the combination of endocrine therapy with HER2-directed treatment may be a reasonable approach. In general, chemotherapy plus dual HER2-inhibition remains the first-line standard-of-care.

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Conflict of interest R. Bartsch declares the following relations: advisory role for Astra-Zeneca, Celgene, Daiichi, Eisai, Eli-Lilly, MSD, Novartis, Pfizer, Roche, Samsung; lecture honoraria from Accord, Astra-Zeneca, BMS, Celgene, Eli-Lilly, Novartis, Pfizer, Roche, Sandoz; research support from Daiichi, Novartis, Roche. E. Bergen declares that she has no competing interests.

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