EFFECTIVENESS OF TARGETING HER2 IN HEAVILY PRETREATED PATIENTS WITH OCCULT HER2-POSITIVE (TISSUE-NEGATIVE, SERUM-POSITIVE AND/OR HER2-POSITIVE CIRCULATING TUMOR CELLS) METASTATIC BREAST CANCER IN THE CLINICAL ROUTINE

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INTRODUCTION

Approximately 25% of breast cancer (BC) patients (pts) are considered to have HER2-positive (HER2+) disease. Recently, HER2-positive is defined as overexpression of the HER2 protein by immunohistochemistry (IHC: DAKO score ≥3+) or amplification of the HER2 gene on chromosome 17 by in situ hybridization (ISH: HER2 CEP17 ≥2.0) (Watt et al. 2013). A considerable proportion of HER2-negative (HER2-) pts with metastatic BC (MBC) may present with elevated serum levels of the HER2 extracellular domain (sHER2) and/or HER2 overexpressing circulating tumor cells (CTCs) (Antonescu et al., 2010). Several studies of large clinical trials such as DETECT-I (HER2+-pts may be candidates for anti-HER2 targeted therapy) (Ti) albeit normally not subjected to such treatment (Antonescu et al., 2010). These results of large clinical trials such as DETECT-I(II) have been set up to address this issue are still lacking. This observational study was initiated to earn more insights into the feasibility of HER2-directed Tx in pts with HER2 positive sHER2 levels and/or sHER2 CTCs in the clinical routine.

METHODS

28 pts with heavily pretreated HER2-BC (n=24, n=4) were included. The majority had visceral or mixed visceral disease. Pts had failed a median of 7 prior systemic treatments (range 2-16). Patients characteristics are summarized in Table 1. aHER2 was measured by a commercial chemiluminescence immunoassay (Semenis Healthcare Diagnostics, Excelsior, Germany). sHER2 (HER2+) was defined as her two sHER2 levels > 15 ng/mL determined within 4 weeks apart. CTCs were determined by using the CellSearch® technology (Van der Rijn, NL, USA) which allows for simultaneously measuring HER2 overexpression by immunofluorescence. HER2-positive was defined as the presence of at least one HER2+ CTC in 7.5 mL blood tested in duplicate. 8 pts in HER2+ CTCs and 14 pts were positive for both sHER2 and HER2 overexpressing CTCs. All pts received anti-HER2 Tx with trastuzumab (H; n=6), lapatinib (L; n=4), trastuzumab + pertuzumab, (H+P; n=6) and/or pertuzumab (P). Treated patients were divided into three groups: (1) stable disease (SD), (2) partial response (PR), (3) clinical remission (CR).

RESULTS

Anti-HER2 Tx was generally well tolerated. In two pts with L and P+H, anti-HER2 Tx was prematurely stopped due to toxicity (diabetes, fatigue). Median treatment duration was 17.0 weeks, range: 1.7-32.6 weeks (Graph A).

sHER2 levels (17.3%) in H+P had 11 pts (33.3%) achieved PR and another 12 pts (40.0%) showed SD accounting for an objective response rate of 39% and a clinical benefit rate of 82% (1/2 Table B).

Median OS was 71.6 weeks (Graph B). In 25 pts, 8 with PR, 12 with SD, and 5 with PD, results of partial sHER2 measurements at baseline and after 3 wks of Tx were available. Percent sHER2 changes are illustrated in Figure 2. Most pts with PD showed increasing sHER2 levels. In the majority of pts with PR or SD, sHER2 decreased by more than 20% from baseline. 2 pts with PR, however, showed increasing sHER2 values. Interestingly, both these pts were treated with L. In 19 pts, 8 with PR, 7 with SD, and 4 with PD, repeated CTC counts at 0 from baseline were available (Graph C). All 3 pts with PD showed increasing CTC counts. All pts with PD and SD presented with decreasing CTC values, most of them normalizing within 6 wks.

CONCLUSIONS

- Study limitation: small sample size.
- Strength: represents a real-world population of patients treated for "occult" sHER2+ MBC.
- Confirmative results of a prospective study of trastuzumab-based therapy in HER2+ MBC with elevated sHER2.
- Anti-HER2 Tx may be validated option for heavily pretreated HER2+ MBC with pathological of sHER2 values exceeding 10 ng/mL.
- Monitoring with PR and SD showed declining sHER2 levels. However two individuals responding to trastuzumab-based therapy presented with an sHER2 increase with may be due to a facilitated HER2 degradation mediated by apoptosis.
- Serial CTC measurements may be the more accurate predictor of response to anti-HER2 treatment.

- Results of randomized phase II trials in "occult" sHER2+ MBC such as DETECT-I are ambiguous. 

REFERENCES

