ANTI-HER2 TREATMENT IN ADVANCED METASTATIC HER2-NEGATIVE BREAST CANCER PATIENTS WITH ELEVATED SERUM LEVELS OF THE HER2 EXTRACELLULAR DOMAIN AND/OR HER2 OVEREXPressING CIRCULATING TUMOR CELLS

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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) [Wu 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 (HER2ECD) and/or HER2 overexpressing circulating tumor cells (CTCs) during their further clinical course [Lipton et al., 2009]. These "locally" HER2ECD-positive pts may be candidates for anti-HER2 targeted therapy (Tx); albeit normally not subjected to such treatment Navadeva et al. (2006). This, however, may be a large-scaled clinical trial such as DETECT-III which have set out to address this issue are still lacking. The observational study was initiated to gain more insights into the feasibility of HER2-directed Tx in pts with tissue HER2-IBC with elevated HER2ECD and/or HER2-CTCs in the clinical routine.

METHODS

21 pts with histologically proven HER2-IBC (25%, n=7) were included. The majority had received or mixed visceral. Pts had failed a median of 4 prior treatment strategies (range 2-10). Patients characteristics are summarized in Table 1. HER2ECD was measured by a commercially available (Keramidas Diagnostics GmbH Diagnostics, Exico, Germany). HER2-positive (HER2+) pts were defined as an HER2ECD level > 15 ng/ml (n=7) within an interval of at least 4 weeks (n=7) by CTCs were determined by using the CellSearch® (Verity, Santa, N, USA) which allows for simultaneous measuring HER2 overexpression by immunofluorescence. HER2-positive was defined as the presence of at least two HER2-CTCs > 7.3 nM and/or several vascular blood vessels in individual at least 3 were HER2ECD into 7 had HER2-CTCs and 16 pts were positive for both HER2 and HER2-overexpressing CTCs. All pts received anti-HER2 Tx with trastuzumab (14.1), lapatinib (10.4), T-DM1 (5.0), or Trastuzumab emtansine (H+I) or HER2-targeted Tx was given alone (n=5), in combination with endocrine agents (n=3), cytostatic drugs (n=7), or other targeted compounds (n=2). Results were scored according to RECIST 1.1. Treatment duration was defined as the time between start of FIGO and the cessation of the particular with HER2-regimen, death or loss to follow-up. Overall survival (OS) was calculated from the start of anti-HER2 Tx and death from any reason or loss to follow-up by using Kaplan-Meier statistics.

RESULTS

Anti-HER2 Tx was generally well tolerated. In two pts with L1 and one pt with HL, anti-HER2 Tx was prematurely stopped due to toxicity (dizziness, fatigue). Median treatment duration was 17.0 weeks, (IQR 6.5) range 2-40 weeks (Figure 1). Whereas 6 pts (13.4%), had PD, 12 pts (37.3%) achieved PR and another 13 pts (41.9%) showed SD accounting for an objective response rate (ORR) of 36.7% and a clinical benefit rate (CBR) of 60.6% (Table 2). Median OS was 17.1 weeks (Figure 1B). 14 pts. 5 PD, 12 PR, 12 SD, and 4 PD, results of serial HER2ECD measurements at baseline and after 3 to 6 weeks was available. Percent HER2ECD changes are illustrated in Figure 2. The majority of pts with PR or SD, HER2ECD decreased more than 20% from baseline. 2 pts with PR, however, showed increasing HER2ECD. Interestingly, these two pts were treated with L, 20 PD, with PR, and 5 PD, repeated CTCs at 5 weeks was available (Table 2). 3 pts with PD showed increasing CTCs. All pts with SD PR and PD presented with decreasing CTCs, most of them normalized within 6 weeks.

Table 1: Patients’ characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>52.5</td>
<td>35-84</td>
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Table 2: Effectiveness of anti-HER2 therapy

<table>
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<tr>
<th>Response according to RECIST 1.1</th>
<th>n (%)</th>
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<tr>
<td>Complete response (CR)</td>
<td>12 (33.3)</td>
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<tr>
<td>Partial response (PR)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>12 (33.3)</td>
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<tr>
<td>Clinical benefit rate (CBR)</td>
<td>0.63</td>
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CONCLUSIONS

- Study limitation: small sample size.
- Strengths: represents real-world population of patients treated for "locally" HER2-IBC.
- Limitations: results of a previous study of trastuzumab-based therapy in HER2-IBC with elevated HER2ECD (Richter et al. 2011) (Figure 2).
- Conclusion: HER2-CTCs overexpression on CTCs appears to be measurable in patients with HER2-metastatic breast cancer.
- Improvements: more pts with PD should decline HER2ECD levels. However, two individuals responding to lapatinib-based therapy presented with an elevated HER2ECD increase with may be due to a facilitated HER2 signaling by trastuzumab.
- Serial CTCs measurements may be the more accurate predictor of response to anti-HER2 treatment.

References


Figure 1: Kaplan-Meier plot showing (A) duration of and (B) overall survival after anti-HER2 therapy for pts with "locally" HER2-IBC MBC. Detailed lines represent the 95% CI.

Figure 2: Absolute changes in CTC counts within 6 weeks from start of therapy: (A) patients with progressive disease, (B) patients with stable disease; (C) patients with partial responses. 5 pts were included and all patients with PD had increasing CTC counts whereas all patients with SD or PD had decreasing and often normalized CTC counts.