Retreatment with trastuzumab-based therapy after disease progression following lapatinib in HER2-positive metastatic breast cancer

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Background: Preclinical data suggest that treatment with lapatinib reinduces sensitivity to trastuzumab in human epidermal growth factor receptor 2(HER2)-positive breast cancer cells.

Patients and methods: Between January 2007 and November 2010, 179 HER2-positive metastatic breast cancer patients were treated with lapatinib and capecitabine at nine Italian institutions. We evaluated the clinical outcome of 69 patients (38.5%) retreated with trastuzumab after lapatinib progression.

Results: Visceral metastases were identified in 51 (74%) and brain metastases in 16 patients (23%). All patients were pretreated with both trastuzumab- and lapatinib-based therapy. We observed with retreatment with trastuzumab-based therapy: 1 complete remission (2%), 18 partial remission (29%) and 10 stable disease 6 months (14%) and 47% of clinical benefit (CB). Median duration of response was 8.1 months [95% confidence interval (CI) 5.5–10.7]. No unexpected toxic effects occurred. At a median follow-up of 13 months, median progression-free survival was 4.9 months (95% CI 4.2–5.6) and overall survival (OS) 19.4 months (95% CI 14.0–25.0). Median OS was longer for patients experiencing CB (not reached versus 13.4 months for patients without CB, \( P = 0.002 \)). Brain involvement was associated with lower median OS (17.3 versus 23.3 months for patients without brain disease; \( P = 0.021 \)).

Conclusion: Retreatment with trastuzumab-based therapy showed CB in 47% of patients progressing during lapatinib-based therapy, leading to a prolonged OS.

Key words: HER2, metastatic breast cancer, trastuzumab after lapatinib
introduction

The development of trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of human epidermal growth factor receptor 2 (HER2), has represented a major breakthrough in the treatment of HER2-positive breast cancer. Randomized trials have shown that trastuzumab-based therapies prolong survival of these patients both in the metastatic and adjuvant setting [1–4].

In HER2-positive metastatic breast cancer, HER2 remains an effective therapeutic target even in the presence of disease progression due to trastuzumab treatment. Three phase III randomized trials have been conducted in HER2-positive metastatic breast cancer patients who have progressed after trastuzumab-based therapy. In two studies, trastuzumab beyond progression given in combination with capecitabine or with lapatinib (the dual HER1/HER2 tyrosine kinase) resulted more effective than capecitabine alone or single-agent lapatinib, respectively [5, 6]. The third study has shown that lapatinib plus capecitabine significantly improves the time to progression compared with capecitabine monotherapy [7], and in 2007, this combination was approved for the treatment of HER2-positive metastatic breast cancer pretreated with an anthracycline, a taxane, and trastuzumab [8]. Nonetheless, it is necessary to know how to treat patients after disease progression on lapatinib and capecitabine.

Preclinical evidence could support the reuse of trastuzumab after treatment with lapatinib. The development of acquired resistance to trastuzumab might also be due to receptor degradation and down-regulation [9, 10]. Lapatinib, inducing stabilization and accumulation of inactive HER2 receptor at the cytoplasmic membrane, could potentially re-activate HER2-positive tumor cells to the action of trastuzumab [11].

This study reports on the clinical outcome of HER2-positive metastatic breast cancer patients who were rechallenged with trastuzumab following disease progression on lapatinib.

patients and methods

patient population

Between January 2007 and November 2010, a total of 179 patients were identified who had been treated with lapatinib and capecitabine combination at nine Italian institutions. Sixty-nine of out 179 patients (38.5%) were identified who had been treated with lapatinib and capecitabine (the dual HER1/HER2 tyrosine kinase) resulted more effective than capecitabine alone or single-agent lapatinib, respectively [5, 6]. The third study has shown that lapatinib plus capecitabine significantly improves the time to progression compared with capecitabine monotherapy [7], and in 2007, this combination was approved for the treatment of HER2-positive metastatic breast cancer pretreated with an anthracycline, a taxane, and trastuzumab [8]. Nonetheless, it is necessary to know how to treat patients after disease progression on lapatinib and capecitabine.

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Between January 2007 and November 2010, a total of 179 patients were identified who had been treated with lapatinib and capecitabine combination at nine Italian institutions. Sixty-nine of out 179 patients (38.5%) were rechallenged with trastuzumab-based therapy after lapatinib progression. HER2 positivity was determined locally and defined as immunohistochemical (IHC) staining of 3+ (HercepTest®; Dako A/S, Glostrup, Denmark) or 2+ with evidence of gene amplification at FISH (PathVision® HER2 DNA probe kit; Vysis Inc., Downers Grove, IL).

Tumor response was analyzed in patients with measurable disease and assessed by using RECIST [12]. Overall response rate (ORR) was defined as the proportion of patients achieving complete or partial remission (CR + PR) among those with measurable disease. Clinical benefit rate (CBR) was defined as the proportion of patients with CR, PR or a stable disease (SD) lasting 6 months.

Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02) grade scaling.

statistical analysis

Progression-free survival (PFS), duration of response (DOR) and overall survival (OS) were calculated by the Kaplan–Meier method for all patients. For the three outcomes, the starting point was the date in which rechallenge with trastuzumab-based therapy started. The dates of tumor progression or death due to any cause were used to calculate PFS and DOR, whereas that of death for any cause was used to calculate OS. Survival curves in patients grouped according to variables of interest were compared by the log-rank test. Surviving patients were censored at the date of the last follow-up contact.

Univariate and multivariate Cox proportional hazards analyses was used to identify variables that were independently associated with PFS and OS in all patients undergoing rechallenge with trastuzumab. The proportionality of hazards assumption was checked by the log-minus-log survival plot method. Statistical significance was set at P < 0.05. All the analyses were conducted by the SPSS 17.0 statistical package (Chicago, IL).

Being a retrospective analysis of clinical outcomes, no specific written informed consent was required for this study. However, the process of data collection was conducted in compliance with the ethical requirements of each of the participating institutions.

results

patients characteristics

The characteristics of the 69 patients at the time of rechallenge with trastuzumab are summarized in Table 1. All breast cancers were HER2 positive: 56 were 3+ by IHC and 13 FISH amplified. In 13 patients, breast cancer was metastatic at presentation. Visceral metastases were identified in 51 patients (74%) and brain metastases, with or without visceral involvement, in 16 patients (23%).

All patients were pretreated with both trastuzumab- and lapatinib-based therapy. Previous systemic treatments are reported in Table 2. Seventy-five percent of the patients received neo- and/or adjuvant chemotherapy: in 38 of out these 52 patients (73%), anthracycline-based regimen with or without taxanes was administered. Four patients relapsing during or within 1 year from completion of adjuvant trastuzumab received lapatinib-based therapy as first treatment of metastatic disease. However, in the evaluation of total duration of prior trastuzumab, lapatinib-based therapy was also included. Most patients were heavily pretreated in the metastatic setting and, before rechallenge with trastuzumab-based therapy, had received HER2 targeting agents for a median of 2 years.

The median number of chemotherapeutic lines for metastatic disease before trastuzumab retreatment was 2 (range: 1–8), and the median number of trastuzumab-based regimens for metastatic disease was 2 (range: 0–6). The median duration of prior lapatinib was 6 months (range: 1–20) and clinical benefit was reported in 38% of the patients (Table 2).

In Table 3, the details of rechallenge with trastuzumab-based therapy are summarized. In all but four patients, trastuzumab was combined with chemotherapy.

clinical outcome

Sixty-one patients had measurable disease and were evaluated for tumor response to rechallenge with trastuzumab-based therapy (Table 4). The rechallenge with trastuzumab-based therapy was associated with 1 CR (2%), 18 PR (29%) and 10 SD ≥ 6 months (14%), with an ORR of 31% [95% confidence interval (CI) 21% to 44%] and a CBR of 47% (95% CI 35% to 60%). The median DOR was 8.1 months (95% CI 5.5–10.7). At a median follow-up of 13 months (range 1–37 months) from the start of rechallenge with trastuzumab-based therapy, 55 patients had progressed and 31 had died.
Table 1. Tumor and patient characteristics (n = 69)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>57 (26–80)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (33)</td>
</tr>
<tr>
<td>1</td>
<td>30 (44)</td>
</tr>
<tr>
<td>2</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>11 (16)</td>
</tr>
<tr>
<td>HR status (cut-off ≥10%)</td>
<td></td>
</tr>
<tr>
<td>ER and or PgR positive</td>
<td>30 (44)</td>
</tr>
<tr>
<td>ER and PgR negative</td>
<td>39 (56)</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>17 (25)</td>
</tr>
<tr>
<td>G3</td>
<td>41 (59)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Stage at first diagnosis of breast cancer</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>29 (42)</td>
</tr>
<tr>
<td>I/IB</td>
<td>18 (26)</td>
</tr>
<tr>
<td>I/IC</td>
<td>9 (13)</td>
</tr>
<tr>
<td>IV</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Median DFI, months (range)*</td>
<td>24 (0–200)</td>
</tr>
<tr>
<td>Median time from diagnosis of metastatic</td>
<td>40 (8–163)</td>
</tr>
<tr>
<td>disease, months (range)</td>
<td></td>
</tr>
<tr>
<td>Pattern of metastatic disease at the time of trastuzumab retreatment</td>
<td></td>
</tr>
<tr>
<td>Bone/Soft tissue only</td>
<td>16 (23)</td>
</tr>
<tr>
<td>Visceral (no CNS)</td>
<td>37 (54)</td>
</tr>
<tr>
<td>Visceral + Viscera</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Visceral no Viscera</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*From the initial diagnosis of breast cancer to the first occurrence of metastatic disease. For patients with stage IV disease at breast cancer onset, DFS was assumed to be equal to 0.

ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; ER, estrogen receptor; PgR, progesterone receptor; DFI, disease-free interval; CNS, central nervous system; DFS, disease-free survival.

The median progression-free survival (PFS) was 4.9 months (95% CI 4.2–5.6) and median OS 19.4 months (95% CI 14.0–25.0) (Table 4).

OS was evaluated according to pattern of metastatic involvement. Median OS was not reached for patients with bone/soft tissue metastases without central nervous system (CNS) involvement, it was 15.8 months (95% CI 9.8–26.2) for patients with visceral metastases without CNS disease and 17.3 months (95% CI 3.4–32.2) in patients with CNS involvement with or without visceral metastases.

However, overall CNS metastatic involvement was associated with lower median OS (17.3 versus 23.3 months for patients without CNS involvement; \( P = 0.021 \)).

Patients achieving clinical benefit from lapatinib-based therapy had significantly longer median OS (not reached) compared with those failing to achieve clinical benefit (15.7 months, 95% CI 11.7–19.7; \( P = 0.041 \)). Similarly, patients staying on lapatinib-based therapy for >6 months achieved longer median OS (not reached) compared with those on lapatinib for ≤6 months (13.4 months, 95% CI 8.8–14.0; \( P = 0.010 \)).

Median OS evaluated according to response to rechallenge with trastuzumab-based therapy showed that patients achieving clinical benefit had significantly longer survival (median OS not reached) compared with patients failing to achieve clinical benefit (14.9 months, 95% CI 9.8–20.0; \( P = 0.012 \)).

Univariate comparisons according to clinical variables showed that bone/soft tissue involvement without CNS metastases, clinical benefit to prior lapatinib-based therapy, longer time on lapatinib-based therapy and clinical benefit to rechallenge with trastuzumab-based therapy were significantly associated with longer median OS (Table 5). At multivariate analysis, the risk of death was significantly higher in patients with visceral involvement and in those with CNS involvement with or without other metastatic sites, while it was significantly reduced in patients achieving clinical benefit to rechallenge with trastuzumab-based therapy (Table 6).

No unexpected toxic effects occurred during rechallenge with trastuzumab.

Most toxic effects observed were grade 1–2.
Cardiotoxicity was reported in two patients, both of whom had been treated with anthracycline, taxane and trastuzumab before lapatinib. Both patients had obtained a partial response to retreatment with trastuzumab plus chemotherapy. In one patient with hypertension, grade 3 cardiotoxicity was observed (1.4%), due to a symptomatic left ventricular ejection fraction (LVEF) reduction (30%). This patient received angiotensin converting enzyme inhibitor and beta blocker-based therapy with a recovery of clinical cardiac symptoms and LVEF. After the development of cardiotoxicity, trastuzumab was definitively stopped and paclitaxel was resumed as monotherapy. An asymptomatic LVEF reduction (48%) was observed in another patient, in which the treatment with trastuzumab plus carboplatin was continued.

**Discussion**

In this retrospective study, the clinical outcome of 69 patients with HER2-positive metastatic breast cancer retreated with trastuzumab-based therapy after lapatinib progression was evaluated. In 61 patients assessable for response, an objective response rate of 29% (median DOR: 8.1 months) and a CBR of 47% were observed. For all patients, median PFS was 4.9 months and median OS was 19.4 months.

Median OS evaluated according to response to rechallenge with trastuzumab-based therapy showed that patients achieving clinical benefit had significantly longer survival (median OS not reached) in comparison with patients failing to achieve clinical benefit (14.9 months, 95% CI 9.8–20.0; \( P = 0.012 \)).

At multivariate analysis, the risk of death was significantly higher in patients with visceral involvement and in those with CNS involvement with or without other metastatic sites, while it was significantly reduced in patients achieving clinical benefit to rechallenge with trastuzumab (Table 6). Treatment was well tolerated and no unexpected toxic effects occurred during rechallenge with trastuzumab; only one patient developed grade 3 cardiotoxicity (1.4%).

Many observational retrospective [13–17] and prospective trials [18] have shown that the continuation of anti-HER2 therapies in patients progressing during trastuzumab-based treatment was associated with improved clinical outcome in HER2-positive metastatic breast cancer patients. Only four studies compared survival of patients who continued trastuzumab beyond disease of progression with that of patients who halted trastuzumab after first progression. Three of them reported a longer survival for patients who maintained trastuzumab [16–18], while in the Italian study survival of patients who continued or discontinued trastuzumab was identical [19].

Some phase III randomized trials [5–7] have shown that the continuation of anti-HER2 therapies in patients progressing during trastuzumab-based treatment was associated with improved PFS [6, 7] or time to progression [5].

To date, the therapeutic options beyond trastuzumab progression are represented by trastuzumab in combination with a different chemotherapy [5], trastuzumab plus lapatinib [6] or lapatinib plus capecitabine [7].

With the introduction of lapatinib and capecitabine for the treatment of metastatic breast cancer pretreated with trastuzumab-based therapy...
trastuzumab, there is a new problem: how do we treat the patients progressing on lapatinib-based therapy?

Preclinical data could support the reuse of trastuzumab after treatment with lapatinib. Indeed, the development of the acquired resistance to trastuzumab might also be due to receptor degradation and down-regulation [9, 10]. Lapatinib, inducing stabilization and accumulation of inactive HER2 receptor at the cytoplasmic membrane, could potentially re-sensitize HER2-positive tumor cells to the action of trastuzumab [11].

To date, only retrospective data on 21 HER2-positive metastatic breast cancer patients retreated with trastuzumab and chemotherapy after progression on lapatinib and capecitabine have been reported, with a CBR of 48% and a median time to progression of 4.5 months [20].

In our series of 69 patients, these preliminary results were confirmed in patients who had been heavily pretreated in the metastatic setting and who, before rechallenge with trastuzumab-based therapy, had received HER2 targeting agents for a median of 2 years.

Our results suggest that the continuation of anti-HER2 treatment is associated with improved clinical outcome in HER2-positive metastatic breast cancer patients progressing to lapatinib-based therapy.

However, this study was retrospective and the results obtained could have been the consequence of more favorable clinical characteristics of patients treated with trastuzumab-based therapy after progression on lapatinib plus capecitabine. Indeed, patients achieving clinical benefit from lapatinib-based therapy had significantly longer median OS (not reached) with trastuzumab compared with those failing to achieve clinical benefit (15.7 months, 95% CI 11.7–19.7; \( P = 0.041 \)). Similarly, patients remaining on lapatinib-based therapy for >6 months achieved with treatment with trastuzumab longer median OS (not reached) compared with those on lapatinib for ≤6 months (13.4 months, 95% CI 8.8–14.0; \( P = 0.010 \)).

The number of HER2-targeted therapies continues to grow and some drugs are in clinical development in trastuzumab-pretreated patients, alone or in combination with other agents. All new anti-HER2 treatments delivered to HER2-positive metastatic patients pretreated with trastuzumab resulted in 24%–26% of objective response rate in phase II trials.

With neratinib, an oral irreversible pan-ErbB receptor tyrosine kinase inhibitor, an objective response rate of 24% was reported, although diarrhea of grade 3–4 was observed in 30% of cases, which required dose reduction in 29% of patients [21].

Pertuzumab, a monoclonal antibody directed against the highly conserved dimerization domain of HER2 that inhibits HER2 homo- and heterodimerization, was evaluated in combination with trastuzumab and an objective response rate of 24% was reported [22].

In 112 patients treated with Trastuzumab-DM1 (T-DM1), which combines trastuzumab’s HER2-blocking activity with targeted delivery of the highly potent antimicrotubule agent maytensine derivative (DM1), an objective response rate by independent assessment of 26% and a median PFS of 4.6 months were observed. In a post hoc exploratory analysis, the objective response rate in patients who received both prior trastuzumab and lapatinib was 24.2% with a PFS of 5.3 months [23].

Other targeted agents are being evaluated after trastuzumab progression. Everolimus in association with trastuzumab and paclitaxel [24] and tanespimycin, the heat shock protein 90 inhibitor, in combination with trastuzumab [25] showed an objective response rate of 20% and 24%, respectively.

However, only T-DM1 was administered in a subgroup of patients pretreated with trastuzumab and then with lapatinib [23]: the rate of objective response reported (24.2%) in this phase II trial was similar to that obtained in our retrospective series with rechallenge trastuzumab (31%).

In conclusion, our results show improved clinical outcome in HER2-positive metastatic breast cancer patients by resuming trastuzumab after disease progression on lapatinib plus capecitabine.

Few clinical data regarding benefit by rechallenge trastuzumab in metastatic breast cancer that progressed during lapatinib therapy are available, but these results confirm that HER2 remains an effective therapeutic target even in the presence of disease progression to anti-HER2 treatment.

Rigorous translational studies are needed to discover the mechanisms of resistance and identify the predictive markers of response to all anti-HER2 drugs so to define an optimal sequence of anti-HER2 treatments for every patient.

disclosure

FM has reported honoraria received from GlaxoSmithKline Spa as member of Advisory Boards. The other authors have reported no conflicts of interest.

references


