From the trastuzumab era to new target therapies: beyond revolution

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In the October 2005 edition of The New England Journal of Medicine, Gabriel Hortobagyi claimed that "the results of trastuzumab adjuvant trials are not evolutionary but revolutionary" [1]. In effect, from the early results of the first target therapy, tamoxifene, this is the first time that such enthusiastic and dramatic results, in terms of outcome of an adjuvant therapy, have been realized.

Interim analysis of four randomized phase III trials, in patients with HER2-positive early-stage breast cancer, indicated significant improvement in disease-free survival (DFS) compared with chemotherapy alone [hazard ratio (HR) 0.48–0.64] and an overall survival (OS) benefit in three of the four trials (NCCTG N9831/NSABP B-31: HR 0.67, \(P = 0.015\); HERA: HR 0.66; \(P = 0.0115\)) when trastuzumab was added to standard therapy. It is obvious that there are certain limitations in the use of this extraordinary drug.

The first is that trastuzumab can only be used in a small number of patients; the majority (HER-2 negative) cannot benefit from its use. The second problem is the potential cardiotoxicity of this treatment. In clinical practice, treatment with trastuzumab can be resumed when the patients are no longer symptomatic and cardiac function is normalized.

The third dilemma is whether the duration of therapy should be short or prolonged.

The fourth problem concerns the high cost of trastuzumab treatment to the National Health Service, which is not to be disregarded. Finally, the fifth dilemma is to decide which patients should be treated with trastuzumab. It is obvious that all node-positive patients should receive treatment, but probably not all node-negative patients. Other potential strategies for evaluating response to trastuzumab therapy might include the assessment of surrogate markers of critical HER2-mediated signaling pathways, including the PI3K/Akt pathway, and circulating HER2 extracellular domain levels. In addition, the NSABP B-31 trial identified c-Myc amplification as a predictive factor for responsiveness to trastuzumab. Acquired and de novo resistance to trastuzumab is a significant clinical challenge.

bevacizumab

The addition of anti-vascular endothelial growth factor (VEGF) therapy to chemotherapy has been found to be beneficial principally in first-line therapeutic regimens, especially in those used for the treatment of colorectal, breast, renal, and lung cancers. The binding of VEGF initiates downstream signaling, which in turn enhances endothelial cell survival, proliferation, permeability, migration, and invasion. As blood vessels become permeable, they allow the leakage of proteins, hence allowing endothelial cell migration into the matrix and ultimately the formation of new blood vessels. One anti-VEGF agent is bevacizumab, an monoclonal antibody (mAb) (93% human and 7% mouse) that binds to the VEGF family member VEGF-A reducing the availability of the VEGF ligand for its receptors (VEGFR1 and 2) and thereby preventing receptor activation.

Clinical trial findings indicate that a synergistic interaction may occur between chemotherapy and bevacizumab.

Results of a phase I trial with the combination of anti-HER2 and anti-VEGF mAbs (trastuzumab and bevacizumab) indicated a potentially enhanced anticancer effect with the combination, with no influence on pharmacokinetics of either agent [2]. A phase II trial using this combination included 37 chemotherapy-naïve patients. An overall response rate (ORR) of 54% was obtained [3].

On the basis of these preliminary data, a phase III randomized trial was undertaken to evaluate bevacizumab in women with heavily pretreated metastatic breast cancer (MBC). A total of 462 patients were randomized to receive bevacizumab plus capecitabine or only capecitabine [4]. The primary end point of the trial, progression-free survival (PFS), was statistically identical in the two arms: capecitabine versus capecitabine plus bevacizumab, 4.2 versus 4.9 months. RRs were significantly higher with the combination versus capecitabine alone (19.8% versus 9.1%; \(P = 0.001\), N0432 is a phase II trial that enrolled 45 chemotherapy-naïve patients in the metastatic setting (63% with visceral disease). They were treated with docetaxel, bevacizumab, and capecitabine [5]. There were two complete responses (CRs), 22 partial responses (PRs), and 19 patients with stable disease (SD), for a RR of 53%. Median duration of response was 9.9 months and median OS has not yet been reached.

A recent randomized phase III trial compared the use of bevacizumab and paclitaxel with paclitaxel alone as first-line
therapy in patients with MBC [6]. The primary end point was PFS; ORR and OS were also evaluated. Patients on the bevacizumab and paclitaxel arm achieved an increase in PFS (11.4 versus 6.11 months; \( P < 0.0001 \)) and ORR (30% versus 14%; \( P < 0.0001 \)) compared with those who received paclitaxel alone. In addition, patients with measurable disease on the first arm experienced a significant increase in ORR (38% versus 16%; \( P < 0.0001 \)). However, there is no significant difference in OS at this time. Several questions remain to be answered, e.g. if bevacizumab should be continued after progression in patients receiving bevacizumab-containing therapy. Another question pertains to predictors of response. Predictive markers of the efficacy of anti-VEGF therapy are lacking.

**lapatinib**

Breast cancer is frequently associated with an increased expression and activation of the epidermal growth factor receptor (EGFR) tyrosine kinases that are involved in the regulation of normal breast development. The receptors are not fixed in one position in the plasma membrane, and upon ligand binding to the extracellular domain, dimerization occurs.

Lapatinib ditosylate (GW572016/Tykerb®) is an oral dual tyrosine kinase inhibitor (TKI) targeting both the ErbB-1 and the ErbB-2 receptors and has shown promising activity in preclinical investigations and clinical trials.

A phase III trial examined the efficacy of lapatinib with capecitabine [7]. Patients with progressive HER2+ MBC or locally advanced breast cancer pretreated with anthracycline, taxane, and trastuzumab were randomized to receive either capecitabine or capecitabine plus lapatinib 1250 mg/day p.o. for 2 every 3 weeks. Median time to progression (TTP) was significantly longer in the lapatinib and capecitabine arm (36.9 versus 19.7 weeks, HR 0.51, \( P = 0.00016 \)). Median PFS was also significantly longer with lapatinib and capecitabine (36.9 weeks versus 17.9 weeks, HR 0.48, \( P = 0.000045 \)). There was a trend toward the improvement in ORR (22.5% versus 14%, \( P = 0.113 \)) as well as fewer central nervous system (CNS) metastases (4 versus 11, \( P = 0.110 \)) in the 160 patients receiving lapatinib plus capecitabine compared with the 161 receiving capecitabine alone.

Patients with ErbB-2-overexpressing breast cancer were found to have a significantly higher risk of developing brain metastases.

Lapatinib, being a small molecule capable of penetrating the blood–brain barrier, has been used in clinical trials for the treatment of brain metastases.

Results from a phase II trial with lapatinib for ErbB-2-overexpressing breast cancer patients with brain metastases are known [8]. Patients received lapatinib at a dose of 750 mg b.i.d. The primary end point was objective response in the CNS. Two patients (5%) had a PR as the best CNS response and 4 out of 16 patients (25%) with measurable disease had a PR as the best non-CNS response.

In the EGF20009 study, locally advanced or MBC patients with ErbB-2 amplification were randomized to receive lapatinib at a dose of either 1500 mg qds or 500 mg b.i.d. Eligible patients were trastuzumab naive for metastatic disease. The primary end point was RR. By independent radiology review, 35% patients had a PR and a further 5% had unconfirmed PRs; 35% patients had SD, 12.5% had progressive disease, and 12.5% were not assessable [9].

Very intriguing are first results of lapatinib and paclitaxel therapy in newly diagnosed inflammatory breast cancer (IBC) [10]. Twenty-five patients with IBC were treated with lapatinib 1500 mg/day for 2 weeks. Weekly paclitaxel was added for 12 additional weeks. After 14 weeks of therapy, patients underwent surgery. In total, 30% patients responded to only lapatinib by day 14 and 78% patients responded to the combination therapy.

Lapatinib is a potentially ideal therapy for the adjuvant treatment of breast cancer. Two ongoing trials are TEACH and BIG. The objective of the TEACH trial is to determine whether adjuvant therapy with lapatinib for 1 year will improve DFS in women with early-stage ErbB-2-overexpressing breast cancer. The BIG trial randomizes patients to lapatinib or trastuzumab for 1 year versus the combination or the sequence for the same time.

In conclusion, lapatinib is an active and well-tolerated oral dual TKI for the treatment of breast cancer. Clinical efficacy of lapatinib is limited only to the treatment of ErbB-2-overexpressing breast cancer. Lapatinib is active in refractory MBC patients and, as a first-line metastatic treatment, with potential benefit in patients with brain metastases.

**other small-molecule TKI**

Unlike mAbs, small-molecule agents can translocate through plasma membranes and interact with the cytoplasmic domain of cell-surface receptors and intracellular signaling molecules.

Sunitinib is an oral TKI that has multiple targets, including VEGFR, platelet-derived growth factor receptor (PDGFR), c-Kit, and Flt-3. In an open label, single-arm, phase II trial, 64 patients with anthracycline- and taxane-refractory MBC received sunitinib 50 mg/day p.o. for 4 weeks per 6-week cycle. A PR was achieved by 7 patients (11%), and an additional 3 patients (5%) had SD \( \geq \) 6 months for an overall clinical benefit rate of 16% [11].

Sorafenib is an oral TKI that inhibits the tyrosine kinase activity of Raf kinase (Raf-1, wild-type B-Raf, and B-Raf V600E), VEGFR, and PDGFR, potentially enabling the simultaneous blockade of tumor cell proliferation and angiogenesis as well as potentiation of tumor apoptosis. In a phase II study of sorafenib, which enrolled 54 patients with MBC, a PR rate of 2% was achieved, and SD \( \geq \) 6 weeks was observed in 22% patients [12].

Pazopanib, a new multi-targeted TKI of VEGFR-1, 2 and 3, has been shown to selectively inhibit VEGF-mediated endothelial cell proliferation. It has been proposed for phase II and III expansion, including a phase II trial expanding the study of pazopanib/latinib in patients with MBC.

Axitinib is a novel TKI with nanomolar affinity for VEGFR isoforms, PDGFR, and c-Kit. Phase I efficacy results showed 2 PRs (33%) [13].

Gefitinib (Iressa [ZD1839]) is an orally active, selective EGFR TKI that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells. This drug has been
used in MBC patients in combination with chemotherapy in phase I and II trials with no clinical results [14].

Erlotinib (Tarceva®) is a small molecule that reversibly and selectively inhibits the intracellular autophosphorylation of tyrosine kinase in association with the EGFR. A combination with weekly docetaxel as first-line treatment resulted in a RR of 55%. The nonrandomized nature of this study does not clarify the additional value regarding the anti-neoplastic activity of erlotinib [15].

**mTOR inhibitors**

The mammalian target of rapamycin (mTOR) is a protein with many functions. This protein regulates two downstream proteins, P70 S6 kinase and 4EBP-1, both of which play key roles in the ability of a cell to produce proteins. Actually, the first mTOR inhibitor to be studied in the treatment of cancer is temsirolimus (CCI-779), an analogue of rapamycin. There are two other mTOR-inhibiting compounds, although they are not prodrugs of rapamycin: everolimus (RAD001) and AP23573.

Temsirolimus was utilized in MBC after having demonstrated activity in heavily pretreated patients.

Data from a phase II study of CCI 779 monotherapy were collected from 14 European sites. A total of 109 women with previously treated locally advanced or MBC were enrolled. Patients were randomized to receive i.v. CCI-779 weekly at dose levels of 75 or 250 mg. Clinical benefit was observed in 49% patients.

A phase II study of temsirolimus combined with letrozole was presented: patients with measurable MBC were randomized in a 1:1:1 ratio: letrozole or letrozole with CCI 779 daily (the daily arm) or CCI 779 daily for 5 days every 2 weeks (the intermittent arm). Objective responses were as follows: in the 10-mg daily arm, 9 PRs; in the 30-mg intermittent arm, 1 CR and 8 PRs; in the letrozole-alone arm, 2 CRs and 10 PRs. Clinical benefit was 82%, 83%, and 79%, respectively. Median PFS has been reached for the letrozole-alone arm (9.2 months) but not for the combination arms. The combination of RAD001 with letrozole is being studied in a randomized, phase II neo-adjuvant, pharmacodynamic study enrolling newly diagnosed, untreated, localized, estrogen receptor positive (ER-positive) breast cancer patients [16].

**other poli-inhibitors of ErbB receptors**

Other new agents (dual targeting) have been introduced into clinical practice with the aim of blocking both HER1 and HER2 receptors.

Pertuzumab is a fully recombinant humanized mAb that binds to the HER2 receptor at domain II, sterically blocking heterodimerization of HER2 with EGFR and ErbB3, thereby inhibiting intracellular signaling. In breast cancer, a randomized phase II study testing two different doses of pertuzumab has been conducted, the primary end point was RR. Seventy-nine patients pretreated with anthracycline and with low HER2 expression entered the study. Six out of 78 patients of the intent-to-treat population responded or had SD for >6 months [17].

**conclusion**

The therapeutic results obtained with combined therapies in the last years, and not only in cases of breast cancer, will most certainly be improved by the new molecular therapies which are becoming available. Some of these, e.g. trastuzumab, imatinib, bevacizumab and cetuximab, have already increased OS. Many other molecules that are in various stages of experimentation appear to be very encouraging.

But inevitably, alongside the benefits there are many dilemmas, which are in search of an answer:

- Which patients should be treated?
- For how long?
- With which drugs?
- In which order?
- Which combination of drugs should be used?
- What are the therapeutic targets?
- How should the response be evaluated?
- What are the delayed toxic effects?

And last, but not least, with what resources?

There is one point which it is important to stress at a time when pharmaceutical companies are exerting much pressure, and that is the absolute necessity of having well-designed and serious trials with a solid biological rationale. This should avoid rejecting a drug, classified as being useless or inactive, simply because it was not used correctly and not administered to the optimal patient.

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**references**


