Targeted Therapies for the Treatment of Breast Cancer in the Post-trastuzumab Era

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the development of bevacizumab and lapatinib in the treatment of advanced breast cancer and evaluate the present role of these agents in clinical practice.
2. Describe the current state of knowledge on the other small-molecule tyrosine kinase inhibitors using data from orally presented or published studies over the last few years in metastatic breast cancer.
3. Assess the actual dilemmas for oncologists in the study design and prescription of these target agents.

ABSTRACT

Targeted therapies for breast cancer are evolving rapidly. Trastuzumab has revolutionized breast cancer treatment and outcome, reducing the risk for recurrence and significantly increasing survival, at least for a subgroup of patients. Other targeted therapies, such as bevacizumab, a monoclonal antibody targeting angiogenesis, lapatinib, a dual human epidermal growth factor receptor (HER)-1 and HER-2 inhibitor, other small-molecule tyrosine kinase inhibitors, and mammalian target of rapamycin inhibitors, have been developed in phase II and III clinical trials. Although there has been rapid approval of these new drugs by health authorities, some questions have emerged about their application in clinical practice. What is the appropriate drug or sequence of drugs? What is the ideal target? How should tumor response be evaluated? Are financial resources sufficient to treat patients? How do we design trials with these molecules? These are emerging as current dilemmas for clinical oncologists.

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INTRODUCTION

Gabriel Hortobagyi, in the October 2005 edition of The New England Journal of Medicine, stated that: “the results of trastuzumab adjuvant trials are not evolutionary but rev-

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tuzumab (Herceptin®; F. Hoffmann-La Roche, Basel, Switzerland) is a humanized monoclonal antibody of the IgG1 type directed against the extracellular portion of human epidermal growth factor receptor (HER)-2, a transmembrane tyrosine kinase receptor, belonging to the epidermal growth factor receptor (EGFR) family that is overexpressed in 25%–30% cases of human breast cancers.

New insights regarding the trastuzumab adjuvant trials and first-line trastuzumab-containing therapies were presented during the last year at international meetings.

The Breast Cancer International Research Group (BCIRG) 006 trial was designed to assess the role of trastuzumab in a docetaxel-containing chemotherapy regimen with or without doxorubicin. Patients were randomized to one of three regimens: doxorubicin plus cyclophosphamide followed by docetaxel (AC-T), doxorubicin plus cyclophosphamide followed by docetaxel with concurrent trastuzumab (AC-TH), or combined docetaxel, carboplatin, and trastuzumab (TCH) that did not contain an anthracycline. In an interim analysis presented at the 2006 San Antonio Breast Cancer Symposium (SABCS), investigators confirmed that, at a median follow-up of 36 months, the addition of trastuzumab to chemotherapy resulted in a significantly longer survival time than with standard adjuvant chemotherapy alone for patients with HER2–positive breast cancer. A 39% longer ($p < .0001$) disease-free survival (DFS) duration for patients in the AC-TH arm and a 41% longer overall survival (OS) time ($p = .004$) were found, compared with the AC-T control arm. Similarly, a 33% longer ($p = .003$) DFS time for the nonanthracycline arm (TCH) and a 34% longer ($p = .017$) OS time were found, compared with the AC-T control arm. The difference in DFS between the two investigational arms was not considered to be statistically significant.

At the 2007 American Society of Clinical Oncology (ASCO) Annual Meeting, Paik and colleagues presented data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial suggesting that the benefit from adjuvant trastuzumab may not be confined to patients with immunohistochemistry 3+ and/or fluorescence in situ hybridization (FISH)-positive tumors. This finding further underscores the uncertainty regarding HER-2 testing and the benefits of HER-2–directed treatment [2, 3].

Mackey and colleagues conducted a study demonstrating that combined therapy with trastuzumab plus anastrozole resulted in a longer progression-free survival (PFS) time in hormone-dependent HER-2–positive metastatic breast cancer (MBC) patients compared with single-agent anastrozole. This treatment combination was chosen on the basis of the principle that the estrogen receptor (ER) and HER-2 signaling pathways interact with each other. Also, it is estimated that approximately 50% of HER-2–overexpressing breast cancer tumors are also ER positive. Therefore, targeting both of these pathways simultaneously may lead to a further advantage that is distinct and unique from giving either drug alone or in sequence [4]. Pegram and colleagues [5] reported results from an interim analysis of a phase II trial evaluating the activity of trastuzumab (4 mg/kg loading dose followed by 2 mg/kg every week) combined with bevacizumab (10 mg/kg on day 7 and then every 2 weeks) in HER-2–positive recurrent MBC patients. The rationale for that study was based on the finding that there is a strong correlation between HER-2 positivity and a high vascular endothelial growth factor (VEGF) tumor content; both factors are highly angiogenic and implicated in the aggressive phenotype of some breast cancers (see section on bevacizumab below).

At the 2007 SABCS, Fumoleau and colleagues [6] reported data from a phase II multicenter trial of pertuzumab, a monoclonal antibody that inhibits HER-2 dimerization, in combination with trastuzumab for women with HER-2–positive MBC. That study is interesting, both on the merits of the data and in the broader context of HER-2–positive breast cancer. Pertuzumab binds to a region of the extracellular domain more distal from the binding site of trastuzumab and, as a result, it is potentially better at preventing heterodimerization (see section on other polyinhibitors of ErbB family receptors below). Peacock and colleagues found that vinflunine plus trastuzumab was active and tolerable for patients with HER-2–positive MBC. Vinflunine is a new vinca alkaloid that may have some advantages over the currently available agents. This nonrandomized phase II study in patients with HER-2–positive disease reported a very high partial response (PR) rate of 47%, which is reminiscent of the single-center data from the Dana-Farber Cancer Institute initially reported for the combination of vinorelbine and trastuzumab. Vinflunine appears to be an agent that merits further study [7].

There are several reasons that unfortunately limit the widespread use of this extraordinary drug. The first is that only a small number of patients (HER-2 positive) can be treated with trastuzumab; it has no beneficial effect on the majority of patients, who are HER-2 negative. The second problem is the potential cardiotoxicity resulting from this treatment. Although a trastuzumab-related decline in left ventricular ejection fraction (LVEF) appears to be reversible, and congestive heart failure symptoms are controlled with medication in the majority of patients, those with preexisting cardiac dysfunction were automatically excluded from this trial. The long-term cardiac effects of trastuzumab are unknown, in particular in patients who are treatment sensitive.
The third dilemma concerns the duration of therapy. It is unknown whether it should be short, lasting only several weeks, or prolonged, and thus lasting months or even years. In the adjuvant setting, it is probably unnecessary for clinical benefit for patients to undergo prolonged treatment [8].

The fourth problem concerns the expense of trastuzumab treatment for the national health service, which must not be overlooked.

Finally, the fifth dilemma is to decide which patients should be treated with trastuzumab. Without a doubt, all node-positive patients should be treated, but perhaps not all node-negative patients. The key question is: who can benefit from trastuzumab? At a median follow-up of 2 years of the Herceptin® Adjuvant trial, a subset efficacy analysis indicated that the administration of trastuzumab for 1 year resulted in longer DFS and OS in all subgroups classified according to age, menopausal status, nodal status, tumor size, tumor grade, previous chemotherapy, and hormone receptor status. Those patients considered to be at low risk appeared to receive similar benefits from the addition of trastuzumab as those with larger tumors and nodal involvement.

In addition, the NSABP B-31 trial identified c-myc amplification as a predictive factor for responsiveness to trastuzumab. Those patients who exhibited c-myc amplification benefited more from trastuzumab plus chemotherapy than those who did not exhibit c-myc amplification, as demonstrated by a greater difference in the relative risk for recurrence (76% versus 37%) and death (64% versus 1%). Acquired and de novo resistance to trastuzumab is a significant clinical challenge. Most patients with HER-2-positive MBC eventually progress during treatment. Some patients with high levels of HER-2 expression do not respond to trastuzumab, indicating some degree of de novo resistance. Resistance-conferring factors might serve as targets for overcoming resistance and are under active investigation. It is uncertain whether HER-2-negative patients will benefit from this revolution. However, data are available regarding the antineoplastic activity of the antiangiogenic drug bevacizumab, the small-molecule tyrosine kinase inhibitors (TKIs) lapatinib, sorafenib, and sunitinib, and the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus, all being the focal points of our review.

LAPATINIB

Breast cancer is frequently associated with an increased expression level and activation of EGFR tyrosine kinases that are involved in the regulation of normal breast development. These receptors are not fixed in one position on the plasma membrane, and upon ligand binding to the extracellular domain, dimerization occurs. These dimers can be homodimers (i.e., two identical receptors, such as HER-1 and HER-1) or heterodimers (i.e., different receptors, such as HER-1 and HER-2). Upon ligand binding and dimerization, the intracellular cytoplasmic TK domain is activated and autophosphorylation occurs.

Lapatinib ditosylate (Tykerb®; Glaxo-SmithKline, Philadelphia) is an oral dual TKI targeting both the ErbB-1 and ErbB-2 receptors and has shown promising activity in preclinical investigations and clinical trials. Lapatinib acts intracellularly and directly targets the TK domain.

Phase I studies were developed to determine the feasibility and safety of lapatinib first in healthy human volunteers and then in cancer patients. Lapatinib was well tolerated with no severe adverse events reported.

Two phase II trials examined the efficacy of lapatinib at a dose of 1,500 mg/day in HER-2–positive MBC patients progressing while undergoing trastuzumab therapy. In a phase II trial involving 78 patients with ErbB-2–positive tumors, the overall response rate (ORR) was 8%, while 14% of patients had stable disease (SD) and 22% remained progression free after treatment with lapatinib. In the second phase II trial, the patients were divided into two cohorts based on their ErbB-2 status. Of the 140 patients in the ErbB-2–positive cohort, the ORR was 4%, with 9% of patients experiencing SD and 13% remaining progression free at 16 weeks. The 89 patients with ErbB-2–negative tumors did not respond, indicating the efficacy of lapatinib in ErbB-2–positive disease. Another phase II trial examined the efficacy of lapatinib monotherapy in the first-line treatment of ErbB-2–positive MBC or advanced breast cancer. The patients were randomly assigned to receive lapatinib at a dose of either 1,500 mg/day or 500 mg/day twice daily. RRs for both cohorts were comparable—eight of the 29 patients (28%) in the 1,500 mg/day arm versus nine of the 31 patients (29%) in the 500 mg/day twice daily arm responded. No decreases in LVEF were measured that were >20% from baseline and below the lower limit of normal, as required by the serious adverse event criteria [9, 10].

A phase II study evaluated the efficacy of lapatinib in patients with recurring or refractory inflammatory breast cancer [11]. Of the 24 patients with ErbB-2–positive tumors, 62% achieved a PR, compared with only 8% of the 12 patients with ErbB-2–negative tumors. The efficacy of lapatinib with capecitabine was examined in a phase III trial [12]. Patients with progressive HER-2–positive MBC or locally advanced breast cancer who had previously been treated with anthracyclines, taxanes, and trastuzumab, but not capecitabine, were randomized to receive capecitabine at a dose of either 2,500 mg/m² per day or 2,000 mg/m² per day plus lapatinib at a dose of 1,250 mg/day orally for 2 weeks every 3 weeks. The median time to progression...
(TTP) was significantly longer in the lapatinib plus capecitabine arm than in the capecitabine alone arm (36.9 weeks versus 19.7 weeks; hazard ratio [HR], 0.51; \( p = .00016 \)). The median PFS time was also significantly longer with lapatinib plus capecitabine (36.9 weeks versus 17.9 weeks; HR, 0.48; \( p = .000045 \)). There was a trend toward a higher ORR (22.5% versus 14%; \( p = .113 \)) as well as fewer central nervous system (CNS) metastases (4 versus 11; \( p = .110 \)) in the 160 patients receiving lapatinib plus capecitabine, compared with the 161 patients receiving only capecitabine.

Patients with ErbB-2–overexpressing breast cancer have been found to have a significantly higher risk of developing brain metastases. Lapatinib, which is 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 new or progressive brain metastases were presented at the 2006 ASCO Annual Meeting [13]. The primary endpoint was objective response in the CNS. According to the Response Evaluation Criteria in Solid Tumors (RECIST), two patients (5%) had a PR as the best CNS response and four of 16 patients (25%) with measurable disease had a PR as the best non-CNS response. Eight patients had CNS SD at 16 weeks.

In the EGF2009 study, locally advanced or MBC patients with ErbB-2 amplification (as documented by FISH) were randomized to receive lapatinib at a dose of either 1,500 mg daily or 500 mg twice daily. Eligible patients were those who had not previously received trastuzumab for metastatic disease. By independent radiology review, 35% of patients had a PR and a further 5% had an unconfirmed PR; 35% patients had SD, 12.5% had progressive disease (PD), and 12.5% were not evaluable [14, 15].

Based on in vitro results suggesting that lapatinib plus trastuzumab might be more effective than either agent alone, a phase I open-label trial was designed to study the safety, tolerability, and pharmacokinetics of lapatinib plus trastuzumab. The study showed no effect on the pharmacokinetics of either lapatinib or trastuzumab when administered in combination. An ORR of 26% was observed in 27 patients, including one patient who achieved a CR. A phase III ongoing clinical trial is comparing trastuzumab monotherapy with trastuzumab plus lapatinib combination therapy [16].

Perhaps the most eagerly anticipated data at the 2006 SABCS was the presentation of lapatinib and paclitaxel therapy in newly diagnosed inflammatory breast cancer (IBC) [17]. Twenty-five patients with IBC were treated with lapatinib at a dose of 1,500 mg/day for 2 weeks. Weekly paclitaxel was added for 12 additional weeks. After 14 weeks of therapy, patients underwent surgery. The primary endpoint was the pathological complete response (pCR) rate. Three of 21 patients had a pCR in the breast and lymph nodes, including three of 18 with HER-2–positive disease and zero of three without overexpression of HER-2. Thirty percent of the patients responded to only lapatinib by day 14, and 78% patients responded to the combination therapy. During the recent 2007 ASCO Annual Meeting, Di Leo et al. [18] presented data from a phase III randomized, double-blind study of paclitaxel (175 mg/m² every 3 weeks) plus lapatinib (1,500 mg/day) or placebo. In total, 580 MBC patients were randomized, and the primary endpoint was TTP. The addition of paclitaxel to lapatinib resulted in a greater ORR (35% versus 25.3%; \( p = .008 \)), but the TTP, event-free survival time, and OS time were not affected (except in HER-2–positive advanced breast cancer). The combination was associated with greater toxicity (mucositis, diarrhea, vomiting, and rash) and a higher death rate resulting from serious adverse events, possibly related to the pharmacokinetic interaction between these agents [18].

Lapatinib is also a potentially ideal therapy for the adjuvant treatment of breast cancer.

In conclusion, lapatinib is an active and well-tolerated oral dual TKI for the treatment of breast cancer. The clinical efficacy of lapatinib is limited to only the treatment of ErbB-2–overexpressing breast cancer. Lapatinib is active in refractory MBC patients and as a first-line metastatic treatment with potential benefits in patients with brain metastases. Lapatinib appears to have either a very low incidence of or no cardiotoxicity. The most frequently reported adverse events of grade 1 or 2 severity include nausea, fatigue, itching, rash, diarrhea, acne, and dry skin. However, grade 3 and 4 toxicities are rare.

**BEVACIZUMAB**

The addition of anti-VEGF therapy to chemotherapy has proven to be beneficial, principally in first-line therapeutic regimens, especially 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. One of the most important functions of VEGF is the induction of vascular permeability, which plays an essential role in angiogenesis. One anti-VEGF agent is bevacizumab, a humanized monoclonal antibody (93% human and 7% mouse) that binds to the VEGF family member VEGF-A, reducing the availability of the VEGF ligand for VEGF receptor (VEGFR)-1 and VEGFR-2, and thereby preventing receptor activation. Clinical trial findings suggest that a synergistic interaction may occur between chemotherapy and bevacizumab. A potential mechanism is the “normal-
ization” hypothesis pioneered by Jain and colleagues [19]. This hypothesis suggests that anti-VEGF agents can cause a transient vasoconstriction of the large aberrant blood vessels in tumors, which may improve blood flow and decrease hypoxia within the tumor. Better blood flow then allows for better delivery of chemotherapeutic agents, which could help explain the synergistic effect between anti-VEGF therapy and chemotherapy. A straightforward explanation is that anti-VEGF therapy is indeed antiangiogenic or cytostatic, as was originally proposed.

The initial phase I–II trial of bevacizumab in breast cancer consisted of a single-agent dose-escalation study in 75 patients with previously treated MBC [20]. Patients received bevacizumab in doses of 3 mg/kg, 10 mg/kg, or 20 mg/kg administered every 2 weeks. The ORR at the 10-mg/kg dose (n = 41) was 12%, including two patients with a CR.

Results of a phase I trial with the combination of anti-HER-2 and anti-VEGF monoclonal antibodies (trastuzumab and bevacizumab) presented at the 2004 SABCS indicated a potentially enhanced anticancer effect with the combination, without influencing the pharmacokinetics of either agent [21]. Based on these results, a phase II trial, subsequently presented at the 2006 SABCS, was conducted by Pegram and colleagues using this combination without chemotherapy for patients with recurrent or metastatic HER-2–positive advanced breast cancer [5]. That study included 37 patients who were chemotherapy-naïve in the metastatic setting. The overall clinical response rate was 54%.

Based on these preliminary data, a phase III randomized trial was undertaken to evaluate bevacizumab in women with heavily pretreated MBC. In total, 462 patients were randomized to receive bevacizumab (15 mg/kg every 3 weeks) plus capecitabine or only capecitabine [22]. The primary endpoint of that trial, PFS, was statistically identical throughout the entire dose range of bevacizumab (4.2 versus 4.9 months; p = 0.001).

N0432 was a phase II trial that enrolled 45 chemotherapy-naïve patients with MBC in the metastatic setting (63% had visceral disease). Patients were treated with docetaxel (75 mg/m²) and bevacizumab (15 mg/kg) on day 1 and capecitabine (825 mg/m²) on days 1–14 [23]. A recent randomized phase III trial compared bevacizumab and paclitaxel with paclitaxel alone as a first-line therapy in patients with MBC [24]. The primary endpoint was PFS; the ORR and OS time were also evaluated. Patients on the bevacizumab and paclitaxel arm achieved a longer PFS duration (11.4 versus 6.11 months; p < .0001) and greater ORR (30% versus 14%; p < .0001) than those who received only paclitaxel. However, there is no significant difference in OS at this time, although the data do indicate a trend toward a survival benefit in patients who received bevacizumab and paclitaxel (28.4 months versus 25.2 months; p = .12).

In conclusion, anti-VEGF therapy is known to have a dynamic and multifactorial effect on the vasculature. However, several questions remain to be answered. One clinically relevant question is whether or not 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. Furthermore, the intuitive predictive markers, VEGF levels in the tumor and blood and VEGFR expression in the tumor, do not correlate with response to anti-VEGF therapy. Thus, research must continue to determine which patients will benefit the most and to find ways of optimizing the therapy.

**ORAL VEGF TKIs**

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

**Sunitinib**

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 at a dose of 50 mg/day orally for 4 weeks of a 6-week cycle. A PR was achieved by seven patients (11%), and an additional three patients (5%) had SD for ≥6 months, for an overall clinical benefit rate of 16%.

**Sorafenib**

Sorafenib is an oral TKI that inhibits the tyrosine kinase activity of Raf kinase (Raf-1, wildtype B-Raf, and B-Raf V600E), VEGFR, and PDGFR, potentially enabling the simultaneous blockade of tumor cell proliferation and angiogenesis as well as potentiating tumor apoptosis. In a phase II study of sorafenib in 54 patients with MBC, a PR rate of 2% was achieved, and SD was observed in 37% of patients with prolonged SD at 4 and 6 months (22% and 11%, respectively). These findings reflect those obtained in renal cancer, for which SD was the main finding of the Tamoxifen and Arimidex® Randomized Group Efficacy and Tolerability phase III trial. This probably means that these multikinase inhibitors modify the biology and growth rate of cancer instead of reducing tumor mass.
was longer with axitinib (9 versus 6.3 months; \( p = 0.038 \)) and even TTP was longer with axitinib (9 versus 6.3 months; \( p = 0.012 \)). In a first-line combination this antiangiogenic drug has an acceptable safety profile and promising antitumor activity [25–29].

**Small-Molecule EGFR TKIs**

**Gefitinib**

Gefitinib (Iressa®; AstraZeneca, Wilmington, DE) is an orally active, selective EGFR TKI that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells.

In a phase II trial of gefitinib monotherapy (500 mg/day) in advanced pretreated breast cancer patients, there was no significant clinical activity despite EGFR inhibition in skin and breast tissue [30]. A similar experience was published by von Minckwitz et al. [31] with no responses in 58 metastatic patients. Gefitinib in combination with other drugs was tested in phase I–II nonrandomized trials. Thirty-three patients were treated with paclitaxel plus two different schedules of gefitinib. Good antitumor activity (RR, 62.5% and 41.2% in the two groups) was noted. In the same way, the first-line combination with docetaxel (75 or 100 mg/m^2^) in 41 patients showed an RR of 54% [32, 33]. The contribution of gefitinib, if any, is not quantifiable in the absence of a taxane-only arm.

**Erlotinib**

Erlotinib (Tarceva®; Genentech, Inc., South San Francisco, CA) is a small molecule that reversibly and selectively inhibits the intracellular autophosphorylation of TKs in association with the EGFR. A phase I study of dose-escalated erlotinib in combination with standard-dose trastuzumab was presented at the 2004 ASCO Annual Meeting. The combination demonstrated activity and the recommended dose was 150 mg/day [34]. The erlotinib and bevacizumab combination was tested in 13 previously treated patients. In that phase II study, one response in nine evaluable patients was obtained [35].

Shortly thereafter, the combination of erlotinib with chemotherapy was used. A combination with weekly docetaxel as first-line treatment resulted in an RR of 55%. The nonrandomized nature of the study once more does not clarify the added value regarding the antineoplastic activity of erlotinib [36].

**mTOR Inhibitors**

mTOR is a protein that regulates two downstream proteins, P70 S6 kinase and eukaryotic translation initiation factor 4E binding protein 1, both of which play key roles in the ability of cells to produce proteins. In fact, the first mTOR inhibitor to be studied in the treatment of cancer was not rapamycin, but its analogue, temsirolimus (Torisel®; Wyeth Pharmaceuticals, Inc., Madison, NJ). There are two other mTOR-inhibiting compounds, although they are not prodrugs of rapamycin: everolimus (Certican®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) and deforolimus (AP23573; ARIAD Pharmaceuticals Inc., Cambridge, MA). In 14 European institutions, 109 women with previously treated locally advanced breast cancer or MBC were enrolled in a phase II study. Patients were randomized to receive i.v. temsirolimus weekly at a dose level of 75 mg or 250 mg. Clinical benefit for at least 24 weeks (per the RECIST) was observed in 13.8% of patients: 10 PRs and no CR were registered, for an RR of 9.2%.

A phase II study of temsirolimus combined with letrozole was presented at the 2005 ASCO Annual Meeting. Patients with measurable MBC were randomized (approximately 30 evaluable patients per arm) in a 1:1:1 ratio: letrozole alone or letrozole with temsirolimus daily (the daily arm) or temsirolimus daily for 5 days every 2 weeks (the intermittent arm). All patients received 2.5 mg letrozole...
daily. Data collected by November 15, 2004 were presented for the 92 patients enrolled after the amendment (temsirolimus daily, 33; temsirolimus intermittent, 30; letrozole alone, 29). The clinical benefit (CR + PR + SD ≥8 weeks) rates were 82%, 83%, and 79%, respectively. The median PFS duration has been reached for the letrozole alone arm (9.2 months) but not for the combination arms. Early data suggest that PFS may be longer for the combination arms than for the letrozole alone arm. An actively recruiting phase III study is ongoing. The potential for use of everolimus in cancer comes from its antiproliferative and antiangiogenic activities. Strikingly, although preclinical everolimus shows significant single-agent activity, it is becoming clear that this agent may be of greater benefit as a combination partner for other drugs. The safety and pharmacokinetics of combined treatment with letrozole (2.5 mg/day) and everolimus at 5 mg/day or 10 mg/day were examined in 18 breast cancer patients who had not experienced an objective response to letrozole alone after at least 4 months. In total, 16 patients were included in the efficacy evaluation. One CR occurred in the 10-mg everolimus cohort, and there were no PRs. Hence, there was evidence of a more profound antitumor effect as a result of adding everolimus to the treatment regimen, reflecting the preclinical observations. Based on these results, a dose of 10 mg/day everolimus has been recommended for further trials.

Ongoing clinical trials tempting to integrate mTOR inhibitors into standard practice will give us new information about the future of these molecules and the optimal integration of mTOR inhibitors into clinical practice [37–39].

OTHER POLYNHIBITORS OF ERBB FAMILY RECEPTORS

Other new agents (dual targeting) have been introduced in numerous studies with the aim of blocking both HER-1 and HER-2 receptors.

Pertuzumab, for example, is a fully recombinant humanized monoclonal antibody that binds to the HER-2 receptor at domain II, sterically blocking heterodimerization of HER-2 with EGFR and ErbB-3, thereby inhibiting intracellular signaling. A phase I study showed activity in prostate, ovarian, and islet cell cancers, moving on to various phase II studies. In breast cancer, a randomized phase II study testing two different doses of pertuzumab was presented at the 2005 ASCO Annual Meeting. In that study, the primary endpoint was the RR. Seventy-nine anthracycline-pre-treated patients with low HER-2 expression levels entered the study. Six of 78 patients in the intent to treat population responded or had SD for >6 months. The monoclonal antibody pertuzumab administered i.v. every 3 weeks is safe and well tolerated, but there was evidence of limited activity in this study [40]. Interesting results were obtained with pertuzumab combined with trastuzumab after progression on combination therapy with the latter (up to three lines of trastuzumab combination therapy were permitted). Fumoleau et al. [6] at the 2007 SABCS presented data on the combination of pertuzumab (420 mg every 3 weeks after a loading dose of 840 mg) with trastuzumab weekly (2 mg/kg every week or 6 mg/kg every 3 weeks). The confirmed PR and CR rate was 18%. Only one patient had a decrease in LVEF to <50% and >10%. The main adverse events were diarrhea, fatigue, nausea, vomiting, and rash, but most were mild to moderate (only one case of grade 3 diarrhea, rash, and thrombosis) [6].

ANTI-EGFR MONOCLONAL ANTIBODY

Cetuximab (Erbitux®, Merck & Co., Inc., Whitehouse Station, NJ) is a human–mouse chimeric monoclonal antibody that competitively binds to the accessible extracellular domain of the EGFR to inhibit dimerization and, subsequently, inhibit tumor growth and metastasis.

Preclinical studies have indicated a synergistic effect for the combination of anti-EGFR therapy plus paclitaxel in breast cancer models. A dose-escalation phase I trial using cetuximab plus paclitaxel was conducted in patients with MBC to evaluate the feasibility of this combination. Treatment consisted of weekly cetuximab therapy and every-3-weeks paclitaxel, with dose escalation of cetuximab until the maximum-tolerated dose was reached. Twelve patients were enrolled to three treatment cohorts. Unfortunately, because of prohibitive dermatologic toxicity and disappointing preliminary efficacy, the combination of paclitaxel plus cetuximab was not considered promising in this population, although further study of this regimen might be warranted [41].

At the 2007 SABCS, Carey et al. [42] presented data on cetuximab in triple-negative advanced breast cancer. Eligible patients had measurable MBC, three or fewer prior chemotherapies, and no prior platinum or EGFR inhibitor. Patients randomized to arm 1 received cetuximab alone (400 mg/m², then 250 mg/m² weekly) with carboplatin (area under the concentration–time curve [AUC], 2, weekly, 3 of 4 weeks) added upon PD. Patients in arm 2 received cetuximab plus carboplatin throughout. The primary endpoint was objective response (RR = CR + PR). The authors concluded that cetuximab alone was well tolerated but had a low single-agent RR (PR, 4%), and so failed the criteria for ongoing study. Rapid progression in this population may have limited the evaluation of efficacy. The cetuximab plus carboplatin arm is ongoing, expecting completion during 2007 [42].

During the same meeting, O’Shaughnessy and col-
leagues showed data for cetuximab in combination with carboplatin and irinotecan in MBC patients. One hundred sixty-three patients with measurable disease were randomly assigned to either irinotecan (90 mg/m²) followed by carboplatin (AUC, 2) on days 1 and 8 of each 21-day cycle (arm 1) or the same treatment except with cetuximab at a dose of 400 mg/m² i.v. for dose 1 then 250 mg/m² weekly thereafter (arm 2). The preliminary assessment suggested that the addition of cetuximab to chemotherapy may improve antitumor activity (RR, 19% versus 39%) but is associated with greater toxicity [43].

Panitumumab is a fully humanized IgG2 monoclonal antibody that binds EGFR with high affinity and blocks binding of EGF and transforming growth factor α, inhibiting EGF-dependent tumor cell activation and proliferation. Panitumumab causes cell cycle arrest at the G0–G1 interphase in vitro and inhibits tumor colony formation. Blocking EGFR and using xenograft models, panitumumab was shown to be active against several human solid tumors derived from different tissues. These include tumors from the breast (MDA-468), pancreas (BxPC-3 and HS766T), prostate (PC-3), kidney (SK-RK-29), ovary (IGROVI), and colon (HT-29). Up to today no clinical trial with this agent has been developed or is recruiting patients in breast cancer.

CONCLUSION

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

But, inevitably, alongside the benefits there are many dilemmas that are in search of an answer: What combination of drugs should be used and in which sequence? What are the therapeutic targets and how should response be evaluated? And last, but not least, with what resources? It is of the utmost importance to have well-designed and serious trials with solid biological rationale at a time when much pressure is being exerted by pharmaceutical companies. This can prevent the rejection of a drug, classified as being useless or inactive, simply because it was not used correctly and not administered to the correct patient.

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