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REVIEW

An Overview of HER-Targeted Therapy with Lapatinib in Breast Cancer

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ABSTRACT

Breast cancer is a global public health burden with more than one million new diagnoses worldwide each year. As a significant proportion of women with early-stage breast cancer experience a relapse and metastatic breast cancer is generally incurable, therapeutic innovations are ongoing. One notable innovation in recent decades has been the identification of a subset of breast cancers that overexpress the transmembrane glycoprotein human epidermal growth factor receptor 2 (HER2) and the consequent development of HER2-targeted therapy. Given the significant benefits demonstrated with the HER2-targeted monoclonal antibody, trastuzumab, in the adjuvant and metastatic settings, investigators have endeavored to develop novel mechanisms for disrupting HER2-mediated signaling. Lapatinib, an orally available HER1- and HER2-targeted tyrosine kinase inhibitor, represents one such notable innovation. Lapatinib is currently being evaluated in both the adjuvant and metastatic settings and was recently approved by the United States Food and Drug Administration in combination with capecitabine, for the treatment of women with HER2-positive, pretreated, metastatic breast cancer. However, the ideal strategy for incorporating novel HER2-targeted agents, including lapatinib, into existing management paradigms is uncertain.

Keywords: HER2; human epidermal growth factor receptor 2; lapatinib; trastuzumab; tyrosine kinase inhibitor

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INTRODUCTION

Breast cancer is a global public health burden with more than one million new cases diagnosed worldwide each year.[1] Although most new breast cancer diagnoses in developed countries are early-stage disease, approximately one-third of women will experience a distant relapse despite definitive locoregional and systemic therapy.[1] Once distant

metastases have occurred, breast cancer is generally incurable with a median survival of only 2 to 3 years.[1] Consequently, investigators strive to improve disease-specific outcomes through therapeutic innovation. The detection of a specific subtype of breast cancer, namely human epidermal growth factor receptor 2 (HER2)-positive breast cancer, and the subsequent development of HER2-targeted therapy, represents a significant recent innovation in breast cancer management. HER2, a transmembrane glycoprotein with tyrosine kinase activity, is overexpressed in approximately 20%-25% of human breast cancers and has historically been associated with a poor prognosis compared with HER2-normal breast cancers.[2-4] However, the prognostic impact of HER2 status has been largely ameliorated with the advent of so-called "targeted therapy," whereby the unique biologic features of specific cancer cells that participate in carcinogenesis are pharmacologically exploited. Perhaps the most notable example of targeted therapy in breast cancer to date has been the development of trastuzumab, a humanized, HER2-directed monoclonal antibody. Trastuzumab has demonstrated significant survival benefits in both the adjuvant[5,6] and metastatic settings.[7] Yet, because a significant proportion of women with HER2-positive early-stage breast cancer experience a recurrence despite adjuvant trastuzumab[5,6] and because a significant proportion of women with HER2-positive metastatic breast cancer (MBC) experience disease progression on trastuzumab,[7-9] investigators strive to identify alternative mechanisms for disrupting HER2-mediated signaling. Lapatinib, a tyrosine kinase inhibitor with specificity for the HER1 and HER2 receptors, represents one such therapeutic innovation, with promising activity demonstrated in preliminary reports.[10-22] The clinical impact of targeted therapy with lapatinib in HER2-positive breast cancer will be reviewed here.

LAPATINIB MECHANISM OF ACTION

The human epidermal growth factor receptor family is comprised of four transmembrane receptors (HER1, HER2, HER3, and HER4) that are known to mediate angiogenesis, growth factor signaling, proliferation, and metastasis.[10] Each of the four receptors is comprised of a transmembrane segment, an extracellular binding domain, and with the exception of HER3, an intra-cellular tyrosine kinase domain. Homo- and heterodimerization of these receptors induce tyrosine kinase activation via autophosphorylation, downstream signal transduction, and ultimately angiogenesis, growth factor signaling, proliferation, and metastasis. As tyrosine kinases are known to mediate the signal transduction cascades that promote cellular proliferation and survival, inhibitors of HER2-mediated tyrosine kinase activity in women with HER2-positive breast cancer represent an active area of investigation.

Lapatinib is an oral, small molecule, dual tyrosine kinase inhibitor with specificity for HER1 and HER2 that has demonstrated significant preclinical and clinical activity.[10-22] There is a growing body of preclinical evidence indicating that lapatinib exerts its antitumor effects by inducing growth arrest and/or apoptosis, as well as blocking downstream MAPK and Akt signaling pathways.[11] Furthermore, cell line models indicate that the ability of lapatinib to specifically inhibit trastuzumab-resistant cell growth may reflect its inhibitory effects on insulin-like growth factor-1 signaling.[12] As a result of these dis-

tinct features, lapatinib represents a promising therapeutic innovation for the treatment of both trastuzumab-naïve and trastuzumab-resistant HER2-positive breast cancer.

PHASE 1 CLINICAL STUDIES OF LAPATINIB

In 2005, the first phase 1 study of lapatinib monotherapy was reported.[10] In this study, 67 patients with heavily pretreated HER1-expressing and/or HER2-overexpressing advanced-stage refractory solid tumors were randomized to one of five lapatinib dose cohorts ranging from 500 to 1600 mg daily.[10] The most frequently reported adverse events in this study were diarrhea (42%) and rash (31%), with no grade 4 drug-related adverse events reported. Interestingly, of the four observed partial responses in this study, all had trastuzumab-resistant MBC.

The foundation for the phase 3 study, which led to United States Food and Drug Administration (FDA) approval of lapatinib in combination with capecitabine,[13] was established with the reporting of a phase 1 study evaluating this combination in 45 patients with advanced solid tumors.[14] In this phase 1 study, oral lapatinib was administered continuously once daily. Oral capecitabine was administered twice daily for 14 days every 21-day cycle. The doses of lapatinib and capecitabine were escalated based on dose-limiting toxicities in the first treatment cycle or until the optimally tolerated regimen (OTR) was established. The reported OTR in this study was lapatinib at 1250 mg daily and capecitabine at 2000 mg/m^2 daily. Similar to the lapatinib monotherapy phase 1 study, two of the most common drug-related adverse events were diarrhea and rash, although adverse events typically associated with capecitabine administration (including nausea/vomiting, palmar-plantar erythrodysesthesia, mucositis, and stomatitis) were also frequently observed. There were no grade 4 drug-related adverse events reported in this study.

Based on preclinical evidence for synergy with lapatinib in combination with trastuzumab, a phase 1 study of the combination was undertaken in 54 patients with advanced HER2-positive breast cancer.[15] A dose escalation design of continuous once-daily lapatinib at doses ranging from 750 to 1500 mg with conventionally dosed trastuzumab (4 mg/kg loading dose followed by weekly doses of 2 mg/kg) was implemented. The OTR was determined from the first cohort of 27 patients, and pharmacokinetic studies were performed in the second cohort of 27 patients. No grade 4 drug-related adverse events were reported. The most frequently reported grade 3 adverse events were diarrhea, fatigue, and rash. The reported OTR was 1000 mg lapatinib daily in combination with conventionally dosed weekly trastuzumab. A complete response was observed in one patient and confirmed partial responses of 56 to 266 days in duration were observed in seven patients. Thus, the authors concluded that at the OTR, the combination was well tolerated and demonstrated clinical activity in this heavily pretreated population of women with HER2-positive advanced breast cancer. Results of phase 2 studies of the combination are anticipated.

PHASE 2 CLINICIAL STUDIES OF LAPATINIB

Several phase 2 studies evaluating lapatinib monotherapy in MBC have recently been reported. In study EGF20002, 78 women with HER2-positive MBC who had experi-

enced disease progression on first- or second-line trastuzumab were treated with lapatinib at 1500 mg daily.[16] The overall response rate was 8% and the 15-week progression-free survival rate was 22%. In study EGF20008, 140 women with HER2-positive MBC and a history of disease progression on anthracycline-, taxane-, capecitabine- and trastuzumab-containing regimens, were enrolled and treated with lapatinib.[17] As lapatinib has specificity for both HER1 and HER2, 89 women with HER2-normal, anthracycline-, taxane-, and capecitabine-resistant MBC were also included. Lapatinib was administered at 1500 mg daily. The investigators reported no objective responses for the HER2-normal population and a response rate of 4.3% for the HER2-positive population. However, the response rate for the HER2-positive population was significantly less on independent assessment at 1.4%. Therefore, one may conclude that the activity of single-agent lapatinib in EGF20008 was modest, at best, for the HER2-positive subset, as might be expected in such a heavily pretreated population.

In a randomized phase 2 study, EGF20009, first-line oral lapatinib at either 1500 mg daily or 500 mg twice daily was evaluated in 138 women with advanced or metastatic HER2-positive breast cancer.[18] In this study, women with stable central nervous system (CNS) metastases were included, but women with bone-limited disease were excluded. Although none of the enrolled patients ultimately received prior trastuzumab, the eligibility criteria stipulated that patients were permitted to receive prior adjuvant trastuzumab more than 12 months before study entry. No significant differences were detected between the study arms for objective response rate (1500 mg once daily, 22%; 500 mg twice daily, 26%; P=0.691), clinical benefit rate (1500 mg once daily, 29%; 500 mg twice daily, 33%; P=0.714), median duration of response (1500 mg once daily, 27.6 weeks; 500 mg twice daily, 29 weeks), or 6-month progression-free survival (1500 mg once daily, 41%; 500 mg twice daily, 45%). Furthermore, no significant differences in toxicity rates were observed between the two arms, with diarrhea (46%) and rash (32%) most frequently reported. The authors concluded that further studies of lapatinib in the adjuvant and first-line metastatic settings were warranted for women with HER2-positive breast cancer.

Although cross-study comparisons are not recommended, it is notable that the response rates reported with first-line lapatinib monotherapy are similar to those reported with first-line trastuzumab monotherapy in trastuzumab-naïve patient populations.[8,9] This observation suggests that lapatinib may represent an alternative, potentially equally efficacious mechanism for disrupting HER2-mediated signaling. However, because in developed countries adjuvant trastuzumab is administered to most women with HER2-positive early-stage breast cancer, it is unlikely that a head-to-head study of first-line lapatinib versus trastuzumab in HER2-therapy-naïve patients will be feasible. Nevertheless, it is anticipated that the ongoing adjuvant studies will provide further insights.

PIVOTAL STUDIES WITH LAPATINIB IN MBC

The clinical success with HER2-targeted therapy with trastuzumab, the biologic underpinnings for dual tyrosine kinase inhibition, the emerging evidence for trastuzumab resistance, and the growing preclinical and clinical evidence provided a strong foundation for the evaluation of lapatinib in ran-

domized, phase 3 studies. In one of these studies, women with HER2-positive advanced or MBC that progressed despite prior therapy including trastuzumab were randomized to receive either capecitabine alone or in combination with lapatinib.[13] Capecitabine was administered alone at 2500 mg/m²/day on days 1-14 every 21 days or at 2000 mg/m²/day on days 1-14 every 21 days in combination with continuous lapatinib at 1250 mg once daily. Therefore, it is important to remember that the interpretability of the study results are somewhat confounded by the introduction of two variables, namely the administration of lapatinib versus not, and different capecitabine doses in each of the study arms. Furthermore, although enrollment of 528 women was planned, enrollment was discontinued after the reporting of a prespecified interim analysis of 324 patients. At the time of the interim analysis, the primary endpoint of median time to progression was 27.1 versus 18.6 weeks (HR 0.57, *P*=0.00013) and the objective response rate was 22% versus 14% (*P*=0.09) in favor of the combination by independent review. Although no survival benefits were reported, these results confirmed that despite disease progression on prior HER2-targeted therapy, the HER2 pathway could still be effectively targeted. At a recent study update with data from 399 enrolled women, a significant improvement in time to progression from 4.3 to 6.2 months (HR 0.57, *P*=0.001) and a nonsignificant trend toward a survival benefit (HR 0.78, *P*=0.177) in favor of the combination were reported.[19] Based on the results of this study, in 2007 the US FDA granted approval to lapatinib in a once-daily dose of 1250 mg for use in combination with capecitabine for the treatment of patients with advanced or metastatic anthracycline-, taxane-, and trastuzumab-pretreated HER2-positive breast cancer. At present, the combination of capecitabine and lapatinib is the only US FDA-approved therapy for the treatment of trastuzumab-refractory HER2-positive MBC.

However, it is notable that the treatment paradigm for patients with HER2-positive, trastuzumab-refractory MBC has recently been further complicated by the reporting of a randomized phase 3 study of capecitabine versus capecitabine plus trastuzumab in this setting.[23] In this study, patients were randomized to capecitabine at 2500 mg/m² on days 1-14 every 21 days with or without trastuzumab administered at 6 mg/kg every 21 days after disease progression on an adjuvant or first-line metastatic trastuzumab-based regimen. Despite an accrual goal of 482 patients, enrollment was stopped early on the recommendation of an independent data monitoring committee after the US FDA registration of lapatinib. For the 156 enrolled patients, the addition of trastuzumab to capecitabine was associated with a significant improvement in the primary endpoint of time to progression from 5.6 to 8.2 months (HR 0.69, *P*=0.034) after a median 15.6-month follow-up period. A nonsignificant trend toward a survival benefit from 20.4 to 25.5 months (HR 0.76, *P*=0.26) was also reported. Therefore, this study provided the first and only evidence to date for a common clinical practice, namely continuation of trastuzumab beyond disease progression in MBC.

In the absence of a head-to-head trial of lapatinib versus trastuzumab in trastuzumab-resistant breast cancer, the optimal strategy for managing these patients remains uncertain. Although many clinicians will continue to favor a trastuzumab continuation strategy given the relatively favorable associated safety and tolerability profile, forthcoming results

from an adjuvant study of trastuzumab alone, lapatinib alone, or the combination, may ultimately influence this practice.[24]

As lapatinib targets both the HER1 and HER2 receptors, it was hypothesized that the benefits of lapatinib therapy may not be confined to HER2-positive patients. In a phase 3 study, first-line paclitaxel (175 mg/m^2 i.v. every 3 weeks) was evaluated in combination with lapatinib (1500 mg daily) or placebo in women with HER2-negative and HER2-uncharacterized MBC.[20] HER2 status was retrospectively determined by immunohistochemistry and fluorescent in-situ hybridization in a pre-planned analysis. Overall, no significant differences were observed in time to progression (29 vs. 22.9 weeks for paclitaxel with or without lapatinib, respectively; *P*=0.142) or survival (99.1 vs. 87 weeks for paclitaxel with or without lapatinib, respectively; *P*=0.216) between the two arms. But when evaluated by HER2 status, the 86 HER2-positive patients demonstrated statistically significant improvements in time to progression (36.4 vs. 25.1 weeks, *P*=0.005) and response rate (63.3% vs. 37.8%, *P*=0.023) in favor of the lapatinib-containing regimen. However, superiority was not observed for time to progression (24 vs. 25.1 weeks, *P*=0.662) or response rate (23.5% vs. 30.2%, *P*=0.128) with either paclitaxel alone or in combination with lapatinib, respectively, in the HER2-negative cohort. These data are consistent with several other studies that have indicated that the benefits of HER2-targeted therapy are likely confined to women with HER2-positive breast cancer.[17,25] However, it is important to note that accurate HER2 status determination remains an ongoing clinical challenge.

Lapatinib may also have a unique role to play in the prevention and treatment of HER2-positive CNS metastases, which occur in approximately 30% of women with HER2-positive MBC.[26] Historically, it has been clinically challenging to effectively treat CNS metastases due, in part, to the limited ability of most drugs to penetrate this "sanctuary site." Lapatinib does not appear to cross the intact blood-brain barrier to significant degrees in preclinical models, but it may penetrate a permissive blood-tumor barrier.[27] For example, in the phase 3 study of capecitabine with or without lapatinib it was notable that fewer cases of CNS involvement were observed at first progression with the combination (2% vs. 6%, respectively; *P*=0.045).[13] In a recently reported phase 2 study, 39 trastuzumab-pretreated patients with CNS metastases were treated with lapatinib at 750 mg twice daily after cranial radiotherapy.[21] As one might expect after treatment with cranial radiotherapy, a modest objective response rate, with no complete responses and one partial response, was reported. Although notably, seven patients (18%) had stable CNS and non-CNS disease at 16 weeks. Thus, it is likely that lapatinib has a unique role to play in the prevention and management of HER2-positive CNS metastases.

ADJUVANT STUDIES

Given the promising activity demonstrated in the metastatic setting, several adjuvant studies of lapatinib-containing regimens were warranted. At present, the highly anticipated Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) study is underway.[24] In this large, international, phase 3 study, women with operable HER2-positive breast cancer are being randomized to conventional chemotherapy with trastuzumab alone, lapatinib alone, or a combination of the two. It is anticipated that this study will

provide important insights into the efficacy and tolerability of single-agent versus combined therapy with trastuzumab and/or lapatinib. It is hoped these results will not only refine the treatment algorithm for women with HER2-positive early-stage breast cancer, but will also provide some head-to-head trastuzumab-lapatinib data, which, in turn, might be extrapolated to refine MBC treatment recommendations.

ADVERSE EVENTS

When novel agents are being evaluated, the documentation of related adverse events is critical. Whether lapatinib would demonstrate significant cardiac toxicity beyond trastuzumab-associated incidence rates[5,6,28,29] when administered alone or in combination with other agents was uncertain. Consequently, many lapatinib studies have incorporated stringent cardiac monitoring strategies. Although safety analyses are ongoing, the recent reporting of preliminary cardiac data from clinical trials of lapatinib and trastuzumab coadministration in the metastatic setting has provided some reassurance. Specifically, in a pooled analysis of data from four early-phase clinical studies, the cardiac event rate with lapatinib and trastuzumab coadministration did not exceed the incidence rates typically associated with trastuzumab administration.[30] Although investigators and clinicians may be reassured by study event rates that prove lower than anticipated, investigators are occasionally faced with unexpected adverse events or adverse event rates. For example, in a recent phase 2 study of adjuvant adriamycin/cyclophosphamide (AC) administered every 2 weeks, followed by weekly paclitaxel with concurrent trastuzumab-lapatinib followed by maintenance trastuzumab-lapatinib, the rate of diarrhea, a well-documented sequela of lapatinib therapy, proved unacceptable, and the study was ultimately terminated early.[22] In another notable example, paclitaxel and lapatinib coadministration was associated with a 2.7% incidence of fatal adverse events versus 0.6% with paclitaxel alone in a phase 3 study of women with MBC.[20] Most of these fatal events occurred early with the incidence declining markedly with time. Many of these fatal events were ascribed to diarrhea-associated sepsis, and the observed marked decline ascribed to the introduction of guidelines for the management of lapatinib-related diarrhea. Whether pharmacokinetic interactions between paclitaxel and lapatinib contributed to the unexpected fatal adverse event rate is uncertain. But, as a consequence of these early reports, it is likely that many of the ongoing adjuvant lapatinib trials will be modified accordingly. Thus, as investigators continue to strive for therapeutic innovation, vigilance in adverse event reporting, and thus, patient safety, remains paramount.

CONCLUSIONS

Lapatinib is an exciting new agent in the therapeutic arsenal against HER2-positive breast cancer. Although data from head-to-head studies of lapatinib and trastuzumab are not available, and although cross-study comparisons should be discouraged, it is notable that when administered as monotherapy in the first-line MBC setting, lapatinib demonstrated similar responses to those observed with trastuzumab in trastuzumab-naïve patient populations. However, now that trastuzumab is broadly accepted as a standard component of the management strategy for women with HER2-positive breast cancer, the optimal strategy for incorporating lapatinib into mod-

ern treatment paradigms is uncertain. In the coming years, studies evaluating lapatinib in combination with other cytotoxic agents and targeted therapies in the adjuvant, neoadjuvant, and metastatic settings are anticipated. It is hoped that the results from the highly anticipated adjuvant ALTTO study, which is evaluating adjuvant chemotherapy with lapatinib, trastuzumab, or the combination, will provide some granularity on outstanding questions about superiority. However, it is also anticipated that the HER2 management paradigm will become increasingly complex as novel agents, including several tyrosine kinase inhibitors, a second monoclonal antibody, several heat shock protein 90 inhibitors, and at least one linked antibody-chemotherapy agent are being investigated. In the interim, the activity demonstrated with lapatinib-containing regimens in trastuzumab-resistant HER2-positive MBC, has not only provided the much-needed reassurance to clinicians and their patients that HER2-mediated signaling may be effectively targeted after disease progression on trastuzumab, but also justified ongoing active investigation in this area. In addition, small molecules, such as lapatinib, may represent new opportunities for effectively treating HER2-positive CNS metastases, which have historically proven resistant to systemic therapy. It is also hoped that improvements in HER2 status determination will enable clinicians to tailor recommendations regarding HER2-targeted therapies to the women most likely to derive benefit. Thus, as identification and treatment strategies undergo further refinements, it is anticipated that the clinical management of women with HER2-positive breast cancer will continue to improve, and it is hoped that these improvements will translate into further survival benefits in both the adjuvant and metastatic settings.

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