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Dual Kinase Inhibition in the Treatment of Breast Cancer: Initial Experience with the EGFR/ErbB-2 Inhibitor Lapatinib

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Key Words. *EGFR · Tyrosine kinase inhibitor · Quinazoline · Paclitaxel · Letrozole · Capecitabine · Trastuzumab · HER-2*

LEARNING OBJECTIVES

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

1. Identify the rationale for the development of dual ErbB receptor inhibitors.
2. Describe safety data from early-phase clinical trials of the dual EGFR/ErbB-2 tyrosine kinase inhibitor lapatinib.
3. Describe evidence of biologic and clinical activity from early-phase clinical trials of the dual EGFR/ErbB-2 tyrosine kinase inhibitor lapatinib.

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ABSTRACT

Dual inhibition of ErbB-1 (EGFR) and ErbB-2 (HER-2) tyrosine kinases has been found to exert greater biologic effects in the inhibition of signaling pathways promoting cancer cell proliferation and survival than inhibition of either receptor alone. The novel dual EGFR/ErbB-2 tyrosine kinase inhibitor lapatinib (GlaxoSmithKline; Research Triangle Park, NC) has been shown to inhibit tumor cell growth in vitro and in xenograft models for a variety of human tumors. Preliminary findings in a phase I study of lapatinib in patients with solid tumors indicate doses up to 1,800 mg per day are well tolerated. No grade 4 toxicities were observed and only two of 43 patients had grade 3 toxicity (diarrhea). Clinical activity of lapatinib was observed in these patients; nine patients with a variety of tumors remained on study for ≥4 months, one with a complete response (head and neck cancer). In a phase IB study in pretreated metastatic cancer patients with disease that could be biopsied, grade 1 or 2 diarrhea and rash were the most common adverse events. Three patients with breast cancer refractory to trastuzumab (Herceptin®; Genentech, Inc.; South San Francisco, CA) had partial responses and 12 patients with a variety of tumors had stable disease. Assessment of biologic correlates in these patients indicates that increased tumor cell apoptosis on the terminal deoxynucleotide transferase-mediated dUTP nick-end labeling assay correlates with clinical response. Lapatinib currently is being evaluated in phase II and phase III trials in patients with metastatic breast cancer. ***The Oncologist*** *2004;9(suppl 3):10-15*

INTRODUCTION

The ErbB family of cellular type I receptor tyrosine kinases (TKs) plays a central role in normal cell proliferation, survival, and differentiation in a variety of tissues. Ligand binding to the epidermal growth factor receptor (EGFR, ErbB-1) induces receptor homodimerization or heterodimer-

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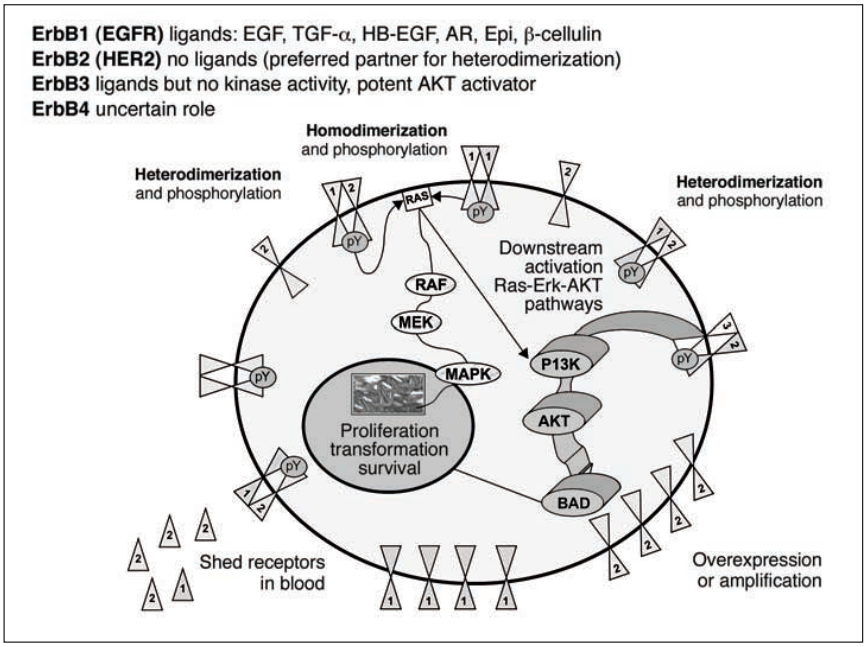

Figure 1. ErbB signal transduction cascade. *Abbreviations: HB = heparin-binding; AR = androgen receptor; Epi = epiregulin*

ization, resulting in receptor autophosphorylation and activation; ErbB-2 (HER-2) has no known ligands but is a heterodimerization partner for EGFR and other members of the ErbB receptor family, with transactivation of ErbB-2 occurring following heterodimerization. Autophosphorylation activates receptor TKs, resulting in activation of signaling pathways involved in cell proliferation, survival, and transformation, including the well-characterized mitogen-activated protein kinase (MAPK) (Erk1/2) and phosphatidylinositol 3′ kinase (PI3K)/AKT pathways (Fig. 1) [1-3]. Overexpression or constitutive activation of the EGFR or ErbB-2 receptors results in cell transformation and is associated with poor clinical outcome in a number of malignancies [4, 5]. The potential roles of the EGFR and ErbB-2 receptors in tumor cell proliferation and survival have prompted the development of monoclonal antibodies that inhibit the receptor and agents that inhibit receptor TKs; for example, cetuximab (Erbitux®; ImClone Systems, Inc.; New York, NY) and trastuzumab (Herceptin®; Genentech, Inc.; South San Francisco, CA) are monoclonal antibodies to the ErbB-1 and ErbB-2 receptors, respectively, and gefitinib (Iressa®; AstraZeneca Pharmaceuticals; Wilmington, DE) inhibits the ErbB-1 TK. There is considerable rationale for combined receptor/kinase inhibition, including the potential for overcoming redundancy in cell signaling pathways with the use of broader inhibition and the potential application to a wider range of patients based on epidemiologic evidence implicating EGFR and ErbB-2 receptors in a variety of tumor types. Lapatinib (GlaxoSmithKline; Research Triangle Park, NC) is a novel dual EGFR/ErbB-2 TK inhibitor that has shown promising activity in preclinical and early clinical investigations, providing support for a dual inhibitor approach in cancer therapy.

Lapatinib Properties

Part of the rationale for the development of lapatinib was provided by preclinical findings of synergistic cell growth inhibition with simultaneous targeting of EGFR and ErbB-2 receptor TKs. For example, treatment with the ErbB-1 TK inhibitor gefitinib plus the anti-erbB-2 (HER-2) receptor monoclonal antibody trastuzumab produced a greater apoptotic effect than either inhibitor alone in the ErbB-2-overexpressing breast cancer cell lines SKBR-3 and BT-474 [6]. Lapatinib was shown to exhibit greater growth inhibition of colon cancer cells activated by the EGFR ligand transforming growth factor alpha (TGF-α) than antagonists targeting either EGFR or ErbB-2 alone [7].

Lapatinib is a large head group quinazoline, distinguishing it from the small head group quinazolines erlotinib and gefitinib. It demonstrates high cell potency (50% inhibitory concentration <0.2 μM), has been shown to inhibit EGFR and ErbB-2 phosphorylated (phospho)-tyrosine, phospho-Erk1/2, phospho-AKT, and cyclin D in tumor cell lines and xenograft models, and has been shown to be efficacious in inhibiting cell growth in xenograft models [8, 9]. The drug exhibited a favorable toxicity profile in rodents and dogs and no evidence of cardiac toxicity during high exposure over 6 and 9 months, respectively.

Phase I Studies of Lapatinib

Oral lapatinib was administered to 135 healthy volunteers in four studies at doses of 10-250 mg and was found to be safe and well tolerated. In phase I studies in cancer patients, the drug was administered at doses of 175-1,800 mg once daily or 500-900 mg twice daily (bid) in 92 patients, with no significant toxicities observed to date. Pharmacokinetic data from these studies are under analysis; pharmacodynamic data derived from skin biopsies and buccal smears taken in all phase I patients are also being analyzed.

Table 1. Preliminary toxicity data by grade in 43 solid tumor patients receiving lapatinib in study EGF10003

Lapatinib dose (mg)	*n* of patients	*n* with adverse events (%)	Common toxicity criteria grade, *n* adverse events (% at dose level)			
			1	2	3	4
175	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
375	4	4 (100)	11 (79)	3 (21)	0 (0)	0 (0)
675	4	4 (100)	15 (100)	0 (0)	0 (0)	0 (0)
900	5	4 (80)	2 (40)	3 (60)	0 (0)	0 (0)
1,200	6	3 (50)	11 (79)	3 (21)	0 (0)	0 (0)
1,600	10	8 (80)	4 (57)	3 (43)	0 (0)	0 (0)
1,800	9	9 (100)	14 (78)	4 (22)	0 (0)	0 (0)
900 bid	3	2 (67)	0 (0)	0 (0)	2 (100)	0 (0)
Total	43	34 (71)	57 (76)	16 (21)	2 (3)	0 (0)

The maximum-tolerated dose study, EGF10003, enrolled 39 cancer patients with no ErbB receptor status requirement [10]. All patients are to receive lapatinib at doses of 175-1,800 mg once daily. Additional patients are receiving doses of 900 mg bid (n = 6), 1,250 once daily to assess food effect (n = 6), 500 mg bid (n = 13), and 750 mg bid (n = 22). Preliminary data in 43 of those patients indicate no grade 4 toxicities; most toxicities were grade 1 or 2, with two cases of grade 3 diarrhea observed at the 900-mg bid dose level (Table 1 and Table 2). Rash, diarrhea, nausea, and fatigue were the most common adverse events. Some evidence of clinical activity has been observed. As shown in Table 3, patients with a variety of tumors have had stable disease for up to 13 months; one patient exhibited a minor response, and one patient with a head and neck tumor had a complete response and remained on study after 19 months. Preliminary pharmacokinetic data indicate that the lapatinib serum concentrations were above the in vitro 90% inhibitory concentration at the 1,200-mg once-daily dose, and pharmacokinetics appear to be linear over the tested dose range (up to 1,800 mg).

Table 2. Preliminary data on adverse events in 43 solid tumor patients receiving lapatinib in study EGF10003

Adverse event	Grade	*n* of patients
Rash, including acneiform rash	1	7
	2	1
Diarrhea	1	6
	2	6
	3	2
Nausea	1	7
	2	2
Vomiting	1	2
	2	1
Constipation	1	4
	2	1
Fatigue	1	8
	2	1
Anorexia	1	5

Study EGF10004 is a phase IB study of lapatinib in heavily pretreated metastatic cancer patients with disease that can be biopsied, and EGFR or ErbB-2 overexpression on immunohistochemistry, erbB-2 gene overexpression on gene amplification, or evidence of activated EGFR and

Table 3. Patients on study EGF10003 for ≥4 months

Diagnosis	Lapatinib dose (mg)	Disease status	Duration on study (months)
Adenocarcinoma, lung	675/900/1,200/1,600	Stable disease	12
Adenocystic/salivary	1,200/1,600	Stable disease	9+
Breast cancer	1,600	Stable disease	7
Nasopharyngeal cancer	1,800	Stable disease	13
Unknown primary site	1,200/1,600/1,800	Stable disease	6
Colorectal cancer	675/900/1,200/1,600	Stable disease	6
Colorectal cancer	1,600	Stable disease	4
Head and neck cancer	1,250	Complete response	19+
Unknown primary site	1,250	Minor response	8

ErbB-2 receptors on immunohistochemistry [11]. Patients are randomized to receive lapatinib at doses of 500, 650, 900, 1,200, or 1,600 mg once daily. The biologic consequences of treatment on growth and survival pathways are being assessed in tumor biopsy samples obtained prior to and 21 days after the start of treatment, and safety and clinical activity are being evaluated. Thus far, 33 patients have been entered in the study, seven at the 500-mg dose, eight at the 650-mg dose, five at the 900-mg dose, six at the 1,200-mg dose, and seven at the 1,600-mg dose; tumor types in these patients consist of breast cancer (33%), ovarian cancer (15%), head and neck cancer (12%), adenocarcinoma of unknown primary site (12%), colorectal cancer (12%), lung cancer (6%), and others (9%). Treatment has been well tolerated, with no grade 4 and one grade 3 toxicity (gastroesophageal reflux). The most common adverse events (all grade 1 or 2) have been diarrhea (27%), rash (25%), and nausea/vomiting (21%). No treatment-related cardiac or pulmonary toxicity has been observed. Partial responses were observed in three patients (10%) at the 1,200-mg (n = 2) and 900-mg (n = 1) doses, with those patients having received therapy for a median of 23 weeks (20 to >25 weeks). Each of the three patients had breast cancer and exhibited both EGFR and ErbB-2 overexpression. Stable disease was observed in 12 patients (36%) at the 500-mg (n = 4), 650-mg (n = 3), 900-mg (n = 1), 1,200-mg (n = 2), and 1,600 mg (n = 2) doses, with a median treatment duration of 19 weeks (14 to >34 weeks) in those patients. Of the 12 patients, 10 had EGFR overexpression and six had ErbB-2 overexpression, including all breast cancer patients with stable disease. Overall, the tumor types responding to treatment (partial response or stable disease) have consisted of trastuzumab-refractory breast cancer (n = 7), colorectal cancer (n = 2), ovarian cancer (n = 2), lung cancer (n = 1), adenocarcinoma of unknown primary site (n = 1), granular cell carcinoma (n = 1), and head and neck cancer (n = 1).

Biologic correlates in a patient (patient A) with trastuzumab-refractory inflammatory breast cancer who had a rather dramatic partial response to lapatinib are shown in Table 4. That patient had received previous adjuvant therapy, hormonal therapy, and chemotherapy in addition to trastuzumab. Decreases in phospho-erbB-1 and phospho-erbB-2, phospho-Erk index, cyclin D, and TGF-α were observed, with a dramatic increase in tumor cell apoptosis using the terminal deoxynucleotide transferase-mediated dUTP nick-end labeling (TUNEL) assay. Patient B also exhibited a partial response to lapatinib after progression of metastatic breast cancer following treatments with paclitaxel, carboplatin, and trastuzumab, and with vinorelbine and trastuzumab. Biologic correlates in that patient also indicate a marked increase in apoptosis on the TUNEL assay (Table 4). In contrast, correlates in a patient (patient C) with progressive disease on lapatinib after failing two previous courses of chemotherapy plus trastuzumab indicate an absence of effect on apoptosis. In patients assessed thus far, clinical responses have been observed only in those with a positive effect on the TUNEL assay. The prognostic utility of the other correlates is currently being evaluated. Figure 2 shows that a ≥75% inhibition of phospho-erbB-1, phospho-erbB-2, phospho-Erk1/2, or phospho-AKT expression was reliably achieved at lapatinib doses of 650 mg and greater.

Table 4. Biologic correlates in select metastatic breast cancer patients with or without response on lapatinib in study EGF10004

	EGFR	Phospho-EGFR	ErbB-2	Phospho-erbB-2	Phospho-Erk index	Cyclin D	Phospho-AKT	TGF-α	TUNEL
Patient A: partial response (900 mg)									
Day 0	35	5	70	29	2,397	28	20	54	3
Day 21	32	1	65	5	760	12	20	21	72
% change	-9	-80	-7	-83	-68	-57	0	-61	+2,400
Patient B: partial response (1,200 mg)									
Day 0	7	11	50	8	378	20	48	38	4
Day 21	2	5	41	8	10	4	30	25	34
% change	-71	-54	-18	0	-97	-80	-37	-34	+850
Patient C: progressive disease (900 mg)									
Day 0	14	16	44	3	1,081	42	36	49	0
Day 21	19	3	32	3	0	10	33	23	0
% change	+35	-81	-27	0	-100	-76	-8	-53	0

Phospho-Erk index: (% positive cells) × (OD reading); OD = optical density

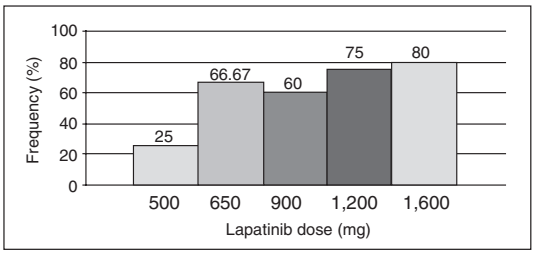

Figure 2. Frequency of achieving a ≥75% inhibition of phospho-EGFR, phospho-ErbB-2, phospho-Erk1/2, or phospho-AKT expression in tumors at day 21 compared with baseline according to lapatinib dose in study EGF10004.

In summary, preliminary findings from the EGF10003 trial indicate that lapatinib was well tolerated at all doses tested. Clinical responses were observed at a variety of doses in these heavily pretreated patients with metastatic disease. Partial responses were observed in ErbB-2-expressing breast cancer that had progressed on previous trastuzumab-containing regimens, and disease stabilization was observed in patients with a variety of other tumor types. Lapatinib inhibited signaling pathways implicated in tumor growth and survival. Data in this regard suggest that, although inhibition of phospho-Erk1/2, phospho-AKT, or cyclin D may be necessary for clinically detectable antitumor effects, they are not sufficient for producing such effects; induction of tumor cell apoptosis, as reflected in TUNEL assay measurements, appeared to correlate with clinical response.

Ongoing Studies of Lapatinib in Advanced Breast Cancer

The activity of lapatinib against breast cancer in preclinical models and its safety and activity in initial clinical experience have prompted the initiation of phase II and phase III trials in the setting of advanced breast cancer. In an open-label, multicenter, single-arm phase II trial (EGF20002/EGF20008), lapatinib is to be used as single-agent therapy in patients with advanced or metastatic breast cancer who progressed while receiving trastuzumab-containing regimens. A phase III randomized, open-label, multicenter trial (EGF100151) is comparing lapatinib plus capecitabine with capecitabine alone in patients with refractory advanced or metastatic breast cancer. EGF30001 is a randomized, double-blind, placebo-controlled, two-arm, multicenter phase III trial of lapatinib plus paclitaxel versus paclitaxel alone in previously untreated patients with advanced or metastatic disease. EGF30008 is a randomized, double-blind, placebo-controlled, multicenter phase III trial comparing lapatinib plus letrozole with letrozole alone in patients with estrogen/progesterone-receptor-positive advanced metastatic breast cancer. Findings in these trials should help to clarify the potential roles of this new dual EGFR/ErbB-2 inhibitor in the treatment of advanced breast cancer.

Conclusion

Lapatinib is a novel dual EGFR/ErbB-2 receptor TK inhibitor being studied in patients with advanced and metastatic cancer. Phase I data indicate good tolerability, with grade 1 or 2 rash and gastrointestinal effects being the most common observed toxicities, and evidence of clinical activity in patients with a variety of tumor types. Phase II and III trials have been initiated in patients with advanced breast cancer to assess lapatinib used alone or combined with agents such as capecitabine, a taxane, or hormonal therapy, and include previously treated and untreated patients. Preliminary assessment of biologic correlates in patients treated with lapatinib suggests that induction of tumor cell apoptosis as measured by the TUNEL assay correlates with clinical response.

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