Lapatinib - Overview and Current Role in Metastatic Breast Cancer

Arlene Chan, M.D.

Consultant Medical Oncologist, Mount Medical Centre, Australia

BACKGROUND

Breast cancer is a heterogeneous disease in terms of its natural history and response to various modalities of treatment. It has been known since the early 1990's that the presence of Her2 neu over-amplification is associated with a more aggressive tumour phenotype and a worse prognosis (1). The Her2 neu gene is one of a family of four transmembrane growth factor receptors. There are similarities between each of these four receptors, namely the presence of an extracellular ligand binding domain, a single transmembrane domain and an intracellular tyrosine kinase domain.

Following activation of the erbB receptors, these receptors undergo hetero- or homodimerisation. Subsequently a cascade of downstream pathways are activated following initiation of phosphorylation and signal transmission results in gene transcription that ultimately impacts on cell division, apoptosis, adhesion, migration or further differentiation (2).

Currently, it is thought that up to 20% of breast cancers have Her2 neu over-amplification. It is clearly established that the use of trastuzumab (Herceptin) has an important role in the treatment of these cancers; both in the metastatic and adjuvant setting. This agent is a monoclonal antibody which specifically binds with the Her2 neu receptor resulting in downstream inhibition of tumour cell growth (3).

Despite the efficacy of trastuzumab (Herceptin), most patients will develop resistance to this drug eventually in the metastatic setting and some patients receiving this agent in the adjuvant setting will develop recurrence. Lapatinib (Tykerb) is a small molecule tyrosine kinase that exhibits dual inhibition of both Her2 neu and epidermal growth factor receptor (EGFR or Her1).

PRECLINICAL DATA

Lapatinib is an orally active agent which works intracellularly to target the tyrosine kinase domain of both Her2 neu and EGFR. Upon binding to the adenosine triphosphate (ATP)

binding site of the kinase, the downstream activation of P13K and Akt are inhibited. This inhibition is dose dependent and several in vitro studies have demonstrated a greater potency of Lapatinib inhibition towards ErbB1 and ErbB2 compared with many other agents. The homodimerisation of ErbB1 and heterodimerisation between ErbB1 and ErbB2, suggests that theoretically an agent capable of inhibiting signalling of both these processes, may be more effective than inhibition of either tyrosine kinase alone. Further, preclinical studies have demonstrated increased expression of other growth factor receptors (insulin-like growth factor receptor 1, vascular endothelial growth factor receptor 1, transforming growth factor- α receptor). The complex interaction between these various transmembrane growth factor receptors may suggest that dual inhibition by an intracellularly active agent may have greater therapeutic benefit then solely targeting the extracellular domain of a single receptor (4).

CLINICAL DATA

Phase I studies have been conducted using Lapatinib in pre-treated women with Her2-positive metastatic breast cancer. Patients in these studies had uniformly received trastuzumab prior to disease progression and results show that there is a lack of cross resistance with trastuzumab. It is recognised that women receiving trastuzumab therapy for metastatic breast cancer may develop CNS diseases despite ongoing response in extra-cranial metastatic sites. It is thought that monoclonal antibodies such as trastuzumab have a low likelihood of penetrating the blood brain barrier in levels sufficient to treat intracerebral disease. A further possible advantage of Lapatinib is the finding that other small molecule tyrosine kinase inhibitors have the ability to penetrate the blood brain barrier, particularly in the presence of altered the blood-tumour barrier associated with brain metastases (5~7).

EGF10009 evaluated 42 patients with solid tumours including six patients with breast cancer. Patients received Lapatinib at doses ranging between 1,250 to 1,500 mg/d in combination with Paclitaxel 135~225 mg/m². Although tolerability of this combination was the primary focus of the study, partial response was achieved in three breast cancer patients, with stable disease in one patient. The most common non-haematological toxicity seen in this study included grade 1 or 2 diarrhoea, neuropathy, rash, fatigue and arthralgia.

Metastatic breast cancer patients who experienced disease

Correspondence: Arlene Chan, Mount Medical Centre, Suite 41, 146 Mounts Bay Rd, Perth 6000, Western Australia. (Tel) 61-8-9481-4522, (Fax) 61-8-9481-4544, (E-mail) arlene.chan@bigpond.com

progression following first or second-line trastuzumab therapy, were evaluated in EGF20002. Of 41 patients reported in an interim analysis, the objective response rate of 46.3% was considered extremely encouraging.

In study EGF20009, patients with Her2-positive locally advanced or metastatic breast cancer were treated with two dose levels of Lapatinib. Preliminary results demonstrated partial response rate of 35%, with a similar proportion of patients achieving stable disease.

Safety results from Phase I studies indicate that Lapatinib administered orally is generally well tolerated in doses ranging up to 1,800 mg daily. The majority of adverse events were either grade I or II. These included diarrhoea, skin rash, fatigue, anorexia, nausea and vomiting. With respect to serious adverse effect, dyspnoea, dehydration and neutropenia have been reported. To date three episodes of interstitial pneumonitis have been reported, although a definite causal relationship to Lapatinib has been difficult to confirm. As of January 2005 there is an overall incidence of 1.4% of patients experiencing a decrease in left ventricle ejection fraction (5).

TRIAL EGF100151

The first Phase III randomised clinical trial evaluating Lapatinib and Capecitabine versus Capecitabine alone was first presented at ASCO 2006 (8). The protocol was designed to include women with progressive Her2 neu-positive locally advanced or metastatic breast cancer who had received prior treatment with anthracycline, taxane, and trastuzumab. Patients were stratified according to disease site and stage of disease. Time to tumour progression based on intention-to-treat was the primary endpoint; with secondary endpoints including overall survival, progression-free survival, overall response rate, clinical benefit and toxicity. Enrolment was planned for a total of 528 patients to achieve a 90% power to detect a 50% increase in median time to progression, estimated to be three months for patients receiving capecitabine alone to 4½ months in those receiving combination therapy.

1) Patient characteristics

Patient characteristics were well-balanced between the two groups with the median age range 51 to 54 years, ECOG performance status of 0 or 1 in 87% to 95% and hormone receptor positive disease in 85%. The majority of patients had metastatic breast cancer (96%), approximately 50% of patients in both groups had greater than three metastatic sites and 75% of patients had visceral metastatic disease. Only one to 2% of patients in both groups were entered without prior treatment with anthracycline or taxane therapy, and greater than 90% of patients had received trastuzumab in the metastatic setting.

2) Results

The overall response rate was 14.3% (95% CI 9.3 to 20.7%) in patients receiving capecitabine alone compared to 22.5% (95% CI 16.3 to 29.8%) in patients receiving combination therapy, $p=0.113$. There was a statistically significant improvement in time to progression in the combination treatment with a median TTP of 36.9 weeks compared to 19.7 weeks in

the monotherapy group, $p=0.00016$. The progression free survival showed similar superiority for the combination arm with a median PFS of 36.9 weeks versus 17.9 weeks, $p=0.000045$. At the time of reporting there were no significant differences in overall survival with a hazard ratio of 0.93 (95% CI 0.55 to 1.59).

Of interest, a greater number of patients developed CNS disease in the monotherapy group (capecitabine 11 versus lapatinib & capecitabine 4, $p=0.110$).

3) Toxicity

Treatment was well tolerated with slightly more patients in the combination arm experiencing all grade diarrhoea (58% v 39%), plantar- palmar erythrodyesthesia (43% v 34%) and skin rash (30% v 18%).

Cardiac monitoring was mandatory in this study and only 4 patients reported a measurable decline in left ventricle ejection fraction. All patients were asymptomatic with three patients resuming Lapatinib therapy following improvement in cardiac function, without a recurrence of a cardiac event.

4) Conclusion

This important study demonstrates the effectiveness of Lapatinib administered in combination with capecitabine in Her2 neu-positive metastatic breast cancer patients who have developed progressive disease following trastuzumab. The adverse effects of the combination treatment was acceptable and the all oral route of administration of this treatment is likely to be preferred by patients.

5) Ongoing trials

A trial has been conducted at the Dana Farber cancer institute to evaluate Lapatinib in patients with refractory metastatic breast cancer (having received prior anthracycline, taxane, capecitabine and trastuzumab); 120 women with Her2 neu positive disease therapy and 80 patients with Her2 neu negative disease.

Spector et al have reported encouraging response rates of up to 72% in a small group of 34 patients with inflammatory breast cancer. Lin et al have specifically evaluated Lapatinib in patients with progressive brain metastases. They have suggested a greater accuracy of identifying response using volumetric MRI evaluation in 39 patients with objective volumetric reduction of greater than 15~30% in 21% of patients treated.

There are other ongoing trials evaluating Lapatinib in combination with aromatase inhibitors, trastuzumab and other cytotoxic agents in metastatic breast cancer. There are at least six trials evaluating Lapatinib monotherapy or Lapatinib and chemotherapy as neoadjuvant therapy for operable or inflammatory breast cancer.

CONCLUSION

The clinical development of Lapatinib highlights the importance of translational research, where tumour cell targeted therapy can be logically developed for clinical benefit. The availability of Lapatinib as second-line therapy is extremely

encouraging as the majority of Her2 neu-positive breast cancers initially responding to trastuzumab therapy will become resistant. The toxicity profile of this oral tyrosine kinase agent is generally acceptable, although evaluation of the impact of gastrointestinal side-effects and skin toxicity on quality of life is needed, especially if used for prolonged periods. Future studies will need to evaluate this agent compared to Trastuzumab as first-line therapy, the potential increase benefit of combining with agents, identifying other endocrine, cytotoxic and biological agents, that can be used in combination with Lapatinib and most importantly, the optimal way of incorporating this drug into the adjuvant setting.

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