



PINGRY

Lapatinib plus Letrozole as Therapy for HER2+ and ER+ Metastatic Breast Cancer

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ABSTRACT:

The addition of lapatinib ditosylate to letrozole treatment for women with estrogen receptor (ER)+ human epidermal and growth factor receptor (HER)2+ metastatic breast cancer (MBC) proves more effective than letrozole alone.

INTRODUCTION:

Breast cancer is the most common cause of cancer among women with over 1 million new cases estimated to occur worldwide each year (Nelson).

The beginnings of cancer treatment consisted of seemingly random chemotherapy. 20-30 years ago, chemotherapies were essentially poison and would affect DNA in both cancerous and normal cells, killing both; with few benefits came great toxicity. Now, cancer treatments are highly specific, targeting specific mechanisms with mutations that lead to proliferation of tumor cells. Lapatinib and letrozole are two of these highly specific treatments.

Letrozole inhibits the production of estrogen, the ligand for estrogen receptors (ER), by blocking aromatase. Lapatinib binds to the tyrosine kinase domain produced by the dimerization of HER1 and HER2, inhibiting the release of growth signals for the cell. Together, lapatinib and letrozole are used to treat post-menopausal women with ER+ and HER2+ metastatic breast cancer.

HER2+ cancerous cells are more aggressive than HER2- ones, and ER- cancerous cells are more aggressive than ER+ ones. The combination of HER2+ and ER- has the highest probability of becoming cancerous. However, because of the efficacy of lapatinib and letrozole, HER2+ cells (regardless of their ER status) now have a very effective treatment, and HER2- and ER- cells have the highest probability of becoming cancerous instead. Lapatinib and letrozole cancer treatment has turned a previously bad diagnosis into a good one. (Reeder)

FUNCTION OF LETROZOLE:

Aromatase is the enzyme responsible for estrogen development and synthesizes estrogen by converting androgens, male sex hormones, into estrogens, female sex hormones, in a process called aromatization (Reeder).

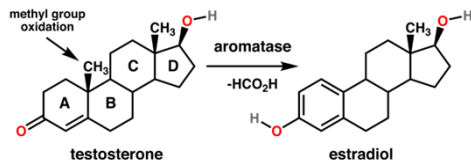


Fig. 1: Aromatization (Testosterone)

Steroids, such as estrogen, are composed of four fused rings (labeled A, B, C, and D in Fig. 1). Here, aromatase aromatizes the left-hand ring (the A-ring) of testosterone through oxidation and subsequent elimination of a methyl group, transforming testosterone into estradiol (Testosterone).

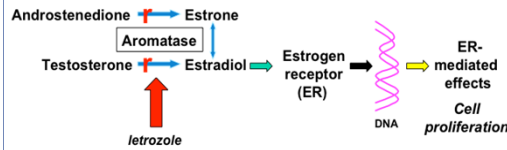


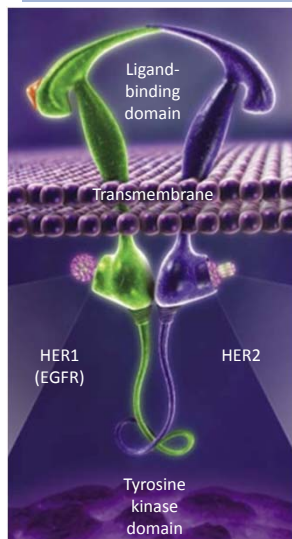
Fig. 2: Mechanism of Estrogen Action (Reeder)

Aromatase converts the androgens androstenedione and testosterone to the estrogens estrone and estradiol. These estrogens then bind to the ER, causing it to pair up and form a dimer. This dimer then binds to specific sites in the DNA, strategically placed next to the genes related to expression of estrogen. Then, the DNA-bound receptor activates the DNA-reading machinery and starts the production of messenger RNA, leading to cell proliferation (Reeder) (Goodsell).

Letrozole inhibits the production of estrogen, the ligand for ERs, by binding to the heme of cytochrome P450 on aromatase, the enzyme responsible for oxidation of androgens (Reeder). Without the ability to oxidize, aromatase cannot transform androgens into estrogens; since estrogen stimulates cell growth, its inhibition results in an end to cell proliferation.

Letrozole was created by Novartis Pharmaceuticals Corporation and was approved by the FDA on December 28, 2005. Letrozole is present in the drug Femara, which is administered orally (FDA approval for letrozole).

FUNCTION OF LAPATINIB:



Lapatinib binds to the tyrosine kinase domain produced by the dimerization of HER1 and HER2 (*The emerging*). HER1 (EGFR) and HER2 are cell membrane surface-bound tyrosine kinase receptors (*In HER2+*).

Lapatinib acts as a competitive inhibitor to ATP for the tyrosine kinase domain.

Tyrosine kinase functions to dephosphorylate ATP to ADP and activate a signal cascade leading to tumor cell proliferation, anti-apoptotic signals, and metastasis (Reeder). Lapatinib's binding to the tyrosine kinase domain inhibits cell growth.

Fig. 3: HER1 and HER2 as tyrosine kinase receptors (*In HER2+*)

Lapatinib was created by GlaxoSmithKline and was approved by the FDA for use in combination with Letrozole on January 29, 2010. Lapatinib is present in the drug TYKERB (FDA approval for lapatinib).

CLINICAL TRIALS:

In order to determine the tolerability and efficacy of the combination of letrozole and lapatinib versus letrozole alone on patients with ER+/HER2+ metastatic breast cancer, a trial was performed on 219 post-menopausal women with ER+/HER2+ metastatic breast cancer beginning on December 9, 2003. Of these 219 patients, 111 were randomized to letrozole plus lapatinib and 108 were to the letrozole plus placebo.

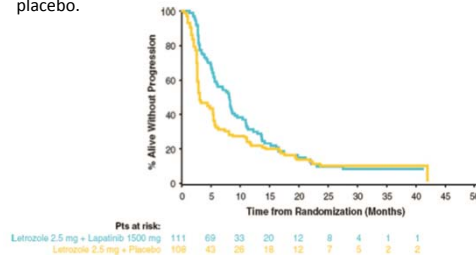


Fig. 4: Progression-free survival in patients with Letrozole plus Lapatinib vs. patients with Letrozole plus Placebo (Schwartzberg)

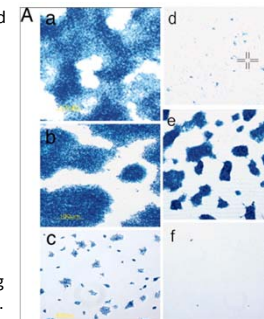
After following the patients for 1.9 years, it was determined that women taking letrozole and lapatinib had a 29% lower risk of disease progression than those taking letrozole and placebo. The median time of progression-free survival (the period of time when the tumor does not grow) was 8.2 months on letrozole and lapatinib in contrast with 3.0 months on letrozole and placebo.

Although the percentage of side effects reported was higher in letrozole and lapatinib (96%) than that of letrozole and placebo (77%), the amount of progression-free survival time for patients taking letrozole and lapatinib was over 5 months more than those taking letrozole and placebo. Patients taking lapatinib and letrozole reported the following side effects (listed in order from most reported to least reported): diarrhea, rash, nausea, fatigue, arthralgia (Schwartzberg).

These side effects were considered tolerable, and the trial evidenced the efficacy of the usage of lapatinib and letrozole together as a treatment against ER+ and HER2+ MBC.

Fig. 5A: BT474 cells treated according to the following conditions

- (a) control (DMSO)
 - (b) ICI 182.780
 - (c) Lapatinib
 - (d) ICI 182.780 plus lapatinib
 - (e) estrogen deprivation,
 - (f) estrogen deprivation plus lapatinib.
- Cell viability was assessed by methylene blue staining after 21 days of treatment.



In an analogous experiment, BT474 cells, cells prone to breast cancer, were treated using combinations of ICI 182.780 (Fulvestrant, an aromatase inhibitor similar to letrozole), lapatinib, and estrogen deprivation to determine their ability to inhibit tumor proliferation (See Fig. 5A).

As shown in Fig. 5A, viability remained essentially unchanged in cells treated with ICI 182.780 alone (b) compared with the control (a). Treatment with lapatinib alone (c) initially resulted in cell death but the appearance of viable cells and small colonies followed by 21 days. In contrast, only rare viable cells were seen at day 21 after the combination of ICI 182.780 plus lapatinib (d). Although estrogen deprivation alone (e) affected cell growth, it did not prevent the outgrowth of viable resistant cells. However, when subjected to estrogen deprivation plus lapatinib (f), virtually no viable cells were observed at day 21.

To ensure the reliability of these results, three identical tests were run to re-evaluate cell viability after 6 weeks of treatment.

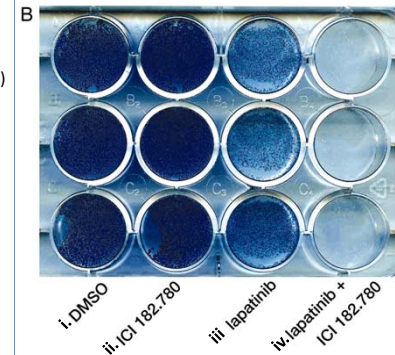


Fig. 5B: The effects of treating BT474 cells with (i) a control alone (ii) ICI 182.780 alone (iii) lapatinib alone (iv) the combination of ICI 182.780 plus lapatinib.

Although the concentration of ICI 182.780 (ii) used in these experiments blocked ER signaling, proteins continued to be expressed. In lapatinib alone, the phosphorylation of tyrosine kinases was inhibited, but small colonies re-formed. In contrast, the combination of ICI 182.780 plus lapatinib markedly inhibited surviving protein and continued to prevent the outgrowth of resistant cells through 6 weeks (Bacus).

As clearly shown, the combination of ICI 182.780 and lapatinib was the most effective inhibitor of cancerous growth of BT474.

CONCLUSION:

Letrozole is an aromatase inhibitor that blocks production of estrogen. Lapatinib is a tyrosine kinase inhibitor that blocks the release of growth signals.

After experimentation it is clear that lapatinib in combination with letrozole is more effective than that of letrozole alone. Together, lapatinib and letrozole are the most effective treatment for post-menopausal women with metastatic breast cancer tumors that overexpress ER and HER2.