This Month in APR

By Chang Hoon Lee, The Section Editor

A mechanistic study on gefitinib-induced apoptosis reveals a new link between EGFR and hTERT in breast cancers

Gefitinib (Iressa) is a quinazoline derivative that inhibits EGFR tyrosine kinase activity by binding to the adenosine triphosphate pocket within the EGFR catalytic domain (Fig. 1; Moon et al., 2009). Gefitinib (Iressa™, ZD1839) was FDA-approved as the monotherapy for patients with locally advanced or metastatic non-small-cell-lung carcinoma after the failure of the platinum-based and docetaxel regimens (Penne et al., 2005). Gefitinib was found to provide a statistically significant survival benefit to Asian patients and to those who had never smoked (Thatcher et al., 2005).

In the case of breast cancer, approximately 20% of all such cancers express high levels of EGFR, which has been implicated in shorter survival rate as well as increased resistance to hormonal therapy (Nicholson et al., 1989). Therefore, it is generally suggested that EGFR-targeted therapy may be an ideal adjuvant therapy for certain breast cancer patients. Relative to HER2-targeted therapy with trastuzumab (Herceptin™), clinical trials of gefitinib against EGFR in the cases of breast cancer remain in the early stages. Gefitinib administered at the daily dose of 500 mg is generally well tolerated, with only mild adverse events such as rash, diarrhea, nausea and vomiting. Baselga et al. reported that a 61.4% clinical benefit to 34 patients was accomplished with a daily dose of 500 mg (Baselga et al., 2005). Robertson et al. also demonstrated a beneficial gefitinib activity in tamoxifen-resistant estrogen receptor (ER)-positive and (ER)-negative breast cancer patients (Robertson et al., 2005). On the contrary, a negative result was reported by von Minckwitz et al. in a multicentre Phase II study on 58 cases of taxane- and anthracycline-pretreated metastatic breast cancer (von Minckwitz et al., 2005). Only 1 patient obtained a partial response (1.7%), and only 2 patients reported a significant improvement in pain at the metastatic sites. These controversial clinical results suggest that optimal selection of breast cancer patients might be a key factor for successful

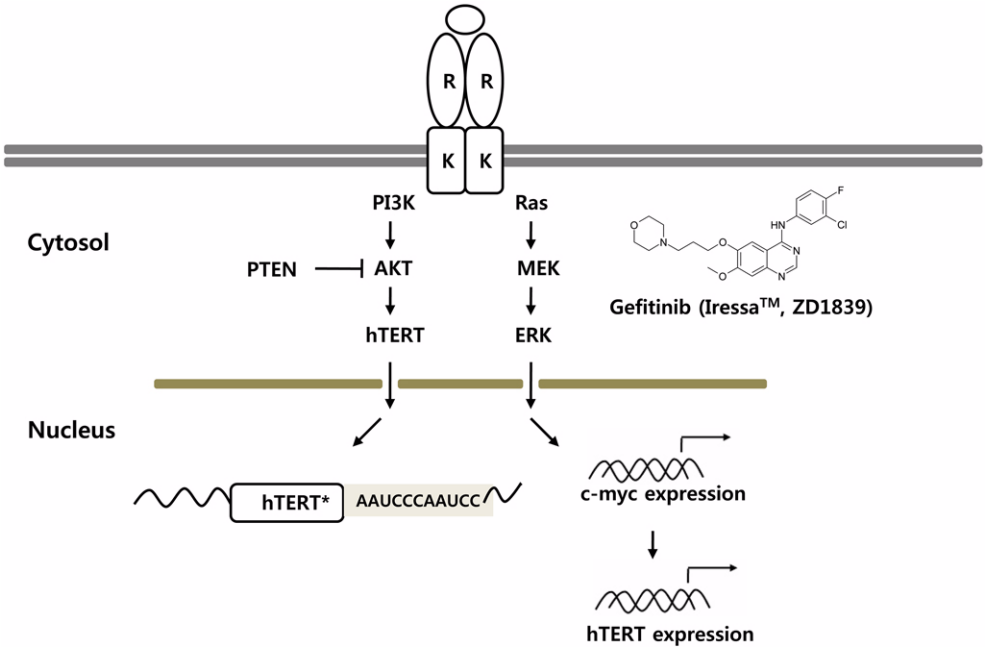

Fig. 1. EGFR signal transduction in MDA-MB-231 cells and action of tyrosine kinase inhibitor, Gefitinib (Iressa™, ZD1839). An overabundance of EGFRs (R) are found on MDA-MB-231 cells. EGFRs are the first step along a detailed signal transduction pathway that leads to cell division and MDA-MB-231 cell growth. Gefitinib blocks tyrosine kinase (K), thereby preventing c-myc expression and phosphorylation of Akt, causing diminished expression of hTERT and suppressing the nuclear translocation of hTERT, respectively.

clinical outcome with gefitinib.

As reported in this issue, Moon et al. investigated the effect and mechanism of gefitinib on apoptosis and telomerase activity in a human breast cancer model. The authors report for the first time that gefitinib strongly induced apoptosis and repressed telomerase activity in MDA-MB-231 cells via transcriptional down-regulation of hTERT through the suppression of c-myc expression and posttranslational modification of hTERT protein (Moon et al., 2009). In this study, hTERT activity was affected by Akt inactivation. Telomerase is a ribonucleoprotein complex comprised of a telomerase reverse transcriptase (hTERT) catalytic subunit, a telomerase RNA template, a telomerase-associated protein and chaperone proteins (Moon et al., 2009). hTERT appears to be especially important for up-regulation of telomerase activity in many human cancer cells. The hTERT promoter contains numerous c-myc-binding sites that directly mediate hTERT transcriptional activation (Wu et al., 1999). In addition, Akt kinase is known to enhance telomerase activity through phosphorylation of hTERT at Ser824 (Kang et al., 1999). In this Moon et al.'s study, the mechanism of gefitinib-induced apoptosis showed a close link between EGFR and hTERT in breast cancers involving c-myc and Akt (Fig. 1). Recently it was reported that circulating hTERT DNA has a better diagnostic value than carbohydrate antigen 15.3 in the early stage of breast cancer, and could be a possible tumor marker candidate in patients with infiltrating ductal carcinoma positive to steroid hormonal receptor and with amplification of HER-2/Neu (Divella et al., 2009).

Therefore, consideration of the factors (EGFR, hTERT, c-myc, and Akt) might be of help to improve its clinical outcome of gefitinib or at least to avoid controversy.

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