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Review

Clinical significance of epidermal growth factor receptor tyrosine kinase inhibitors: Sensitivity and resistance

Shinji Takeuchi[a,b,*], *Seiji Yano*[a,b]

[a]*Division of Medical Oncology, Cancer Research Institute, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-0934, Japan*
[b]*Cancer Center, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa, Ishikawa 920-0934, Japan*

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ABSTRACT

Gefitinib and erlotinib, which are epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs), are highly effective against lung tumors with EGFR activating mutations. However, in 20–30% of cases, there is intrinsic resistance, and even if the treatment is effective, resistance is acquired in one to several years. Possible mechanisms of acquired resistance to EGFR-TKI, thus far, include a gatekeeper mutation of EGFR, activation of an alternate pathway, activation of EGFR downstream signals, transformation to small cell lung cancer, and epithelial–mesenchymal transition (EMT). Recently, BIM (BCL2L11), which is a BH3-only proapoptotic member of the Bcl-2 protein family, was shown to play a central role in inducing apoptosis in response to EGFR-TKI treatment in EGFR mutant lung cancer cells. Moreover, when the expression of active BIM protein was low, there was resistance to apoptosis induction by EGFR-TKI treatment and early disease progression.

A polymorphism of the BIM gene unique to East Asian people has been detected and is now attracting attention as a factor causing resistance to EGFR-TKI due to decreased BIM activity.

Abbreviations: EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; MST, median survival time; HGF, hepatocyte growth factor; FISH, fluorescence *in situ* hybridization; PTEN, phosphatase and tensin homolog deleted from chromosome 10; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinase; EMT, epithelial-to-mesenchymal transition; SRC, sarcoma viral oncogene homolog; APAF-1, apoptotic peptidase activating factor 1; PKC-ε, protein kinase Cε; ABC transporter, adenosine triphosphate-binding cassette transporter; BCRP, breast cancer resistance protein; NFκβ, nuclear factor kappa B; TGF-β, transforming growth factor-β; IL-6, interleukin-6; BCL2L11, Bcl-2-like protein 11; PFS, progression free survival; mRNA, messenger RNA; Hsp90, heat shock protein 90; HDAC, histone deacetylace; BH3, Bcl-2 homology domain 3; PBMC, peripheral blood mononuclear cell; OS, overall survival; NA, not applicable; ORR, overall response rate; NS, not significant

*Corresponding author at: Division of Medical Oncology, Cancer Research Institute, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-0934, Japan. Tel.: +81 76 265 2785; fax: +81 76 234 4524.
E-mail address: takeuchi@staff.kanazawa-u.ac.jp (S. Takeuchi).

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Contents

1. Introduction

EGFR tyrosine kinase inhibitors (EGFR-TKIs) are dramatically effective in lung cancer with epidermal growth factor receptor (EGFR) activating mutations. However, some cases are inherently resistant, and even in cases where there is high effectiveness, tolerance is acquired within several months to several years, leading to recurrence. Recently, many studies have been performed to examine TKI-resistance, and many clinical treatments are being developed to overcome it. In this paper, we summarize the latest knowledge of the molecular mechanisms of resistance to gefitinib and erlotinib, which are EGFR-TKIs, in EGFR mutant lung cancer, and strategies to overcome this resistance.

2. EGFR-TKI efficacy in patients with EGFR mutant lung cancer

EGFR is overexpressed in many solid cancers. In lung cancer with EGFR activating mutations, EGFR-TKIs like gefitinib and erlotinib show dramatic efficacy. EGFR activating mutations include deletion of exon 19 and L858R point mutation in exon 21, and these account for 90% or more of EGFR mutations [1]. In lung cancer with EGFR activating mutations, gefitinib and erlotinib show a marked response, with a response rate of 70–80% [2].

When EGFR-TKI treatment is utilized for treating lung cancer with EGFR activating mutations, the median survival time (MST) of patients is approximately 30 months, and considering that the MST for platinum-based chemotherapy is around 12 months, this is clearly a breakthrough. However, even if there is a complete response, the cancer will recur in several years due to acquired resistance, almost without exception. Moreover, in 20–30% of cases with an EGFR mutation, EGFR-TKI has no effect, known as intrinsic resistance. To better understand and use EGFR-TKI therapy, these two types of resistance need to be resolved.

3. Major mechanisms of resistance to EGFR-TKIs

3.1. *EGFR T790M gatekeeper mutation*

T790M was first reported to be an acquired mutation that leads to TKI-resistance and is known as the gatekeeper mutation in EGFR. Threonine, which is the 790th amino acid located in exon 20 of the EGFR, undergoes mutation to methionine, and T790M is detected in about 50% of tumors with acquired resistance [1,3,4].

If this T790M genetic mutation occurs in addition to the deletion of exon 19 or the L858R mutation in exon 21, the affinity of EGFR for ATP increases and affinity for EGFR-TKIs decreases, and resistance develops [5]. A few cancer cells that have the T790M mutation and EGFR activating mutations are already present before EGFR-TKI treatment, and they are thought to gradually become predominant during EGFR-TKI treatment. Due to the T790M mutation, the kinase activity of EGFR and tumor-forming ability of cancer cells have been