Downregulation of ERCC1 Boosts Efficacy of Platinum-Based NSCLC Chemotherapy

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) may reduce excision repair cross-complementing group 1 (ERCC1) gene expression, potentially enhancing sensitivity to platinum-based chemotherapy in patients with non–small cell lung cancer (NSCLC), according to results from a poster presented by Cheong et al. [Cheong HT et al. *J Thorac Oncol* 2014].

Platinum-based chemotherapy is the standard first-line treatment for patients with EGFR–wild-type NSCLC, whereas EGFR-TKIs are the standard for patients with the ERCC1 mutation. A Phase 3 study showed that intercalated chemotherapy and erlotinib comprise a viable first-line option for patients with EGFR–mutation-positive NSCLC or selected patients with unknown EGFR mutation status [A Randomized, Placebo-Controlled, Double-Blind Phase III Study of the Effect of First-Line Treatment With Intercalated Tarceva Versus Placebo in Combination With Gemcitabine/Platinum on Progression-Free Survival in Patients With Stage IIIB/IV Non–Small Cell Lung Cancer (FASTACT-2: NCT00883779); Wu YL et al. *Lancet Oncol* 2013]. At the same time, it was reported that subgroup biomarker studies showed that patients with EGFR–wild-type and ERCC1-positive NSCLC attained longer progression-free and overall survival.

Based on these data, Cheong et al. postulated that EGFR-TKIs downregulate ERCC1 expression in wild-type EGFR NSCLC cells, thus enhancing the efficacy of chemotherapy. To test this hypothesis, they designed *in vitro* and *in vivo* studies to study the impact of EGFR-TKIs on ERCC1 expression.

H358 and H1993 NSCLC cell lines were treated with EGFR-TKIs for 72 hours, and transient small interfering RNA (siRNA) transfection was performed for ERCC1 suppression. Cisplatin sensitivity of the transfected cells was tested by cell viability assay. The NSCLC cell lines H358 and H1993 were used to establish a xenograft tumor model, and animals were treated with 2 weeks of oral erlotinib. ERCC1 expression was studied by Western blot, and immunohistochemistry (IHC) by the Mab clone 8F1.

Findings indicated that ERCC1 expression is not directly related to EGFR-TKI sensitivity. The expression of ERCC1 was, however, reduced progressively throughout 72 hours of EGFR-TKI exposure. Cell sensitivity for cisplatin was increased in the ERCC1 knockdown model, and the half maximal inhibitory concentration (IC_{50}) for H358 and H1993 was reduced from 11.94 μM to 0.31 μM and from 14.67 μM to 0.16 μM, respectively. Conversely, EGFR-TKIs showed no effect on tumor volume of the EGFR–wild-type xenografts, but there was a significant reduction in the ERCC1 level on IHC staining after treatment with EGFR-TKIs.

Almost 75% of patients with NSCLC are incurable at diagnosis. For many, chemotherapy is a good treatment option that is associated with longer survival and better quality of life. Treatment for those with advanced NSCLC is, however, palliative. Treatments that include cisplatin or carboplatin plus another agent are the most widely used drug combinations, but they can be associated with undesirable toxicity. Thus, it is desirable to have an equally or more effective treatment that is less toxic.

Overall, this pilot study showed that reduction in the expression of the ERCC1 gene increased the sensitivity of NSCLC cells to platinum-based chemotherapy. The observations in this pilot study need to be replicated in larger trials, however.

Peer-Reviewed Highlights From the

European Lung Cancer Conference 2014

March 26-29
Geneva