LETTER

Revisiting The Dual Role of Radiotherapy in EGFR-mutant NSCLC: Implications for Therapeutic Combination Strategies

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To the editor,

The article by *Piffkó A et al.* [1] elucidates the double-edged sword role of radiotherapy in cancer treatment. Radiotherapy stimulates tumor cells to secrete amphiregulin (AREG), which in turn activates $EGFR^+$ tumor-associated mononuclear phagocytes (MNPs). This activation feeds back into the EGFR signaling pathway, impairing the anti-tumor functions of MNPs. Moreover, AREG upregulates the expression of the immune checkpoint protein CD47 in tumor cells, thereby enabling them to evade immune-mediated phagocytosis. These insights hold important implications for clinical trial design and for optimizing therapeutic strategies.

Keywords: non-small cell lung cancer, EGFR, radiotherapy, combination strategies, EGFR-TKI.

Main text

Non-small cell lung cancer (NSCLC), the most prevalent subtype of lung cancer, includes Kirsten rat sarcoma viral oncogene (KRAS) and epidermal growth factor receptor (EGFR) mutations [2]. In East Asian populations, EGFR mutations are the most common genetic alteration [2]. Patients with EGFR mutations derive survival benefits from Osimertinib, a third-generation tyrosine kinase inhibitor (TKI). However, during treatment with Osimertinib, some patients achieve disease control at the primary site, yet develop metastases in other organs [3]. These results underscore the need for combination regimens incorporating Osimertinib to further enhance patient outcomes. Radiotherapy, a conventional anti-tumor modality, has garnered renewed interest for combination strategies following the emergence of stereotactic body radiotherapy (SBRT). This technological advancement has prompted some researchers to explore its integration with EGFR-TKI

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therapy. However, the theoretical foundation supporting such a combination remains inadequately established.

Recent studies [1] have revealed a novel mechanism that may provide theoretical support for the combined strategy of EGFR-TKIs and radiotherapy. Radiotherapy stimulates tumor cells to secrete amphiregulin (AREG), which in turn activates $EGFR^{+}$ tumor-associated mononuclear phagocytes (MNPs). This activation feeds back into the EGFR signaling pathway, impairing the anti-tumor functions of MNPs. Moreover, AREG upregulates the expression of the immune checkpoint protein CD47 in tumor cells, thereby enabling them to evade immune-mediated phagocytosis. Interestingly, Piffkó A and colleagues reported that EGFR-TKI may impede the differentiation of MNPs [1]. According to the findings of Piffkó A and colleagues, EGFR-TKIs and AREG antibody monotherapy exert comparable inhibitory effects on metastatic lesions [1]. Since MNPs do not harbor EGFR mutations and instead express wild-type EGFR, the first-generation EGFR-TKI used in their study—though limited in its ability to block phosphorylation of wild-type EGFR-can nonetheless suppress the differentiation of MNPs, thereby mitigating tumor metastasis This suggests that the immune evasion of tumor cells induced by radiotherapy can be partially counteracted by first-generation EGFR-TKIs, while both modalities exert direct cytotoxic effects on tumor cells. A prospective Phase III study [4] demonstrated that for EGFR-mutated patients, combination therapy significantly extended median progression-free survival time (17.1 months vs. 10.6 months) and overall survival time (34.4 months vs. 26.2 months) compared to first-generation EGFR-TKI monotherapy. These observations underscore the therapeutic advantages of combining EGFR-TKIs with radiotherapy.

In addition, Fang and colleagues found that third-generation EGFR-TKIs downregulate CD47 expression in tumor cells by suppressing EGFR phosphorylation [5]. Compared with first-generation agents, third-generation targeted therapies demonstrate stronger inhibition of EGFR phosphorylation, while retaining modest activity against wild-type EGFR. Consequently, the combination of third-generation EGFR-TKIs with radiotherapy in EGFR-mutant NSCLC offers both a sound mechanistic rationale and substantial translational clinical potential. The optimal treatment strategy for NSCLC patients of EGFR mutations with oligometastatic disease remains controversial. Since radiotherapy can effectively eradicate tumors at local sites, its combination with third-generation EGFR-TKIs, which act as systemic therapy, is expected to yield meaningful therapeutic benefits for patients with oligometastasis or oligoprogression, including those with brain, adrenal, or liver metastases. Several clinical trials (NCT04970693; NCT05089916) are currently investigating the efficacy and safety of third-generation EGFR-TKI combined with radiotherapy. These studies typically involve either concurrent administration of third-generation EGFR-TKI and radiotherapy or the delivery of radiotherapy during ongoing oral third-generation EGFR-TKI treatment. Notably, while radiotherapy exerts direct tumoricidal effects, it may also facilitate tumor immune escape [1]. Therefore, under the premise of ensuring drug safety, using third-generation EGFR-TKI for a few weeks before proceeding with radiotherapy appears to be a more rational therapeutic approach. Therefore, the discovery of the double-edged sword effect may also be the emergence of a new treatment model.

Data Availability Statement

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

AI Use Statement

The authors declare that no generative AI was used in the preparation of this manuscript.

Ethical Approval and Consent to Participate

Not applicable.

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