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LETTER TO THE EDITOR

EGFR-TK1-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients with NSCLC: When Is it Worth The Risk?

Raffaella Mormile[1]

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Nivolumab treatment has been shown to increase the risk of epidermal growth factor-tyrosine kinase inhibitors (EGFR-TKIs)-associated interstitial pneumonitis (IP) in patients with non-small cell lung cancer (NSCLC) [1]. A higher proportion of IP has been observed for nivolumab in combination with EGFR-TKI versus treatment with either drug alone [1]. Lung cancers represent the principal cause of death cancer-related worldwide with a poor survival rate at five years from diagnosis [2]. Advanced NSCLC has a poor prognosis and receives partial advantage from conventional chemioterapy [1, 2]. In recent years, numerous novel therapies have been introduced for treating advanced NSCLC beyond old chemotherapy and EGFR-TKIs such as erlotinib [2]. Immunotherapy including nivolumab has emerged to result in promising clinical activity in advanced NSCLC [2, 3]. Nivolumab is an immune checkpoint inhibitor that has received the FDA and EMA approval for the treatment of NSCLC in second-line setting [2]. Nivolumab is an anti-programmed cell death-1 (PD-1) monoclonal antibody whose administration may be complicated by immune-related adverse events [1–3]. Nivolumab and EGFR-TKI are currently considered the standard-of-care treatments in NSCLC [1]. However, this therapeutic approach remains controversial given the relatively high incidence of treatment–related toxicities connected with combination of EGFR-TKI and immunotherapy [3]. EGFR-TKI has been linked to a significant improvement in clinical outcomes in comparison to chemotherapy in NSCLC patients with sensitizing EGFR gene mutation [3]. However, essentially all patients on therapy with EGFR-TKIs eventually show acquired resistance [3]. It has been detected that activation of the oncogenic EGFR pathway enhances susceptibility of the lung cancers to PD-1 blockade in mouse model, implying that combination of PD-1 blockade with EGFR-TKIs may represent an encouraging therapeutic strategy [3]. Nivolumab plus erlotinib have been found tolerable, with durable responses in patients with EGFR-mutant, TKI-treated NSCLC [4]. Immunotherapy efficacy seems to be less pronounced in patients with such tumors harboring EGFR mutations [4]. The compound EGFR mutations L858R and S768I have been associated with an ongoing response lasting more than 5 years based on investigator records [4]. Patients with EGFR mutation-positive NSCLC who develop resistance after EGFR-TKI treatment with mechanisms other than acquisition of the secondary T790M mutation of EGFR, seem to be more likely to benefit from nivolumab therapy, possibly due to a higher expression of the PD-1 ligand PD-L1 and high CD8+ tumor infiltrating lymphocyte (TIL) counts [5]. Progression free survival has been detected to increase as the PD-L1 expression level increased with cutoff values of ≥10% and ≥ 50% [5]. The proportion of tumors with a PD-L1 level of ≥10% and ≥ 50% has been proved to be higher among T790M- negative individuals than among T790M positive patients [5]. Taken together, I speculate that tumor biopsy specimen should be performed from patients with advanced NSCLC before administering nivolumab plus EGFR-TKI in order to verify whether the specific type of sensitizing EGFR gene mutation is likely to benefit from nivolumab. I conjecture that the increased chance of getting IP during therapy with nivolumab plus EGFR-TKI may be only justified by a therapeutic efficacy and durability of clinical responses notwithstanding the need of a careful monitoring for a prompt recognition of a possible nivolumab-induced IP.

Compliance with Ethical Standards

Conflict of Interest The author declares no conflict of interest.

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✉ Raffaella Mormile
raffaellamormile@alice.it

[1] Division of Pediatrics and Neonatology, Moscati Hospital, Via A. Gramsci, 81031 Aversa, Italy

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