

Early View

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**Pharmacotherapy for Lung Cancer with Comorbid Interstitial Pneumonia:
Limited Evidence requires Appropriate Evaluation**

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Take home message:

This article is a correspondence to the review article on lung cancer with comorbid interstitial pneumonia, particularly with regard to pharmacotherapy. Limited evidence needs to be accurately evaluated and utilized for these patients with poor prognosis.

Key words:

interstitial lung diseases/pulmonary fibrosis, lung cancer, pharmacotherapy

To the Editor,

We have read with interest the article entitled “Lung cancer in patients with fibrosing interstitial lung diseases: an overview of current knowledge and challenges” by Kewalramani N et al.¹ About 10% of lung cancer patients are complicated with interstitial pneumonia (IP) and have a poor prognosis. Although there is a lack of evidence in this area, the article clearly summarizes the current status from epidemiology to treatment, and is very informative for clinicians. However, there were three points that could be misleading to the reader, especially in the description of pharmacotherapy.

First, the authors stated that as second line therapy for lung cancer patients with fibrosing IP, vinorelbine should be administered for squamous cell carcinoma, and pemetrexed for adenocarcinoma. However, Japanese nationwide survey on pharmacotherapy for lung cancer patients with IP reported that acute exacerbations of pre-existing IP occurred in 28.6% of patients treated with pemetrexed and 25% of patients treated with vinorelbine.² On the other hand, docetaxel, which was not recommended by the authors, had a lower incidence of acute exacerbations (15.3%). Together with several past reports on the safety of paclitaxel and nab-paclitaxel in lung cancer patients with IP, the taxanes may have a relatively low risk of acute exacerbations. In addition, S-1, which had the lowest incidence of acute exacerbations in an aforementioned report by Minegishi et al,² is often administered as second-line therapy for lung cancer patients with IP in Japanese clinical practice.

Second, the authors stated that reports of immune checkpoint inhibitors (ICIs) are scarce, with only retrospective cohort studies and limited numbers of patients. While no

prospective studies have been reported to date investigating ICI as first-line treatment for advanced lung cancer patients with IP, all three previously reported prospective trials of second-line or later therapy were on ICI monotherapy for advanced non-small cell lung cancer (NSCLC) with IP, and none were on cytotoxic chemotherapy.³⁻⁵ These three studies of ICI differed in their selection criteria for IP and in the incidence of ICI-induced pneumonitis, which ranged from 0-30%. At present, the safety of ICIs in patients with IP has not been adequately established, and the pros and cons of administration remain controversial. However, retrospective studies on cytotoxic agents (e.g., docetaxel, pemetrexed) as second-line or later therapy in NSCLC patients with comorbid IP showed a 1-year survival of at most 10%, which is far from promising for long-term survival.⁶⁻⁷ On the other hand, phase II trials of ICI for NSCLC patients with IP have consistently shown favorable efficacy; nivolumab trial had a median overall survival of 15.6 months, while atezolizumab trial had a 1-year survival rate of 53.3%.^{4, 8} Since ICI is the only treatment option that can provide long-term survival in poor-prognosis lung cancer patients with IP, an important clinical issue is how to “narrow down” IPs with low risk of ICI-induced pneumonitis.

Third, there were some inaccuracies in the authors' description of the J-SONIC trial, the world's first randomized phase III trial in NSCLC with idiopathic pulmonary fibrosis (IPF). The authors stated that the addition of nintedanib to carboplatin plus nab-paclitaxel prolonged the interval to acute exacerbation. But in fact, the primary endpoint of exacerbation-free survival (defined as the time from randomization to the date of acute exacerbation of IPF or death from any cause) and the secondary endpoint of time to acute exacerbation of IPF were not met, indicating that the addition of nintedanib was not effective in reducing acute exacerbations.⁹ The incidence of acute

exacerbations was low throughout the trial due to the high safety of carboplatin plus nab-paclitaxel itself and the relatively preserved lung function of the enrolled patients. This may have made it difficult to prove the efficacy of nintedanib in preventing acute exacerbations. However, a subgroup analysis of non-squamous NSCLC patients showed significant prolongations in both progression free survival and overall survival, indicating enhanced anti-tumor effect with nintedanib. Therefore, the addition of nintedanib would be one of the treatment options for non-squamous NSCLC patients with IPF.

When an article is published in a high-impact journal like yours, it is highly likely that readers will take the content of the article as it is and reflect it in their clinical practice. For this reason, we are submitting this correspondence article. Meanwhile, we believe that it is very significant that such an excellent review article has been published by European opinion leaders. We hope that this will lead to the generation of further evidence from around the world and the planning of international collaborative studies involving countries in Europe and Asia in the future.

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Author contributions

Yuriko Ishida: Formal analysis, Investigation, Writing (Original Draft). **Satoshi Ikeda:** Formal analysis, Investigation, Writing (Original Draft). **Tomohisa Baba:** Investigation, Writing (Review & Editing). **Akimasa Sekine:** Investigation, Writing (Review & Editing). **Takashi Ogura:** Investigation, Writing (Review & Editing).

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