Pharmacotherapy for lung cancer with comorbid interstitial pneumonia: limited evidence requires appropriate evaluation

Received: 7 July 2022
Accepted: 28 July 2022

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 *et al.* [1]. ~10% of lung cancer patients are complicated with interstitial pneumonia and have a poor prognosis. Although there is a lack of evidence in this area, the article clearly summarises 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 interstitial pneumonia, vinorelbine should be administered for squamous cell carcinoma and pemetrexed for adenocarcinoma. However, a Japanese nationwide survey on pharmacotherapy for lung cancer patients with interstitial pneumonia reported that acute exacerbations of pre-existing interstitial pneumonia occurred in 28.6% of patients treated with pemetrexed and 25% of patients treated with vinorelbine [2]. Conversely, 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 interstitial pneumonia, 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 interstitial pneumonia 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 ICIs as first-line treatment for advanced lung cancer patients with interstitial pneumonia, 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 interstitial pneumonia, and none were on cytotoxic chemotherapy [3–5]. These three studies of ICI differed in their selection criteria for interstitial pneumonia and in the incidence of ICI-induced pneumonitis, which ranged from 0% to 30%. At present, the safety of ICIs in patients with interstitial pneumonia has not been adequately established, and the pros and cons of administration remain controversial. However, retrospective studies on cytotoxic agents (*e.g.* docetaxel and pemetrexed) as second-line or later therapy in NSCLC patients with comorbid interstitial pneumonia showed a 1-year survival of, at most, 10%, which is far from promising for long-term survival [6, 7]. Conversely, phase II trials of ICIs for NSCLC patients with interstitial pneumonia have consistently shown favourable efficacy; a nivolumab trial had a median overall survival of 15.6 months, while an atezolizumab trial had a 1-year survival rate of 53.3% [4, 8]. Since ICIs are the only treatment option that can provide long-term survival in poor-prognosis lung cancer patients with interstitial pneumonia, an important clinical issue is how to "narrow down" interstitial pneumonias 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 randomised 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 randomisation to the

Shareable abstract (@ERSpublications)
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 utilised for these patients with poor prognosis. https://bit.ly/3BGRCz4

Cite this article as: Ishida Y, Ikeda S, Sekine A, *et al.* Pharmacotherapy for lung cancer with comorbid interstitial pneumonia: limited evidence requires appropriate evaluation. *ERJ Open Res* 2022; 8: 00337-2022 [DOI: 10.1183/23120541.00337-2022].

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-tumour 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.

Yuriko Ishida, Satoshi Ikeda, Akimasa Sekine, Tomohisa Baba and Takashi Ogura

Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama City, Japan.

Corresponding author: Satoshi Ikeda (isatoshi0112@gmail.com)

Provenance: Submitted article, peer reviewed.

Acknowledgements: We would like to express our sincere gratitude to Yukiko Ogasawara, Yuka Onoda, Noriko Kanda and Kiriko Sato (Clinical Research Center, Kanagawa Cardiovascular and Respiratory Center, Japan) for their efforts in data collection.

Author contributions: Y. Ishida: formal analysis, investigation and writing (original draft). S. Ikeda: formal analysis, investigation and writing (original draft). T. Baba: investigation and writing (review and editing). A. Sekine: investigation and writing (review and editing). T. Ogura: investigation and writing (review and editing).

Conflicts of interest: A. Sekine has received honoraria for lectures from AstraZeneca, Ono, Eli Lily and Boehringer Ingelheim, outside the submitted work. S. Ikeda has received research funds from Chugai Pharmaceutical Co, Ltd. and AstraZeneca K.K., outside the submitted work; and honoraria for lectures from Chugai Pharmaceutical Co, Ltd., Ono Pharmaceutical Co, Ltd., Boehringer Ingelheim, Eli Lilly K.K, Bristol-Myers Squibb, AstraZeneca K.K., Pfizer and Taiho Pharma, outside the submitted work. T. Baba has received honoraria for lectures from AstraZeneca, Daiichi-Sankyo and Boehringer Ingelheim, outside the submitted work. T. Ogura has received honoraria for lectures from Shionogi, Eisai and Boehringer Ingelheim, outside the submitted work. Y. Ishida has nothing to disclose.

References

1 Kewalramani N, Machahua C, Poletti V, *et al.* Lung cancer in patients with fibrosing interstitial lung diseases: an overview of current knowledge and challenges. *ERJ Open Res* 2022; 8: 00115-2022.
2 Minegishi Y, Gemma A, Homma S, *et al.* Acute exacerbation of idiopathic interstitial pneumonias related to chemotherapy for lung cancer: nationwide surveillance in Japan. *ERJ Open Res* 2020; 6: 00184-2019.
3 Fujimoto D, Morimoto T, Ito J, *et al.* A pilot trial of nivolumab treatment for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia. *Lung Cancer* 2017; 111: 1–5.
4 Fujimoto D, Yomota M, Sekine A, *et al.* Nivolumab for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia: a multicenter, open-label single-arm phase II trial. *Lung Cancer* 2019; 134: 274–278.
5 Ikeda S, Kato T, Kenmotsu H, *et al.* A phase 2 study of atezolizumab for pretreated NSCLC with idiopathic interstitial pneumonitis. *J Thorac Oncol* 2020; 15: 1935–1942.
6 Watanabe N, Niho S, Kirita K, *et al.* Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia. *Cancer Chemother Pharmacol* 2015; 76: 69–74.
7 Kato M, Shukuya T, Takahashi F, *et al.* Pemetrexed for advanced non-small cell lung cancer patients with interstitial lung disease. *BMC Cancer* 2014; 14: 508.

8 Ikeda S, Kato T, Kenmotsu H, *et al.* Atezolizumab for pretreated non-small cell lung cancer with idiopathic interstitial pneumonia: final analysis of phase II AMBITIOUS study. *Oncologist* 2022; 27: 720–e702.
9 Otsubo K, Kishimoto J, Ando M, *et al.* Nintedanib plus chemotherapy for non-small cell lung cancer with IPF: a randomized phase 3 trial. *Eur Respir J* 2022; in press [https://doi.org/10.1183/13993003.00380-2022].