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Early View

Correspondence

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

Manuela Funke-Chambour, Namrata Kewalramani, Carlos Machahua, Venerino Poletti, Athol U. Wells, Jacques Cadranel

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Correspondence

Authors' reply: Pharmacotherapy for Lung Cancer with Comorbid Interstitial Pneumonia: Limited Evidence requires Appropriate Evaluation

Manuela Funke-Chambour[1,2], Namrata Kewalramani[1], Carlos Machahua[1,2], Venerino Poletti[3], Athol U Wells[4], Jacques Cadranel[5]

[1]Department for BioMedical Research DBMR, Department of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland.

[2]Department of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland.

[3]Department of Thoracic Diseases, "GB. Morgagni" Hospita, Forlì, Dipartimento di Medicina Specialistica Diagnostica e Sperimentale (DIMES) University of Bologna, Italy

[4]Royal Brompton and Harefield NHS Foundation Trust, London, UK; National Heart and Lung Institute, Imperial College London, London, UK

[5]Department of Pulmonary Medicine and Thoracic Oncology; Constitutive Reference Center of Rare Pulmonary Diseases, AP-HP, Hôpital Tenon and GRC04 Theranoscan, Sorbonne Université, Paris 75970, France

To The Editor,

We appreciate the interest raised by our recent article [1] and take the opportunity to address the points raised by Ishida et al.

Reply to first Comment:

The corresponding authors questioned our suggestions for second line LC therapy in fILD (Lung Cancer in fibrotic Interstitial Lung Disease) with vinorelbine (squamous cell carcinoma), and pemetrexed (adenocarcinoma). They suggest docetaxel rather than vinorelbine and pemetrexed, but there are opposing arguments. They refer to acute exacerbation rates from one retrospective nationwide surveillance of 396 patients with idiopathic interstitial pneumonia (IIP) and lung cancer in Japan [2]. However, this study does not reflect experience in other populations and regions. Drug-induced lung toxicities vary greatly between studies and ethnicities. For example, the incidence of AE associated with pemetrexed has been as low as 12.5 and 13.3% in IPF and ILD respectively [3]. Drug chemotherapeutic toxicities are reportedly higher in Asians than in Caucasians [4].

Furthermore, docetaxel causes acute exacerbation in 18.4 and 20.8% of patients with ILD and IPF, respectively [3]. In a limited number of patients, the incidence of docetaxel associated ILD exacerbation was reported to be as high as 50%, with none associated with pemetrexed and vinorelbine [5]. Kenmotsu et al. reported the incidence of acute exacerbation of ILD with use of second line chemotherapy in non-small cell lung cancer (NSCLC) to be 26% with docetaxel, 25% with pemetrexed and 20% with vinorelbine [6]. Watanabe et al. found that docetaxel monotherapy has a poor activity and substantial risks when used for the treatment of platinum-resistant NSCLC with interstitial pneumonia [7]. Tamiya et al. explicitly recommended against the use of docetaxel in pre-existing ILD patients with NSCLC due to a high incidence of chemotherapy-associated radiological ILD changes [8]. Finally, in the very recently published results of the J-Sonic Phase III trial using nab-placlitaxel plus carboplatin ± nintedanib in first line setting for LC-fILD, Japanese patients received in 2nd line most frequently S-1 and less frequently but in similar proportions docetaxel, vinorelbine or pemetrexed [9].

Hayashi et al. summarizes why docetaxel represents an inferior choice and elaborate reasons for regional differences in S-1 use [10]. S-1 is an effective anticancer drug in patients with ILD in Japan [11] but is not used in Europe. Firstly, the higher incidence of side effects in Caucasians compared to Asian populations argues against S-1 [12, 13]. Secondly and most importantly, S-1 is authorized for use in advanced gastric cancer and metastatic colorectal cancer [10], but has not been approved in lung cancer patients by the European medicine agency.

Thus, the divergence in views on lung cancer treatments in patients with fibrosing interstitial lung disease is likely to reflect differences in chemotherapy approval and usage, based in part on the variable incidence of side effects in different countries and among ethnicities.

Reply to Second comment:

Lung cancer and fILD are both heterogeneous conditions and treatment plans for both conditions depend on case by case considerations and regional variability. The onset of lung cancer in pre-existing fILDs greatly complicates management, which must be individualized according to patient tolerance, ethnicity, and local resources. This gives rise to considerable variability in reports on anticancer chemotherapy in ILD.

The authors of the correspondence letter aptly summarize the challenge faced with Immune Checkpoint Inhibitors (ICI) trial data. We have pointed out that alarming data concerning the use of ICI were mostly retrospective and have described the only two phase II trials published at the time of our review submission. Owing to editorial constraints, we did not cite the pilot study of six patients treated with nivolumab by Fujimoto et al [14].

We are surprised that the corresponding authors argue for the supposed superior efficacy of immunotherapy, compared to chemotherapy, in lung cancer associated with fILD, based on the recent article of Ikeda et al [15]. This study was halted due to drug-related toxicity.

Reply to third comment:

We acknowledge that we misleadingly formulated the trial design of the J-SONIC trial as a study result. Unfortunately, the publication became available only after submission of our paper [9]. The primary end point of reduced acute exacerbation rate was not met. We have submitted a correction to our publication.

In conclusion, the complexity of "LC-fILD" requires international efforts to better define treatment approaches. However, regional data must be generated as ethnicity influences the phenotype, as well as drug efficacy and toxicities.

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