Reviewer's report

Title: Pemetrexed for advanced non-small cell lung cancer patients with interstitial lung disease

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Reviewer: Markus Joerger

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Kato et al, Pemetrexed for NSCLC in pts with interstitial lung disease
Kato and colleagues retrospectively review 25 patients with different forms of interstitial lung disease who received pemetrexed for NSCLC, and found 3.5% of these patients suffering from pulmonary toxicity during treatment with pemetrexed, with a very high fatality rate. Although the diagnosis of interstitial lung disease is not very obvious in some patients, this report should alert oncologists to pulmonary toxicity of pemetrexed in this specific group of patients.

Major compulsory revisions:

Patients and Methods:
Line 12: „interstitial shadow on a chest CT“ is not a diagnostic or scientific term. The authors should use recognized terms to describe radiological findings in the study patients.

Discussion:
Page 17, limitations of the study: The reviewer agrees with the authors that a retrospective analysis of pemetrexed-associated pulmonary toxicity is an adequate tool to assess this issue, it should be stated here that the low number of patients suffering from ILD (n=25) does not allow to make definite conclusions about clinical endpoints such as PFS and OS (and in comparison with patients not suffering from ILD).

Conclusions:
It is not well understood why patients with IIPs are opposed to patients without ILD, as IIP is a subgroup of patients with ILD (IIP, UIP); this makes the final statements not very clear. In the final statement, the authors say that the risk of pulmonary toxicity is particularly elevated in patients with a UIP pattern, but this – again – is somewhat at odds with the previous statement that pulmonary toxicity is higher for pts with IIP compared to those without ILD. The authors should try to make the Conclusion’s Sections very clear to the reader.

Minor essential revisions:

Abstract:
The authors should explain/write-out the abbreviations (IIP, UIP) in the abstract.

Background:
Line 5 ff: Can the authors also give some numbers about the frequency of ILD in patients diagnosed with NSCLC? Could the authors mention potential inter-ethnic differences in the frequency of ILD between Asians and Caucasians (and other ethnicities), and how this could affect their study results.

Line 7: The authors are encouraged to give a short overview on the major causes of ILD (ex IIP).

Line 15: Are there similar data for the higher occurrence of chemo-associated pulmonary toxicity in patients with ILD for Caucasians or other non-Asian patient cohorts, or is this rather specific for Asian patients?

End of Introduction: Is there any rationale or hypothesis for why chemo-associated pulmonary toxicity is more frequent in Asian compared to Caucasian patients?

Patients and Methods:

Treatment methods, line 13: Standard dose for folic acid is 1mg daily; is there a particular reason the authors use 350ug of folic acid in their patients?

Statistical method, Line 13: It remains unclear which „differences in PFS and OS“ were analyzed (between patients experiencing pulmonary toxicity and those not experiencing pulmonary toxicity?).

Results:

Line 8: Please be careful with abbreviations (HC, honeycombing), better write out.

Line 16: 12% of pts had activating EGFR mutations. Why did these patients receive first-line platinum-based chemo instead of an EGFR inhibitor?

Efficacy and survival: Although disease control rate differed between groups, clinical outcome (PFS, OS) did not differ; therefore, and as of the very small number of patients, the authors’s first reporting should be that treatment response and outcome is not relevantly different between the two groups.

Discussion:

Page 16, line 9: abbreviation DTX (docetaxel?)

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I do not have competing interests