Reviewer's report

Title: Radiation recall dermatitis with soft tissue necrosis after pemetrexed

Version: 3 Date: 8 September 2008

Reviewer: francesca russo

Which of the following following best describes what type of case report this is?: An unexpected event in the course of observing or treating a patient

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:

This case report describes a metastatic Non-Small-Cell-Lung-Cancer (NSCLC) patient that developed a recall radio-dermatitis, straight after two administrations of pemetrexed (two cycles), as a second line treatment. The patient previously received chemo-radiation treatment (Please note that Taxol was one of the two drugs that were administered, concurrently with radiotherapy).

Pemetrexed is a third generation, multitarget antifolate agent, currently approved (in combination with cisplatin) for the treatment of malignant pleural mesothelioma (MPM), and (as a single agent), as a second line therapy for locally advanced / metastatic NSCLC.

Starting February 2004 (original approval in MPM) to September 2007, twelve cases of pemetrexed-related radio-dermatitis recall have been reported to FDA (FDA's Adverse Event Reporting System database).
Please, find below my comments to the report:

- I consider the case report ethical, since the patient was treated according to the current pemetrexed indications.

- Methotrexate, the predecessor of pemetrexed, showed the same effect, and there are some radiation recall effect cases related to methotrexate, reported in the medical literature.

- I would like to underline that since radiotherapy represents a key part of the lung cancer treatment (with both curative and palliative purpose), and pemetrexed is becoming more and more part of that, the risk of facing this adverse event is quite high.

- This case report is worthy to be published, due to the impact it may have on daily clinical practice. Physicians need to be aware about the potential risk the may run when treating patients with pemetrexed, after a previous irradiation, and here is the "diagnostic value" of the report (Knowing it, recognizing it!)

- Although the mechanism of radiation recall is still unknown, several hypotheses have been considered, as vascular damage, idiosyncratic hypersensitivity reaction or epithelial stem cell deficiency/sensitivity. The risk / intensity of recall effect may also be increased or affected by the total dose of radiation received, and by the interval between the time of radiation therapy and drug exposure.

- I strongly recommend a medical native-speaker review, making some sentences more fluent.

- Please, find the following more detailed comments (based on the PDF version):

  - Abstract Page 2, line 8: "Due to a progressive disease..." --> "After disease progression" or "when disease progression occurred..."

  - Page 3, line 3: "Radiation recall dermatitis may develop also without prior radiation toxicity" --> please rephrase!

  - Page 3, line 7: "...smoking history of 20 py..." --> please, write it in full

  - Page 3, line 18: "On treatment with local and systemic steroids the acute dermatitis resolved within three weeks" --> please rephrase!

  - Page 3, line 21: "...the pulmonary metastases were progressive..." --> progressed

  - Page 3, line 23: "...was offered to the patient.." --> proposed

  - Page 3, line 24: "... of 500mg/m2 was given 250 days (eight months) after..." --> I suggest to make all the time-intervals consistent. In the rest of the paper, those are expressed in "months". Do not see the need to translate this in days

- Page 4, line 3: "...could be detected clinically." --> "clinically detected"

- Page 4, lines 18-20: "The patient is alive 20 months after diagnosis of a metastatic non - small cell lung cancer and 10 months without therapy despite of progressive disease" --> please
rephrase!
- Page 5, line 3: "In our case.." --> "In this case" or "in our experience"
- Page 5, lines 5-7: "We advocate therefore careful observation of patients by experienced clinicians and considering the cessation of the treatment in case of new symptoms in the pre-irradiated area. " --> "Therefore, we suggest/recommend careful examination of patients by experienced clinicians and considering the interruption of the treatment in case new symptoms occur in the pre-irradiated area".

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

**Declaration of competing interests:**

Bullet nr 1
The answer is YES
I am an oncologist and I have been working in hospital oncology departments from 1999 to 2005.
I joined Eli Lilly in September 2005, and I am still working with Lilly as Expert Oncology Clinical Research Physician.

- Bullets nr 2, 3, 4, 5
The answer is NO