

Widespread use of pemetrexed in oncology: has it turned it into a new drug?

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Submitted Jan 30, 2014. Accepted for publication Jun 04, 2014.

doi: 10.3978/j.issn.2304-3865.2014.06.05

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2014.06.05>

To the editor,

Pemetrexed is a multitargeted antifolate approved for non-small cell lung cancer, non-squamous type, either as initial treatment in combination with cisplatin or as monotherapy for maintenance or second-line, and for non-resectable malignant pleural mesothelioma in combination with cisplatin (1,2).

Pemetrexed is usually a well-tolerated drug, however, it has got certain side-effects. The most common adverse reactions (occurring in $\geq 20\%$) when used as single-agent are fatigue, nausea and anorexia, but it may have additional complications such as diarrhea, rash or myelosuppression (3), which is generally the dose-limiting toxicity. As expected, when combined with cisplatin some of these side-effects may be more noticeable, especially myelosuppression and stomatitis.

Despite using steroids as prophylaxis, to reduce potential cutaneous toxicities (CT) or their severity, these adverse reactions have been described in up to 14% of the patients treated with pemetrexed alone, and in 22% when combined with cisplatin, being grade 3 or 4 in approximately 0.8-1.3% of cases (4,5).

Though usually mild, with periorbital or facial edema and edema of the limbs (sometimes scleroderma-like edema), CT should be promptly recognized as such on account of its potential severity, leading sometimes to a serious fluid retention or even to the appearance of skin lesions as indication of Lyell's syndrome (toxic epidermal necrolysis) for which intensive management is needed (6). Recently, a few cases of peripheral edema which associated erythema resembling a cellulitis have been described after a prolonged course of pemetrexed and this fact has turned our

attention again towards this drug which was believed less toxic in the past. We have recently seen four similar cases over the last year and though three of them had mild or moderate edema with mild redness associated and gradually resolved after stopping or reducing the dose of pemetrexed, the case of a male in his early 50s was more persistent. He was seen several times by his General Practitioner (GP) who diagnosed him with an infectious cellulitis and thus treated him with antibiotics. The possibility of a DVT was also ruled out.

Though the dose of steroids was increased before and after the chemotherapy thinking of a potential toxicity, each cycle made symptoms and signs worse and he continued receiving antibiotics. After four courses of antibiotics pemetrexed was stopped and the patient experienced a gradual improvement.

Unfortunately the mechanism underlying this toxicity is unknown and though it would be important to understand it, it might be difficult even with regular histopathological assessments.

In any case, a high level of suspicion should be kept especially in patients receiving active anticancer treatment with this drug. The fact is that though pemetrexed was initially thought to have a favourable safety profile, the recent widespread in its use has turned it into an apparently more toxic one being the CT sometimes a dose-limiting toxicity too.

We consider this clinical observation really important as it is able to emphasize the relevance of keeping an alert eye on potential new side-effects from each cytotoxic agent which might have been considered as really rare when starting its use but becoming frequent and relevant when extending its use in clinic. A close relationship with GP would help too with the patients' clinical management

making it easier for the GP to take decisions about their treatment.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Cidon EU, Varga M, Geldart T, Alonso P. Widespread use of pemetrexed in oncology: has it turned it into a new drug? *Chin Clin Oncol* 2014;3(4):53. doi: 10.3978/j.issn.2304-3865.2014.06.05