Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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There have been reports of severe, sometimes fatal, cases of cardiac failure in patients treated with crizotinib, a medicine licensed for the treatment of non-small cell lung cancer. A review by European medicines regulators of data from clinical trials and reports from clinical practice has concluded that this side effect is common (ie, occurs in between 1 in 10 and 1 in 100 patients who take crizotinib). Patients should be monitored for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention). Consideration should be given to reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur.

A review of worldwide data by EU medicines regulators has concluded that vemurafenib, a medicine licensed for the treatment of some types of advanced melanoma, can potentiate radiation toxicity. In phase III and phase IV clinical trials, approximately 1 in 20 patients who received vemurafenib had a radiation-related injury, either radiation recall or radiation sensitisation. These cases occurred in patients who received radiation before, during, or after treatment with vemurafenib. Prescribers should be aware of the risk of potentiation of radiation toxicity with vemurafenib when given before, during, or after radiotherapy. Suspected adverse reactions to vemurafenib should be reported to us on a Yellow Card.

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1 Crizotinib (Xalkori▼): risk of cardiac failure

There have been reports of severe, sometimes fatal, cases of cardiac failure in patients treated with crizotinib.

Advice for healthcare professionals:

- Monitor all patients for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention)
- Consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur

Please continue to report suspected adverse drug reactions to crizotinib or any other medicines on a Yellow Card

Crizotinib (Xalkori▼) is licensed to treat adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer.

Cases of cardiac failure

There have been reports of severe, sometimes fatal, cases of cardiac failure in patients treated with crizotinib. A review by European medicines regulators of data from clinical trials and reports from clinical practice has concluded that this side effect is common (ie, occurs in between 1 in 10 and 1 in 100 patients who take crizotinib).

Up to 25 February 2015, about 14 700 patients worldwide have received crizotinib since licensing. 40 cases of cardiac failure have been reported in the postmarketing setting. In most cases cardiac failure occurred within 1 month of starting treatment with crizotinib, and affected patients with or without pre-existing heart disorders. The reports included some cases with evidence of symptoms of cardiac failure resolving on stopping crizotinib, and cases with evidence of symptoms reoccurring when it was reintroduced.

In the UK, we have received 2 Yellow Card reports* of suspected heart failure with crizotinib up to 3 November 2015, one of which was fatal. Suspected adverse reactions should be reported to us on a Yellow Card.

*Yellow Card reports are spontaneous reports of suspected adverse drug reactions (ADRs) submitted voluntarily by healthcare professionals and members of the public in the UK. The number of reports received should not be used to determine the incidence of an ADR. This is because neither the total number of ADRs occurring, nor the number of patients using the drug is known. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, and the extent of use of a particular drug, and may be stimulated by publicity about a drug.

Further information
Letter sent to healthcare professionals, 14 October 2015

Article citation: Drug Safety Update volume 9 issue 4 November 2015: 1

2 **Vemurafenib (Zelboraf▼): risk of potentiation of radiation toxicity**

Prescribers should be aware of the risk of potentiation of radiation toxicity with vemurafenib when given before, during, or after radiotherapy.

Advice for healthcare professionals:

- Vemurafenib should be used with caution when given before, during, or after radiotherapy and prescribers should be aware of the risk of potentiation of radiation toxicity
- Suspected adverse reactions to vemurafenib should be reported to us on a Yellow Card

Vemurafenib (Zelboraf▼) is indicated as monotherapy for the treatment of adults with BRAF V600 mutation-positive unresectable or metastatic melanoma.

A review of worldwide data by EU medicines regulators concluded that vemurafenib can potentiate radiation toxicity. In phase III[1] and phase IV clinical trials, approximately 1 in 20 patients who received vemurafenib had a radiation-related injury, either radiation recall or radiation sensitisation (see below).

These cases occurred in patients who received radiation before, during, or after treatment with vemurafenib. Most cases were confined to the skin, but some involved visceral organs and resulted in a fatal outcome (including one case of radiation necrosis of the liver and two cases of radiation oesophagitis). Most patients had received doses of radiation ≥2 Gy/day.

1 Chapman PB and others, for the BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364: 2507–16.
Note that the study publication does not include radiation toxicity data; reference is included for information.

Radiation recall

Cases of radiation recall were confined to the previously irradiated area. Most cases (5 of 8) affected the skin, although 2 cases involved the lung and 1 case the bladder. Skin reactions included: eczematous, vesicular, or ulcerative lesions; erythema; and hyperkeratosis. Mean time to onset of radiation recall after vemurafenib initial dose was 12 days (range 7–21) for skin reactions, 24 days for pneumonitis; and 1 day for cystitis.

Radiation sensitisation

Most cases of radiation sensitisation (9 of 12) involved the skin, although there has been a case each involving the oesophagus, liver, and rectum. The nature of skin radiation sensitisation was similar to that seen in radiation recall skin reactions. Except for one case, vemurafenib was given concomitantly with radiation or within 3 days after completion of radiotherapy. When reported, the mean time to onset of the reaction after initiation of radiotherapy or vemurafenib was 10 days (range 3–27).

Up to October 2015, we have received 2 UK Yellow Card reports* of radiation injury and related events in patients receiving vemurafenib. Suspected adverse reactions to vemurafenib should be reported to us on a Yellow Card.

*Yellow Card reports are spontaneous reports of suspected adverse drug reactions (ADRs) submitted voluntarily by healthcare professionals and members of the public in the UK. The number of reports received should not be used to determine the incidence of an ADR. This is because neither the total number of ADRs occurring, nor the number of patients using the drug is known. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, and the extent of use of a particular drug, and may be stimulated by publicity about a drug.

Further information
Letter sent to healthcare professionals, 19 October 2015

Article citation: Drug Safety Update volume 9 issue 4 November 2015: 2

3 **Letters sent to healthcare professionals in October 2015**

A letter regarding crizotinib has been sent to inform about the risk of cardiac failure.

A letter regarding vemurafenib has been sent to inform about the risk of potentiation of radiation toxicity.

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