Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the **MHRA** and its independent advisor the **Commission on Human Medicines**

Volume 7, Issue 2, **September 2013**

Contents

The **MHRA** 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.

NHS Evidence accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

For full details on our accreditation visit **NHS Evidence**

http://www.evidence.nhs.uk/Accreditation

The recombinant granulocyte colony-stimulating factors filgrastim and pegfilgrastim are associated with an important and potentially life-threatening risk of capillary leak syndrome, characterised by: hypotension and oedema; hypoalbuminaemia; and haemoconcentration. Healthcare professionals should note the advice in article A1 to help manage and minimise the risk of this syndrome.

Also this month, findings from a retrospective subset analysis of data from a randomised, multicentre phase III study emphasise the importance of establishing wildtype *RAS* status before prescribing panitumumab alone or in combination with other chemotherapy for metastatic colorectal cancer. In addition, the contraindication in combination with oxaliplatin-containing chemotherapy now includes all patients with mutant or unknown *RAS* status because these findings have shown inferior progression-free survival and overall survival in patients with *RAS* mutations beyond *KRAS* exon 2 who received panitumumab combined with FOLFOX (oxaliplatin-containing) chemotherapy versus FOLFOX alone (see article A2).

Claire Tilstone, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Filgrastim and pegfilgrastim: risk of potentially life-threatening capillary leak syndrome

Capillary leak syndrome (CLS) has been reported in recipients of filgrastim, including patients undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor-cell mobilisation; it has also been reported in recipients of pegfilgrastim undergoing chemotherapy. Episodes varied in severity and frequency. CLS is characterised by: hypotension and oedema; hypoalbuminaemia; and haemoconcentration, and may be fatal unless promptly diagnosed and managed.

Prescribers should monitor patients and healthy donors for signs and symptoms of CLS, and should give standard symptomatic treatment immediately if symptoms occur. Advise patients to seek medical attention immediately if they experience symptoms of CLS

Filgrastim (Neupogen) and pegfilgrastim (Neulasta) are recombinant granulocyte colony-stimulating factors (G-CSF) used to stimulate the proliferation and differentiation of granulocytes, especially polymorphonuclear, in various forms of neutropenia induced by chemotherapy. Filgrastim is also used to help release blood stem cells from the bone marrow of healthy donors.

A review of filgrastim and pegfilgrastim was triggered by postmarketing reports of capillary leak syndrome (CLS). CLS is characterised by: hypotension and oedema; hypoalbuminaemia; and haemoconcentration.

Review of the signal

CLS has been reported in patients with cancer undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor-cell mobilisation who were receiving filgrastim or pegfilgrastim. Reports have generally involved people with advanced malignant disease, sepsis, those taking multiple chemotherapy medicines, or those undergoing apheresis. The mechanism of CLS remains unclear.

Filgrastim

For filgrastim, 34 postmarketing reports of CLS were received worldwide between April 1991 and August 2012, including five reports received via the Yellow Card Scheme. Of these, one case concerned a healthy donor undergoing stem-cell mobilisation and apheresis. In 12 cases, symptoms of CLS improved or recovered with supportive or corticosteroid treatment and discontinuation of filgrastim. In most cases, CLS symptoms occurred after the first dose of filgrastim. In two cases, symptoms occurred after the first dose and then reoccurred during the second. Six cases of CLS had a fatal outcome.

Pegfilgrastim

For pegfilgrastim, four postmarketing reports of CLS were received worldwide between August 2002 and August 2012. CLS symptoms appeared after the second dose in two cases. In one of these cases, CLS occurred 1 day after pegfilgrastim, suggesting a temporal association. In another case, the patient had a fatal outcome from CLS.

Conclusions

The postmarketing adverse reaction reports provide good evidence of a temporal and causal association between filgrastim or pegfilgrastim treatment and CLS. However, the benefits of filgrastim and pegfilgrastim continue to outweigh the risks. Healthcare professionals should note the following to help manage and minimise the risk of CLS:

Continues…

Further information:

Minutes from the meeting of the Pharmacovigilance Risk Assessment Committee, October 2012: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2012/12/WC500135712.pdf

Letter sent to healthcare professionals August 2013: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON309643

Advice for healthcare professionals:

- Closely monitor all patients and healthy donors for CLS symptoms, which commonly have rapid onset. Symptoms include: generalised body swelling; puffiness (which may be associated with less-frequent urination); difficulty breathing; abdominal swelling; and tiredness
- Give standard symptomatic treatment immediately if symptoms occur
- Advise patients and healthy donors to contact their doctor immediately if they develop CLS symptoms
- Any suspected adverse reactions to filgrastim or pegfilgrastim should be reported to us on a Yellow Card (www.mhra.gov.uk/yellowcard)

Article citation: Drug Safety Update September 2013 vol 7, issue 2: A1.

A2 Panitumumab: importance of establishing wildtype *RAS* (*KRAS* and *NRAS*) status before treatment of metastatic colorectal cancer

In the treatment of metastatic colorectal cancer, evidence of wildtype *RAS* status (at exons 2, 3, and 4 of *KRAS* and *NRAS*) is required before initiating treatment with panitumumab alone or in combination with other chemotherapy. Inferior progression-free survival and overall survival have been shown in patients with *RAS* mutations beyond *KRAS* exon 2 who received panitumumab combined with FOLFOX (oxaliplatin-containing) chemotherapy versus FOLFOX alone

Panitumumab (Vectibix) is a treatment for adults with metastatic colorectal cancer. It is given alone or in combination with other chemotherapy.

New safety information is available based on subset analysis of data from a randomised, multicentre phase III study (PRIME study 20050203) of panitumumab plus FOLFOX versus FOLFOX alone in patients with previously untreated wildtype *KRAS* metastatic colorectal cancer. FOLFOX is an oxaliplatin-containing chemotherapy regimen used for treatment of colorectal cancer.

The outcomes of this retrospective analysis indicate inferior progression-free survival and overall survival in patients with *RAS* mutations beyond *KRAS* exon 2 who received panitumumab combined with FOLFOX chemotherapy versus FOLFOX alone.

These findings are important and emphasise that panitumumab is contraindicated in combination with oxaliplatin-based chemotherapy in patients with mutant *RAS* (at exons 2, 3, or 4 of *KRAS* and *NRAS*), or in whom *RAS* status is unknown.

It is also important that evidence of wildtype *RAS* status is established before initiation of treatment with panitumumab in all patients.

Further information:

Letter sent to healthcare professionals August 2013: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON309643

Advice for healthcare professionals:

- Evidence of wildtype *RAS* status (at exons 2, 3 and 4 of *KRAS* and *NRAS*) is required before initiating treatment with panitumumab
- *RAS* mutation status should be determined by an experienced laboratory using a validated test method
- Panitumumab is contraindicated in combination with oxaliplatin-containing chemotherapy (eg, FOLFOX) in all patients with mutant or unknown *RAS* status

Article citation: Drug Safety Update September 2013 vol 7, issue 2: A2.

Other information from the MHRA

O1 Intravenous iron and serious hypersensitivity reactions: clarification of advice on new recommendations regarding initial test dose

We would like to make you aware that on Sept 9, 2013, we updated the information in the recent intravenous (IV) iron and serious hypersensitivity reactions article published in the August 2013 issue of the bulletin. The article advised that an initial test dose on first use of an IV iron product for a new patient is no longer recommended; all references to this recommendation will be removed from relevant product information. However, the article has been updated to clarify that the advice for administration of a product remains otherwise unchanged. For example, for iron dextrans (CosmoFer), a slower rate of administration for the first 25 mg of iron is required for every dose.

The article can be found at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON300398. If you read, downloaded, or shared the article before the update on Sept 9, 2013, please revisit the article to ensure that you have the most up to date information.

Article citation: Drug Safety Update September 2012 vol 7, issue 2: O1.