FDA approves glucarpidase to Reduce Toxic Methotrexate Levels

FDA approved glucarpidase (Voraxaze) for the treatment of toxic plasma methotrexate concentrations (>1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function on 17 January 2012.

Glucarpidase is a recombinant bacterial carboxypeptidase that hydrolyzes the carboxyl-terminal glutamate residue from folic acid and classical antifolates such as methotrexate. It converts methotrexate to its inactive metabolites (DAMPA) and glutamate. Glucarpidase provides an alternate non-renal pathway for methotrexate elimination in patients with renal dysfunction during high-dose methotrexate treatment. It is not indicated for use in patients who exhibit the expected clearance of methotrexate (plasma methotrexate concentrations within 2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered) or those with normal or mildly impaired renal function because of the potential risk of subtherapeutic exposure to methotrexate.

In a single-arm, open-label study in 22 patients who had markedly delayed methotrexate clearance, administration of glucarpidase decreased the methotrexate level to below a critical level (rapid and sustained clinically important reduction or RSCIR, ≤1 μmol/L) within 15 minutes in 10 of the 22 patients; levels stayed at that point for 8 days. Of the 12 patients who failed to achieve RSCIR, 5 patients (23%) attained a transient plasma methotrexate concentration of ≤ 1 μmol/L. In these 5 patients, the median increase of plasma methotrexate concentration from their nadir was 1.4 μmol/L (0.3 to 2.5 μmol/L).

In clinical trials, the most common related adverse events (occurring in >1% of patients) with glucarpidase were paraesthesia, flushing, nausea and/or vomiting, hypotension and headache. Serious allergic reactions, including anaphylactic reactions, occurred in less than 1% of patients.

FDA approves ruxolitinib for myelofibrosis

On 16th November 2011, the U.S. Food and Drug Administration approved ruxolitinib (Jakafi), the first drug approved to specifically treat patients with myelofibrosis.

Myelofibrosis is associated with the deregulation of JAK 1 and 2. Ruxolitinib inhibits enzymes called JAK 1 and 2 (Janus Associated Kinase) that are involved in regulating blood and immunological functioning.

The safety and effectiveness of ruxolitinib was evaluated in two clinical trials with 528 patients. Patients in both trials were resistant or refractory to available myelofibrosis therapy or ineligible for allogeneic bone marrow transplantation. All patients had splenomegaly and were in need of treatment as a result of disease-related symptoms. Patients received treatment with either ruxolitinib, placebo or the best available therapy (hydroxyurea, or glucocorticoids). A greater percentage of patients receiving ruxolitinib experienced more than a 35% reduction in spleen size when compared to patients receiving placebo or best available therapy. Similarly, a greater proportion of patients receiving ruxolitinib saw more than a 50% reduction in their myelofibrosis-related symptoms than was the case in patients receiving placebo.

The most serious side effects seen in patients treated with ruxolitinib include thrombocytopenia, anemia, fatigue, diarrhea, dyspnea, headache, dizziness, and nausea. Ruxolitinib was reviewed under the FDA's priority review program, an expedited six-month review of drugs that may offer significant advances in treatment over available therapy or that provide a treatment when no adequate therapy exists.

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