Submitted by:


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| Date of request: | September 13, 2018 |
| NCCN Guidelines Panel: | Central Nervous System Cancers |

On behalf of BTG, I respectfully request the NCCN Central Nervous System Cancers panel to review the enclosed publications as support for revision to the recommendation on use of glucarpidase currently included in the NCCN guideline for CNS Cancers.

Currently, the NCCN Guideline for CNS Cancers includes a recommendation in footnotes of Primary CNS Lymphoma (on page BRAIN-D 3 and 4 of 8):

*"Consider glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance due to methotrexate-induced renal toxicity."*

The guideline also includes a recommendation in the discussion section of the guideline pertaining to Primary CNS Lymphoma and the text currently reads:

(On page MS-17) *"Renal dysfunction induced by high dose methotrexate therapy is a potentially lethal medical emergency due to heightened toxicities resulting from a delay in methotrexate excretion. Early intervention with glucarpidase, a recombinant bacterial enzyme that provides an alternative route for methotrexate clearance, has shown efficacy in rapidly reducing plasma concentrations of methotrexate and preventing severe toxicity."*

(On page MS-19) *"In the case of methotrexate induced renal dysfunction, consider urgent glucarpidase to aid clearance."*

The specific change we are requesting is to modify the recommendation language based on the consensus guidelines published (Ramsey LB et al. The Oncologist 2017, enclosed).

We propose that the footnote language (on pages BRAIN-D 3 and 4 of 8) be revised to the following:

*"Glucarpidase is strongly recommended in the context of a rising serum creatinine if the 36-hour plasma methotrexate level is above 30 μM, 42-hour level is above 10 μM, or 48-hour level is above 5 μM. Optimal administration of glucarpidase is within 48 to 60 hours from the start of methotrexate infusion."*

In addition, we propose that the discussion section text on page MS-17 and MS-19 be revised to include the plasma methotrexate concentration thresholds as guidelines for when to intervene with glucarpidase.

Rationale: In support of the proposed change, an international panel of clinicians convened to provide expert consensus guidelines for the use of glucarpidase in patients who develop acute kidney injury and delayed methotrexate excretion during methotrexate therapy. The guideline provides specific methotrexate plasma concentrations and times that would indicate when glucarpidase should be given, and recommend administration optimally within 48 to 60 hours from start of methotrexate infusion. These guidelines have been adopted by the Children's Oncology Group, and are also referenced in UpToDate, and therefore should be reflected in the NCCN guidelines as well.

The following articles are submitted in support of this proposed change.


1. Ramsey LB, et al. Consensus Guideline for Use of Glucarpidase in Patients with High Dose Methotrexate Induced Acute Kidney Injury and DelayedMethotrexate Clearance. The Oncologist 2018 2018 Jan;23(1):52-61.

2. LaCasce AS. Therapeutic use and toxicity of high-dose methotrexate. In: UpToDate, Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com


Sincerely,


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