ISOPP is a global society of oncology pharmacy practitioners with a diverse membership representing every continent (excluding Antarctica!)

Our mission is to advance oncology pharmacy care and improve the quality of life of patients with cancer throughout the world. We achieve this by providing education, professional development activities, and the development of global Standards of Practice for oncology pharmacy. Through our Advocacy Task Force, we work together with national and global partners (e.g. UICC) to build oncology pharmacy capacity in under-resourced areas of the world and to advocate for equitable access to oncology and supportive care medicines. As such, we are pleased to be invited to comment on this years proposed additions to the WHO Essential Medicines List for cancer and look forward to working with WHO and the global oncology community.

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MONITORING METHOTREXATE LEVELS IN PATIENTS RECEIVING HIGH DOSE METHOTREXATE REGIMENS

Methotrexate (MTX) is an antimetabolite for folic acid and is considered an essential component of therapy for childhood acute lymphoblastic leukemia (ALL).[1] It is active against other types of cancer including osteosarcoma, non-Hodgkin lymphoma (NHL), some central nervous system tumors, early-stage breast cancer, and gestational trophoblastic neoplasia.[2]

MTX doses of 500 mg/m^2 or higher given intravenously are defined as high-dose (HDMTX).[3] HDMTX administration can cause toxicities such as, acute kidney injury, mucositis and bone marrow toxicity which result in delay/interruption of therapy and in severe cases have been associated with mortality.[4] Despite these toxicities, use of HDMTX can offer a survival advantage to patients with various malignancies[5,6]

Pharmacokinetic monitoring of methotrexate levels has been well established for many years. Numerous studies assessing the relationship between Methotrexate levels and toxicities have been published and have informed standards of supportive care in the form of use of folinic acid (leucovorin) to prevent unacceptable toxicity.[1,3,7] This is particularly relevant when the clearance of methotrexate is impacted by patient factors such as urinary pH, renal function, presence of third space fluid or when interacting drugs are co-administered.[3,8-12]

Access to MTX level monitoring is not always available in low & middle income countries (LMICs) or the capacity to measure MTX may be limited. Studies have been done in these settings evaluating measures/interventions to safely administer HDMTX to children/adolescents with cancer with limited monitoring of levels.[13-15] These studies demonstrate that HDMTX can be administered with 'acceptable' levels of morbidity/toxicity to the patient, with the argument that getting HDMTX is better than not getting it. However, out of necessity due to limited monitoring and supportive

care, the doses administered in these studies do not reach the full level necessary to treat many disease, leaving patients still under-treated for their malignancy.

At the present time, the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE IVD) is considers MTX therapeutic drug monitoring (TDM) as useful only in circumstances where specific patient clinical factors or the use of concomitant medications/treatments may impact on MTX clearance.[16] This decision appears to be made on the basis of only 3 publications, one on a cohort of only 28 patients. In our view, this is too limited of a scoping review of the literature to justify MTX level monitoring being only a 'moderate' priority. Per SAGE IVD criteria, MTX fulfills the criterion for 'Good correlation between the pharmacologic response and plasma concentration. An increase in drug concentration in the plasma is related with toxicity of the drug'.

Additionally, monitoring of MTX levels is also of benefit in terms of identifying patients (children, adolescents and young adults in particular) at risk for a poorer disease outcome due to low/subtherapeutic levels. In particular when genetic polymorphisms in MTX transporters are taken in to consideration permitting interventions to improve MTX levels to be initiated.[5,6, 17-21]

As professionals involved in the treatment of patients receiving HDMTX and in interpreting MTX levels to minimize toxicity and optimize survival outcomes, we feel that access to MTX monitoring should be made a high priority.

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