Title of the Project: Evaluation of Drug interaction between Levetiracetam and High dose Methotrexate in primary central nervous system Lymphoma: A Retrospective cohort study

Principal Investigator: Dr Roopali Somani

Comments Given	Changes made
Mention 'Primary' CNS Lymphoma	Thanks for the comment. The title has been revised accordingly
Primary Objective: Why Mtx levels 24 hrs post infusion, what is the expected time delay for Mtx to reach non-toxic levels if levetiracetam is co-administered.	**Standard practice in HDMTX monitoring** to check 24-hour post-infusion levels to: • Assess clearance rate early, • Guide leucovorin rescue dosing, • Identify patients at risk of delayed elimination. Hence primary end point of 24 hours was chosen
Secondary objectives: Assessing the influence of dosage of Mtx and levetiracetam on the degree of interaction can address literature gap on the same.	Any dose of methotrexate above ≥ 1 g/m² of methotrexate is considered as high dose methotrexate therapy. The dose of methotrexate is decided based on clinician discretion. However primary CNS lymphoma patients receiving chemotherapy as per the institutional records is a rare entity with less than 10 cases per annum. So The numbers maybe too small to assess the influence of dosage on degree of interaction.
How will be the potential of cumulative toxicity or delayed elimination be factored in patients receiving multiple cycles of HDMTX with repeated co-administration of Levetiracetam	There is no potential for cumulative toxicity with high-dose methotrexate, as it is administered at defined intervals during chemotherapy only after complete elimination has been achieved from the previous cycle.
Outcome measures: As the proposed drug interaction alters elimination kinetics of Mtx, relying solely on the 24-hour level may miss delayed elimination.	• **In addition to Serum methotrexate 24 hour levels, observations made at 42 hours, 48, 72 and 96 hours post-infusion values will be recorded in the case record form.** • **Time to methotrexate non toxic concentration is defined as** ➢ **24 value < 10 µmol/L** ➢ **48hours < 1 µmol/L** ➢ **72 hours <0.1 µmol/L** **So delayed elimination will not be missed.**