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Navigating the Methotrexate Shortage in Hematologic Malignancy – A Qualitative Analysis

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INTRODUCTION

A nationwide shortage of 301 drugs, including chemotherapeutic agents, was declared in the first quarter of 2023[1]. The FDA also reported a shortage of methotrexate (MTX) in March 2023, which is one of the few agents that can effectively penetrate the blood-brain barrier. This shortage forced clinicians to ration supplies and consider alternate therapies for patients with central nervous system (CNS) lymphoma and leukemia.

AIMS

- To describe the interventions aimed at mitigating MTX shortages at our institution.
- To describe our approach in selecting alternate regimens to MTX therapy -- specifically for 3 patients with CNS lymphoma or leukemia at our institution.

METHODS

The Department of Pharmacy at our institution spearheaded weekly meetings with both adult and pediatric oncologists to discuss the status of the MTX shortage. In addition to this, an email thread discussion kept track of the expected MTX needs for hospitalized patients. This channel for ongoing dialogue helped to quantify the hospital's need for MTX and assisted in the development of an institutional workflow for rationing MTX for current and anticipated admissions. We also pursued the scant alternatives to MTX for the management of our patients with CNS lymphoma or leukemia.

DISCUSSION

Patient 1: A 59-year-old woman with a 5-month history of worsening headaches who was diagnosed with primary CNS lymphoma (PCNSL) involving the right parietal and temporal regions. There was no evidence of metastatic disease in the lungs, liver or bone.

Patient 2: A 51-year-old man with a 4-year history of Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia (B-ALL) who presented with left-sided vision loss. CSF analysis on lumbar puncture revealed CNS involvement by B-ALL.

Patient 3: An 82-year-old man with a history of polio since 1956 and wheelchair dependence since 2013 who presented with 3-week history of altered mental status. Brain biopsy led to the diagnosis of PCNSL.

MTX is the mainstay of induction therapy used in CNS lymphoma and leukemia due to its ability to penetrate through the blood-brain barrier. Our first patient was started on rituximab, MTX, vincristine, and procarbazine (RMVP) induction chemotherapy for PCNSL. The addition of cytarabine (ara-c) to MTX-based induction chemotherapy has shown a 2.27-fold improvement in the complete response in a meta-analysis study[2]. However, with the shortage of MTX, we explored the option of high-dose ara-c (HiDAC) induction based on a 100% complete response achieved in 15 patients with isolated CNS disease[3] in addition to rituximab. Given her relatively young age and good overall performance status, we advocated for providing her MTX-based regimens and she was able to complete treatment with RMVP therapy as planned.

Our second patient had CNS involvement secondary to inadequately treated Philadelphia chromosome-positive B-ALL. Since there are no evidence-based treatment guidelines for metastatic CNS lymphoma secondary to ALL, we proceeded with rituximab, HiDAC, and dasatinib. He received only partial dosing for personal reasons and preferred being followed outpatient. He was found to have p.F317I mutation in his BCR-ABL tyrosine kinase domain that caused resistance to dasatinib, so he was eventually started on ponatinib, another BCR-ABL tyrosine kinase inhibitor (TKI). Ponatinib has shown good CNS penetration in preclinical models and has demonstrated benefit in BCR-ABL TKI mutations resistant to first- and second-generation TKIs[4]; this, coupled with its availability in oral form, made it the most appropriate choice for this patient.

Our third patient was an elderly man with impaired performance status and newly diagnosed PCNSL. Given his functional status, we anticipated significant side effects from high-dose MTX therapy. Based on the 77% clinical response observed in relapsing/remitting PCNSL[5], we proposed ibrutinib and rituximab therapy for him. He tolerated the therapy well and was discharged on oral ibrutinib. He has demonstrated improvement both clinically and on imaging with shrinkage of brain lesions on MRI and a negative PET scan.

There were no severe early side effects noted with any of the alternate agents in our patients.

CONCLUSIONS

Our approach can be replicated at other institutions with the ongoing drug shortages. It would ensure equitable distribution and avoid harmful delays or lack of treatment.

Frequent pharmacy-led communications and open dialogue among the specialist provides a sound approach to triaging and rationing chemotherapies in times of shortages. Since the MTX shortage is anticipated to last for a few more months, it is reasonable to consider alternative regimens for CNS lymphoma and leukemia patients - such as rituximab with ara-c for younger, more fit patients or alternatively, rituximab with ibrutinib for older, less fit patients.

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