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LETTER TO THE EDITOR

Good tolerance of high dose cytosine arabinoside and methotrexate after severe myelosuppression secondary to intrathecal administration of the same agents

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Methotrexate, a folate antimetabolite, is a widely-used anti-cancer agent against various cancers including osteosarcoma, non-Hodgkin's lymphoma, leukemias and breast cancer. Aside from cytosine arabinoside, it is one of the few agents which can be used intrathecally to treat, or for prophylaxis against malignant meningeal involvement. Although neurotoxicity is a well-known side effect of intrathecal methotrexate, owing to systemic release, it may cause myelosuppression, which is usually overlooked [1-4]. However, severe myelosuppression is unusual without concomittant systemic chemotherapy. Here, we share our experience a patient who suffered from severe myelosuppression secondary to intrathecal chemotherapy and who subsequently tolerated well a high dose of methotrexate and cytosine arabinoside.

A 37-year-old man was admitted to our institution because of non-Hodgkin's lymphoma with central nervous system (CNS) relapse. Two years earlier, he had been diagnosed elsewhere as having "lymphoblastic lymphoma," staged as IIA. After he had responded completely to the salvage chemotherapy for his 2nd relapse, he had been referred to our institution for high-dose chemotherapy with hematopoietic stem cell support. Radiological imaging, peripheral smear, bone marrow aspiration and biopsy did not reveal any sign of relapse. Soon after his admission, he had complaints of diplopia and headache. Cranial magnetic resonance imaging was normal. A diagnostic lumbar puncture was performed and methotrexate 15 mg, cytarabine 40 mg and dexamethasone 4 mg were given intrathecally for probable meningeal involvement. As cytological examination revealed atypical lymphocytes proving CNS involvement, it was decided to continue intrathecal chemotherapy. Seven days after the 2nd dose, his neutrophil and thrombocyte counts unexpectedly dropped to 20/mL and 9000/mL, and he developed febrile neutropenia and imipenem and amikacin were started. However, he was febrile despite the antibiotic therapy for three days and flucaonazole and acyclovir were instituted for oral

candidiasis and herpes zoster. The clinical picture was complicated further with grade 4 diarrhea and mucositis. Since his neutropenia was predicted to be prolonged, filgrastim was also given at a dose of 5 μg/kg until his white blood cell count was sufficient. He was neutropenic for nine days despite filgrastim support and needed platelet transfusion five times. We later omitted methotrexate from the intrathecal therapy and administered only cytarabine and dexamethasone six additional times. Lumbar puncture was cleared after the first administration.

After his recovery, he was evaluated for systemic relapse, especially for presumed bone marrow infiltration. However, bone marrow was normocellular and there was no lymphomatous infiltration. Although we were concerned about a severe toxicity since a severe unexpected myelotoxicity was observed after intrathecal chemotherapy, we decided to give systemic chemotherapy with 1 g intravenous methotrexate and 12 g intravenous cytarabine in four divided doses with filgrastim prophylaxis and folinic acid rescue to control both possible systemic disease and CNS involvement. Grade 4 neutropenia (40/mL) and thrombocytopenia (12000/L) developed on the 7th day. However, this time; neither febrile neutropenia, nor mucositis and diarrhea developed. He required platelet transfusion only once. We were surprised by a very severe myelosuppression secondary to small amounts of intrathecal chemotherapy, and a second time by relatively less myelosuppression after large amounts of the same chemotherapeutic agents. Allogeneic transplantation from his HLA full-match sibling was performed. However, he died on the 14th day after stem cell infusion secondary to infectious complications.

Methotrexate shows different pharmacokinetic properties in the presence of pleural effusion or ascits [5]. The same pharmacokinetics probably hold true for intrathecal administration. Small amounts of methotrexate released from the CNS for up to seven days or more [6] may accumulate in the liver, spleen, lymph nodes and kidneys [7]. Drug levels are even higher after intrathecal versus oral route [6]. It may require folinic acid rescue. The data on pharmacokinetics of cytosine arabinoside after intrathecal administration are sparse.

Intrathecal chemotherapy, mostly methotrexate, has small but significant systemic toxicity, which may lead to potentially life-threatening complications like severe myelosuppression and febrile neutropenia at times. Folinic acid rescue must accompany in case of anticipated systemic toxicity, like in patients having repeated and frequent administrations, systemic concurrent chemotherapy or previous irradiation of a substantial percentage of bone marrow. Experiencing severe systemic toxicity after intrathecal administration does not necessarily mean intolerance to systemic chemotherapy. Even high-doses methotrexate and cytosine arabinoside can be safely applied in such patients with filgrastim support and folinic acid rescue.

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