

## High Dose Cytarabine-Induced Peripheral Neuropathy in a Patient with Acute Myelocytic Leukemia

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### Abstract

High dose (1-3 g/m<sup>2</sup> every 12 hours) cytosine arabinoside (ara-C) is a potent treatment for acute myeloid leukemia (AML) in consolidation therapy which is well known that improves the disease-free-survival (DFS). Cerebellar neurotoxicity is well-recognized complication following high-dose cytosine arabinoside ( $\geq 3$  g/m<sup>2</sup> every 12 hours), but peripheral neurotoxicity is not common as well. This potential side effect of cytarabine during and after the consolidation treatment must be considered.

**Keywords:** Cytarabine; Peripheral Neuropathy; Cytosine Arabinoside

### Introduction

Cytotoxic medical treatment in AML (Acute Myelocytic Leukemia) contains two phases as remission induction and post-remission treatments. The common standard induction treatment are a combination of cytosine arabinoside (ara-C) and anthracycline. If the blast rate is < 5% in post-treatment bone marrow aspiration control, full remission is accepted and consolidation treatment is applied. Among these treatments, high dose ara-C (HiDAC) treatment provides the maximum rate of disease-free survival (DFS) [1]. The central nervous system toxicity especially cerebellar neurotoxicity of high-dose cytosine arabinoside is well recognized, but the peripheral nervous system toxicity has been infrequently reported [2]. Pure peripheral neurotoxicity without central nervous system affected is extremely rare [2]. In this paper we present an extraordinary case that progressive and reversible peripheral neuropathy occurred after high-dose cytosine arabinoside treatment (1.5 g/m<sup>2</sup> twice a day) as consolidation therapy.

### Case

The 66 year old woman presented with asthenia and normochromic normocytic anemia. Subsequent investigations showed numerous blasts on bone marrow smear with diagnosis of AML. Patient achieved complete full remission following two induction treatments. HiDAC (1.5 g/m<sup>2</sup> twice a day for 5 days; total, 15 g/m<sup>2</sup>) planned as consolidation therapy. After the second dose, the patient started to complain about paresthesia, formication and topognosis in hands and feet. The third dose has been postponed. In bilateral lower and upper extremities of the patient, whose vital symptoms were stable, there was paresthesia from distal towards proximal. Numbness in her feet was progressively run up to thigh and motor deficit also occurred. Electromyogram and nerve-conduction studies showed peripheral neuropathy in both peroneal nerves. During this, high fever and dyspnea have been observed. In high resolution chest tomography, cavitory lesion has been detected in lower lobe of left lung, which may be coherent with aspergilloma and anti-fungal treatment has been started. Generalized tonic clonic convulsion occurred in service monitoring of the patient and in consultation with neurology depart-

ment, computerized brain tomography (CT), brain diffusion magnetic resonance imaging (MRI) and electroencephalography (EEG) have been requested. No pathologies have been detected in CT, MRI and EEG. Peripheral neurotoxicity symptoms have been progressed and respiratory insufficiency has been finally occurred. Mechanic respiratory support provided without spending time. EMG was repeated and peripheral polyneuropathy, which affected heavy axonal and demyelinating sensorial and motor fibers, has been observed in upper and lower extremities. In routine examinations of the patient, no secondary reasons that might cause polyneuropathy were found and it was attributed to high dose cytarabine-induced toxic polyneuropathy. Steroids have not been provided due to existing pulmonary infection. Antineoplastic treatment of the patient has been postponed. Per-oral vitamin-B complex and pregabalin 75 mg 2 x 1 treatment has started. The patient has experienced flask tetraparesis and areflexia for 2 weeks. The dose of pregabalin has been increased to 150 mg 2 x 1. After one month, the patient started to complain less about paresthesia. Respiratory functions came back and in EMG control, a regression in peripheral neuropathy has been observed. High fever has disappeared after anti-fungal treatment applied for aspergillosis. Regression has been observed in existing lesion in control HRCT. At this point, the patient refused to get chemotherapy. The patient, who has been monitored for about two months in remission in hematology department, has been released to get supportive care. When the literature is analyzed, very few similar cases have been encountered.

### Discussion

Neurotoxicity has developed in this patient during consolidation treatment, who has been monitored with AML diagnosis. Cerebellar and cerebral toxicity have not been detected and the clinical signs are all with peripheral neuropathy. Steroid treatment, which may have been beneficial, could not be applied due to the pulmonary infection. The treatment has been maintained with pregabalin and vitamin-B complex. Regression has been observed after diagnosed with distal symmetrical sensorimotor polyneuropathy with EMG results. However, this regression has taken almost 2 months.

Demyelinating polyneuropathy develops in approximately 1% of HiDAC therapy and produces severe motor disability [2]. The risk factors of peripheral neuropathy are older age (greater than 60 years), drug dose/schedule/administration, cumulative drug dose, renal and hepatic dysfunction, and concomitant use of neurotropic antiemetic agents. Clinical experiences achieve that the most important risk factor is older age [2].

Oral prednisolone and plasmapheresis have been tried in some cases of peripheral neuropathy due to HiDAC and response has been determined [3]. Progressive peripheral neuropathy may also be fatal in some patients [4].

Although the mechanisms of peripheral neuropathy are still unclear, high-dose cytosine arabinoside is a therapy that is potentially toxic to the peripheral nervous system, and auto/alloimmunity may play an important role in these mechanisms. Neurologic complications of cytarabine may result from direct toxic effects on the nervous system or indirectly from drug-induced metabolic derangements or autoimmune disorders. Vasculitis is another suspected mechanism of peripheral neurotoxicity [5]. Predominantly axonal loss changes with demyelination in nerve biopsy and neurologic atrophy in muscle biopsy revealed in some cases those who have peripheral neuropathy due to HiDAC regimen [6]. Discontinuation of the offending agent may prevent irreversible injury and supporting treatments such as B complex vitamins and anticonvulsant agents as pregabalin, may help to achieve quick recovery. Further studies needed for explanation and treatment of neuropathy mechanism but clinicians should consider this important side effect during HiDAC regimen.

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