

When the Rescue Therapy Turns Neurotoxic: A Case Report

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Abstract

Case Report

Background: Nelarabine is a purine nucleoside analogue used in relapsed or refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. Although effective, it may cause severe, dose-dependent neurotoxicity, ranging from paresthesias to irreversible paralysis. **Case presentation:** We report the case of a 34-year-old woman with relapsed T-cell lymphoblastic lymphoma who developed rapidly progressive neurological toxicity four days after initiating a nelarabine based regimen. Symptoms began with symmetrical paresthesias in the lower limbs and progressed within days to ascending sensorimotor weakness, areflexia, quadriplegia, and respiratory muscle paralysis. Cerebrospinal fluid analysis revealed albuminocytologic dissociation, while infectious and lymphomatous involvement were excluded. Electrophysiological studies demonstrated a severe demyelinating sensorimotor polyneuropathy compatible with a Guillain-Barré-like syndrome. Despite corticosteroid therapy, plasma exchange, and intensive respiratory support, the patient experienced progressive neurological deterioration and ultimately died from respiratory failure. **Discussion:** Nelarabine-based combination regimens have been associated with improved survival and higher rates of transplantation in broader relapsed/refractory T-ALL/LBL populations. This case illustrates an unusually early onset of severe nelarabine-associated neurotoxicity, occurring only four days after treatment initiation, compared with the more typical latency of several weeks. Prior intrathecal chemotherapy was the only identified potential risk factor. The absence of response to plasma exchange suggests that established neurological injury may be irreversible or poorly responsive to standard immunomodulatory treatment. **Conclusion:** Nelarabine-associated neurotoxicity can occur early and progress rapidly to fatal respiratory failure. Close neurological monitoring, patient counseling, prompt treatment adaptation, and further research into predictive factors and effective therapies are essential to improve the safety of nelarabine-based regimens.

Keywords: Nelarabine, polyradiculoneuritis, neurotoxicity, lymphoblastic T cell lymphoma, case report.

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INTRODUCTION

Nelarabine is a purine nucleoside analog associated with improved outcomes in lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia (ALL).

Nelarabine, however, carries a risk of dose-dependent neurotoxicity, characterized by weakness and paralysis resembling Guillain-Barré syndrome. This adverse effect can be severe, sometimes irreversible and may be fatal.

We report the case of a 34-year-old female treated with nelarabine for relapsed lymphoblastic T cell lymphoma, who developed, few days after receiving Nelarabine, ascending motor weakness suggestive of a Guillain-Barré-like syndrome. This case highlights the rapid onset, and the severity, of neurological toxicity of

nelarabine and underscores the importance of close neurological monitoring and early treatment adaptation.

CASE REPORT

Here, we present a case of a 34-year-old female with lymphoblastic T cell lymphoma who developed such neurotoxicity leading to quadriplegia. Our patient was diagnosed at age 34. The diagnosis was established following the discovery of a mediastinal mass causing superior vena cava syndrome. Histological examination of a mediastin mass biopsy showed a diffuse proliferation without nodular architecture, composed of medium-sized cells with very scant cytoplasm. Immunophenotype: CD1a+, CD2+, CD3+, CD4+, CD5+, CD7+, CD8+, CD10+, CD99+, TdT+, CD45+, CD34-, CD20-, CD79a-, CKIT-, PAX5-, CKAE1/AE3-, Ki-67: > 95%. A bone marrow aspiration was performed, revealing a hypercellular marrow with

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normal distribution of all cell lineages and no evidence of blast infiltration. FDG-PET at diagnosis found a mediastinal and breast involvement. There was no evidence of neuromeningeal involvement on the lumbar puncture. The first phase of treatment consisted of a prephase followed by induction chemotherapy following GRAALL-T 2024. During induction, the patient received two intrathecal injections of methotrexate and intravenous chemotherapy with daunorubicin, vincristine, L-asparaginase (*E. coli*), and cyclophosphamide. At the end of induction, FDG-PET imaging demonstrated a partial response, with a 62% reduction in the size of the mass. She subsequently received consolidation chemotherapy. After one course of consolidation, including triple intrathecal therapy, FDG-PET showed clear disease progression. The multidisciplinary team decided to switch to second-line therapy, inspired by the NECTAR phase I trial [1], which combined nelarabine, etoposide, and cyclophosphamide in relapsed T-cell lymphoblastic lymphoma. Four days after initiation of chemotherapy, the patient developed ascending symmetrical paresthesias starting in the feet, initially without objective sensory or motor deficits. By day 7, symptoms had progressively worsened, with an evolving clinical picture suggestive of acute polyradiculoneuritis: ascending sensorimotor deficits, loss of deep tendon reflexes, and rapid progression to complete bed rest. Examination of the cranial pairs revealed no abnormalities, and the patient remained conscious throughout her stay in our department. The temporal relationship with chemotherapy initiation, combined with the classic pattern of acute, ascending,

symmetrical weakness and areflexia, raised strong suspicion for Guillain-Barré syndrome. Urgent neurological evaluation, cerebrospinal fluid analysis, and nerve conduction studies were performed. Cerebrospinal fluid analysis showed an acellular fluid with no lymphomatous infiltration, protein 120 mg/dL, WBC 2 cells/ μ L, consistent with albuminocytologic dissociation. A multiplex PCR panel on cerebrospinal fluid was negative, making an infectious etiology unlikely. Brain and spinal MRI demonstrated diffuse contrast enhancement of the cranial nerve pairs and uncertainty regarding contrast enhancement of the cauda equina roots; mild “ground-glass” appearance of the diffuse sustentorial white matter. Electrophysiological studies were highly suggestive of a demyelinating sensorimotor polyneuropathy, showing prolonged distal motor latencies, slowed conduction velocities, prolonged or absent F-wave latencies, and conduction block in multiple nerves. Corticosteroid therapy was initiated since day 7. However, the onset of respiratory distress due to respiratory muscle weakness, two days later, necessitated transfer to the intensive care unit (ICU), where she received PFPP plasma exchange sessions, along with fibrinogen supplementation. A rapid decline in the patient's condition was observed, requiring non-invasive ventilatory support. In the absence of response to the administered treatments, the clinical course culminated in fatal respiratory failure, which was attributed to extensive sensory and motor neuropathy involving diaphragmatic dysfunction. The clinical course is illustrated in the timeline shown in Figure 1.

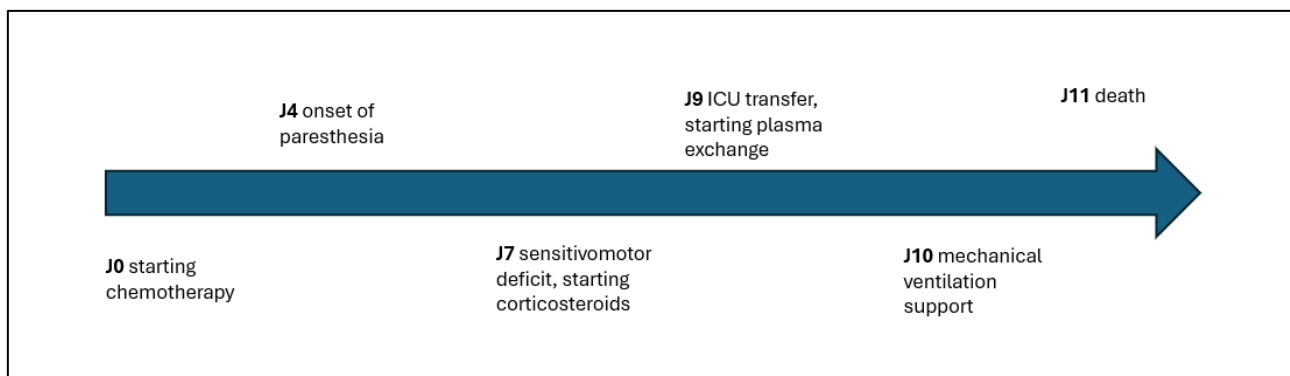


Figure 1: Timeline of events following initiation of nelarabine-based therapy

DISCUSSION

Nelarabine is a purine nucleoside analogue approved for the treatment of relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL). Nelarabine is approved as a single agent based on the results of previous studies which showed CR rates of 27% to 55% and 31% in pediatric and adult patients, supporting its clinical use despite well-documented neurotoxicity [2,3][9].

To increase the likelihood of response to this agent, Nelarabine was combined with two additional drugs in the NECTAR phase I trial, which evaluated the addition of etoposide and cyclophosphamide to nelarabine to improve response rates. Nelarabine-based combination regimens have been associated with improved survival and higher rates of transplantation in broader relapsed/refractory T-ALL/LBL populations [1]. We treated our patient according to these combination regimens. Nelarabine-induced neurotoxicity spans a wide clinical spectrum of severity, from mild and reversible paresthesia to severe complications such as transverse

myelitis, irreversible paraplegia, or progressive neurologic deterioration. Our patient developed early-onset nelarabine-induced neurotoxicity, occurring earlier than typically reported in the literature, where neurotoxicity generally develops 30–51 days after treatment initiation [3]. Our case is consistent with the literature regarding the spectrum of MRI abnormalities reported in nelarabine-induced neurotoxicity, although spinal cord hyperintensities have also been described [4]. Cerebrospinal fluid studies usually rule out leukemic, infectious, or ischemic etiologies. Reported risk factors include recent or concurrent intrathecal chemotherapy, concomitant CNS-penetrating agents such as high-dose cytarabine, and intensive transplant-conditioning regimens [5]. In our patient, the only identified risk factor was prior intrathecal therapy during induction and consolidation. Incidence estimates differ by age and study setting. In the phase II Children's Oncology Group (COG P9693) trial evaluating single-agent nelarabine in pediatric patients with relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL), grade ≥ 3 neurologic adverse events were reported in 18% of patients [6]. By comparison, severe neurotoxicity appears less common in adults treated with single-agent nelarabine, with reported rates of approximately 7–10% in the CALGB 19801, GMALL, and Italian real-world studies [7].

Peripheral nervous system involvement can also occur. In a cohort of 135 patients with T-ALL treated with frontline or salvage nelarabine-based combination regimens, three patients developed a neurologic syndrome consistent with Guillain-Barré syndrome, highlighting the potential for rare but severe peripheral neurotoxicity associated with nelarabine exposure [8,9].

In Guillain-Barré syndrome, intravenous immunoglobulin and plasma exchange are considered similarly effective in severe cases, when initiated early. Plasma exchange has also been shown to be superior to supportive care alone, whereas corticosteroids are not part of standard therapy and have not demonstrated benefit [10]. However, in our case, plasma exchange did not lead to clinical improvement; suggesting either irreversible neuronal injury or a pathophysiology not responsive to standard immunomodulation. The lack of response to plasma exchange in our patient underscores that prevention and early detection remain the mainstays; current treatments may not reverse established injury in all cases.

CONCLUSION

Nelarabine-associated neurotoxicity can present early and with severe, sometimes treatment-refractory manifestations. Enhanced vigilance, patient counseling, and further research to identify predictors and effective

interventions are essential to optimize the safe use of this molecule.

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