Clinical Reversible Myelopathy in T-Cell Lymphoblastic Lymphoma Treated with Nelarabine and Radiotherapy: Report of a Case and Review of Literature of an Increasing Complication

Maria Chiara Tisi1*, Giuseppe Ausoni1*, Maria Gabriella Vita2, Tommaso Tartaglione3, Mario Balducci4, Luca Laurenti1, Patrizia Chiusolo1, Stefan Hohaus1 and Simona Sica1

*the first two authors contributed equally
1Institute of Hematology, 2Institute of Neurology, 3Institute of Radiology, 4Institute of Radiation Oncology, Catholic University S. Cuore, Rome

Competing interests: The authors have declared that no competing interests exist.

Abstract. Eleven cases of neurological defects in T-ALL patients treated with nelarabine have been described in the last 4 years, seven of these after stem cell transplantation (SCT) for T Lymphoblastic Lymphoma (T-LBL). Most of these patients had an unfavorable outcome or irreversible neurological damage. We now report the case of a 41-year-old woman suffering from T-LBL who presented with severe, but reversible myelopathy after receiving nelarabine-based treatment and mediastinal radiotherapy, and we provide a review of the literature on the topic.

Citation: Tisi M.C., Ausoni G., Vita M.G., Tartaglione T., Balducci M., Laurenti L., Chiusolo P., Hohaus S., Sica S. Clinical Reversible Myelopathy in T-Cell Lymphoblastic Lymphoma Treated with Nelarabine and Radiotherapy: Report of a Case and Review of Literature of an Increasing Complication. Mediterr J Hematol Infect Dis 2015, 7(1): e2015025, DOI: http://dx.doi.org/10.4084/MJHID.2015.025
Published: March 1, 2015 Received: November 22, 2014 Accepted: January 8, 2015

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Dr. Maria Chiara Tisi, Istituto di Ematologia, Università Cattolica del Sacro Cuore, L.go A. Gemelli, 1. 00168 ROMA. Tel: +39-06-30154278. Fax: +39-06-3017319. E-mail: mchiarat@libero.it

Introduction. Clinical responses to Nelarabine have been demonstrated in various T-cell malignancies, but neuropathy is the most predominant adverse effect associated with this drug.1 The vast majority of nelarabine-related toxicity cases described in the last 4 years also received radiotherapy as part of the planned treatment or the conditioning regimen. Most of these patients had an unfavorable outcome or irreversible neurological damage. Herein we describe the case of a 41-year-old woman suffering from T Lymphoblastic Lymphoma, who presented with severe, but reversible myelopathy after treatment with nelarabine and radiotherapy.

Case Report. A 41-year-old woman with a medical history of thyroiditis presented at our Institution with a mediastinal mass up to 9 centimeters in diameter, without involvement of other organs or lymph nodes (LN). A biopsy of the mass was performed, and a diagnosis of T Lymphoblastic Lymphoma was established (Ki67 90%). The peripheral white blood cell (WBC) count was normal, and a bone marrow biopsy was inconclusive. No involvement of the central nervous system (CNS) was detected. Chemotherapy according to the GMALL protocol2 was started, including intrathecal CNS prophylaxis with Methotrexate alternated with Cytarabine. A complete remission (CR) by conventional criteria2 was achieved after two cycles of induction chemotherapy, although a residual infiltrate of T lymphocytes (6%) was documented in the bone marrow biopsy. The patient then underwent mediastinal (2400 cGy), and cranial radiotherapy (2400 cGy) followed by consolidation with HDAC/MITOX and HDMTX/ASP.2 During chemotherapy, major adverse effects were gastrointestinal symptoms caused by a documented cytomegalovirus colitis. The planned treatment was stopped ahead of schedule because the patient was not...
considered in CR due to residual disease in the bone marrow. In order to enhance the response in preparation for allogeneic stem cell transplantation, she was then given nelarabine (two cycles of 1500 mg/square meter on days 1, 3 and 5 of a 21-day cycle).

One month after the last dose of nelarabine, she was submitted to an unrelated matched hematopoietic stem cell transplant. During the conditioning regimen with busulfan and cyclophosphamide, she developed progressive sensory loss in the lower limbs, paraparesis, and ataxia, (grade 3 toxicity according to NCI-CTCAE v4.03). In addition, she complained of urinary retention that required bladder catheterization. Treatment was continued, and she received hematopoietic stem cells peripheral blood G-CSF mobilized; cyclosporine, rabbit anti-thymocyte globulin and MTX were administered as GVHD prophylaxis. Spinal Magnetic Resonance Imaging (MRI) with gadolinium revealed a hyperintense T2w signal from vertebral level D5 to D11, consistent with inflammatory myelitis (Figure 1a,c). A lumbar puncture was performed that was negative for both leukemic and/or infectious CNS involvement. The patient received steroid therapy with dexamethasone 4 mg twice daily for 15 days. Later, when the patient recovered from aplasia, intensive rehabilitation physical therapy was started, with progressive improvement. The last MRI performed 5 months later (Figure 1b,d) showed the persistence of spinal cord alteration. At the moment of writing this report, 22 months after the initial damage, the patient is in complete remission and able to walk with a mobility aid (5/6 according to ADL-Activities of Daily Living score).

**Figure 1 a,b,c,d.** Sagittal and axial FSE T2w images at the onset of symptoms (a,c) and after 5 months (b,d). MR images obtained at the onset of symptoms show a diffuse hyperintensity of the dorsal spinal cord gray matter (arrows in a and c). After 5 months MRI shows only a linear residual hyperintensity involving the posterior spinal cord gray matter (arrows in b and d)

**Discussion.** A frequent major dose-limiting side effect of many chemotherapeutics agents, including vinca alkaloids, taxanes, thalidomide and newer agents such as bortezomib, is peripheral neuropathy. The incidence and degree of neuropathy depends on the type of cytotoxic drug, the duration of administration, the cumulative dose, and pre-existing peripheral neuropathy. The damage is, in many cases, only partially reversible, and sometimes even completely irreversible. In this study, we report the case of 41-year-old woman suffering from severe myelopathy after nelarabine treatment, mediastinal radiotherapy and allogeneic stem cell transplantation for T-LBL.

Nelarabine is a nucleoside pro-drug of 9-beta-D-arabinofuranosyl guanine (ara-G). It was approved in October 2005 for the treatment of pediatric and adult
### Table 1. Cases of neurological defects in T- ALL patients treated with nelarabine previously reported in the literature.

| Case/Reference | Papayannidis C, [9] Am J Hematol 2010 | Forcade E, [10] Biol Blood Marrow Transplant 2013 | Kawakami M, [11] Am J Hematol 2013 | Gollard R, [12] J Clin Oncol 2013 | Hartz B, [13] Am J Hematol 2013 | Ngo D, [14] J Oncol Pharm Practice | This report |
|----------------|--------------------------------------|-----------------------------------------------|----------------------------------|----------------------------------|----------------------------------|---------------------------------|-----------|
| N of patients  | 1                                    | 4/11                                          | 3/6                              | 1                                | 1                                | 1                               | 1         |
| Diagnosis      | ALL-T                                | ALL-T                                         | ALL-T                            | ALL-T                            | ALL-T                            | T lymphoblastic lymphoma         | T lymphoblastic lymphoma         |
| Previous treatment | Standard CHT/Nelarabine | Standard CHT/allo-BMT Nelarabine after allo-BMT | Standard CHT/ allo-BMT Nelarabine after allo-BMT (1/3) Radiotherapy 1/3 | Standard CHT/Nelarabine          | Standard CHT/autologous-BMT Nelarabine before allo-BMT+ it cytarabine | Standard CHT/allo-BMT Nelarabine before allo-BMT Radiotherapy |
| CNS involvement | no                                   | 2 patients at relapse                         | no                               | no                               | no                               | no                             | no        |
| Conditioning regimen | Transplant not performed | Myeloablative(TBI)/RIC (TBI unspecified) | n1 RIC-BCNU                      | n2 MAC including TBI             | n3 MAC including TBI             | Transplant not performed        | Transplant not performed        |
| Neurological symptoms | Paresthesias in lower limbs, defect in equilibrium and walking impairment Sphincteric dysfunctions | 1pt Dysautonomia (G1) 1pt Paraparesis (G1) 1pt Peripheral sensory neuropathy (G2) 1pt Ataxia/peripheral sensory neuropathy (G2/3) | n1 Paresthesias and muscle weakness in lower limbs; urinary dysfunction n2 Muscle weakness and walking impairment n3 generalized paresthesia and muscle weakness in lower extremities, walking impairment | Left foot drop, paraplegia, weakness of upper extremities evolving to complete flaccid paralysis, ataxia Urinary retention | Seizures, Guillan-Barré-like syndrome; loss of sensitivity and reflexes of the lower limbs, dysesthesia of the arms and loss of motor control. | Bilateral lower extremity numbness, gait instability; urinary incontinence | Progressive sensory loss in lower limbs, paraparesis, ataxia. Urinary retention |
| MRI findings | Spinal cord alterations consistent with transverse acute myelitis T5 | Not described | N1 and n2 (n3 not described) T2-weighted and FLAIR hyperintensity of spinal cord (cervical and thoracic) | T2-weighted and FLAIR hyperintensity at vertebral level T6-T12 | Increased T2 signal within the dorsal columns from C2 to C6 consistent with subacute combined generation | Hyperintense T2w signal from vertebral level T5 to T11, consistent with inflammatory myelitis |
| Treatment | Intravenous corticosteroids | Not described | Intravenous immunoglobulin | Dexamethasone, cyanoethylamine, folate and multivitamin | Not described | Intensive rehabilitation physiotherapy | Dexamethasone 4 mg twice daily dosing for 15 days; Intensive rehabilitation physiotherapy |
| Outcome | Irreversible complete paraplegia | Not described | Death (n1 and n2 progression of lymphoma/n3 gastrointestinal hemorrhage: GVHD) | Death (recurrence of leukemia) | Death (blight crisis) | Partial recovery from damage; progression of lymphoma (palliative radiotherapy) | Recovery from damage; CR at 16 months after transplantation |

**Abbreviations:** N_number; CNS_Central Nervous System; MRI_Spinal Magnetic Resonance; ALL-T_T-cell acute lymphoblastic leukemia; CHT_Chemotherapy; allo-BMT_alllogenic Bone Marrow Transplantation; TBI_Total Body Irradiation; RIC_Reduced Intensity Conditioning; pt_patient; G_grade; BCNU_carmustine; n_number; MAC_Myeloablative Conditioning; it_intrathecal; CR_Complete Remission.
patients diagnosed with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), refractory or relapsed after treatment with at least two chemotherapeutic regimens. Clinical responses to nelarabine have been demonstrated in various T-cell malignancies, but neuropathy is the most predominant adverse effect associated with this drug. The incidence of neuropathy correlates with the dose administered. The reported neurological symptoms occur around the 12th day after the beginning of treatment; they are often preceded by transient somnolence, malaise, and overt fatigue, occurring 6 to 8 days after the initiation of nelarabine treatment. The patient described in our report developed a severe myelopathy with sensory loss, paraparesis, ataxia and sphincteric dysfunction. Since leukemia infiltration and ischemic, hemorrhagic or infectious etiology were ruled out, the myelopathy was attributed to cumulative drug toxicity from nelarabine and the damage caused on the spinal cord to the mediastinal radiotherapy.

The neurological dose-limiting toxicity of nelarabine was initially described in a phase I study by Kurtzberg et al., where 72% of patients enrolled experienced a neurological event. Substantial neurological toxicity was also observed in a phase II study by Berg et al., who described a grade ≥3 neurological event in 18% of patients. DeAngelo et al. reported 39 refractory or relapsed T-ALL and T-LBL in adults treated with nelarabine as single-agent: the drug showed a substantial activity, with a complete remission rate of 31% and an overall response rate of 41%. In this study there was only one grade 4 adverse event of the nervous system.

To date, eleven cases of irreversible neurological defects in T-ALL patients treated with nelarabine have been described in the last 4 years, seven of these after stem cell transplantation (SCT) for T-LBL. Detailed clinical information on these previously reported cases are summarized in Table 1. Patients received nelarabine either prior to SCT or after SCT for lymphoma progression. The vast majority also received radiotherapy as part of the planned treatment or in the conditioning regimen. In the report from Kawakami et al., an excess of nelarabine neurotoxicity (up to 50%) was detected after HLA-haploidentical SCT. In the recent paper from Ngo et al, concurrent administration of single dose intrathecal cytotoxic arabinoside was felt to exert an additive neurotoxic effect due to the close timing of administration to nelarabine. MRI findings, when reported, are superimposable resulting in T2-weighted and FLAIR hyperintensity predominantly at thoracic or cervical level. In conclusion, we emphasize that the onset of not specific symptoms, like “symmetric neurologic symptoms”, seldom reversible despite intensive rehabilitation, should raise the suspicion for nelarabine toxicity in patients who received a previous treatment with this active drug usually after a short latency period, particularly if combined with radiotherapy or intrathecal administration of cytotoxic drug.

References:

1. Cohen MH, Johnson JR, Massie T, Sridhara R, McGunn WD Jr, Abraham S, Booth BP, Goheer MA, Morse D, Chen XH, Chidambaram N, Kenna L, Gobburu JV, Justice R, Pazdur R. Approval summary: nelarabine for the treatment of T-cell lymphoblastic leukemia/lymphoma. Clin Cancer Res. 2006 Sep 15;12(18):5329-35. http://dx.doi.org/10.1158/1078-0432.CCR-06-0906. PMid:17000665

2. Hoelzer D, Gökbuget N, Digel W, Faak T, Kneba M, Reutzel R, Romejko-Jarosinska J, Zwozinski J, Walewski J. Outcome of adult patients with T-lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. Blood 2002; 99:4379-85. http://dx.doi.org/10.1182/blood.2002-01-0100. PMid:12036865

3. Cheson BD. Role of functional imaging in the management of lymphoma. J Clin Oncol 2011 ;29:1844-54. http://dx.doi.org/10.1200/JCO.2010.32.5225. PMid:21482982

4. Common terminology criteria for Adverse Events (CTCAE); v4.03; June 14, 2010. National Institute of Health; National Cancer Institute.

5. Reilly KM, Kisof DF. Profile of nelarabine: use in the treatment of T-cell acute lymphoblastic leukemia. Onco Targets Ther 2009; 2:219-28. PMid:20616909 PMid:PMC2886323

6. Kurtzberg J, Ernst TJ, Keating MJ, Gandu V, Hedge JP, Kisof DF, Lager JJ, Stephens C, Levin J, Krenitsky T, Elion G, Mitchell BS. Neurological dose limiting toxicity of nelarabine. Hematol J 2010; 11:560-6. http://dx.doi.org/10.1038/jhh.2010.56754. PMid:19908652

7. Berg SL, Blaney SM, Devidas M, Lampkin TA, Margo A, Bernstein M, Billet A, Kurtzberg J, Reaman G, Gaynon P, Whitlock J, Krailo M, Harris MB; Children's Oncology Group. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol. 2005 May 20;23(15):3376-82. http://dx.doi.org/10.1200/JCO.2005.03.426. PMid:15908649

8. DeAngelo DJ, Yu D, Johnson JL, Coutre SE, Stone RM, Stopeck AT, Gockerman JP, Mitchell BS, Appelbaum FR, Larson RA. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood. 2007 Jun 15;109(12):5136-42. http://dx.doi.org/10.1182/blood-2006-11-057654. PMid:17344466. PMid:PMCID:PMC1941786

9. Papayannidis C, Iacobucci I, Abbenante MC, Curti A, Paolini S, Parisi S, Baccarani M, Martelli G. Complete paraplegia after nelarabine treatment in a T-cell acute lymphoblastic leukemia adult patient. Am J Hematol 2010 ;85: 608. http://dx.doi.org/10.1002/ajh.21719. PMid:20658590

10. Forcade E, Leguay T, Vey N, Baruchel A, Delaunay J, Robin M, Socié G, Donnifret H, Pefautif de Latour R, Raffoux E. Nelarabine for T cell acute lymphoblastic leukemia relapsing after allogeneic hematopoietic stem cell transplantation: an opportunity to improve survival. Biol Blood Marrow Transplant 2013 ;19: 1112-6. http://dx.doi.org/10.1016/j.bmct.2013.04.010. PMid:23648236

11. Kawakami M, Taniguchi K, Yoshihara S, Ishii S, Kaida K, Ikegame K, Okada M, Watanabe S, Nishina T, Harada H, Nakagawa M, Ogawa H. Irreversible neurological defects in the lower extremities after haploidentical stem cell transplantation: possible association with nelarabine. Am J Hematol 2013; 88: 853-7. PMid:23757212

12. Gollard RP, Selco S. Irreversible myelopathy associated with nelarabine in T-cell acute lymphoblastic leukemia. J Clin Oncol 2013 ;31:327-31. http://dx.doi.org/10.1200/JCO.2012.45.4728. PMid:23715575

13. Hartz B, Löbel U, Hagel C, Escherich G. Fatal neurological side effects with nercisosis of spinal cord following nelarabine treatment in a child with relapsed T-cell acute lymphoblastic leukemia. Am J Hematol 2013 ;88:1096-7. http://dx.doi.org/10.1002/ajh.23550. PMid:23873785

14. Ngo D, Patel S, Kim EJ, Brar R, Koontz MZ. Nelarabine
neurotoxicity with concurrent intrathecal chemotherapy: Case report and review of literature. J Oncol Pharm Pract 2014;0:1–5.