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Case Report

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Nelarabine-associated myelopathy in a patient with acute lymphoblastic leukaemia: Case report

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Abstract

Introduction: Nelarabine is a purine analogue approved for the treatment of patients with T-cell lymphoblastic lymphoma and T-cell acute lymphoblastic leukaemia (T-ALL) that have relapsed or are refractory to two previous chemotherapy regimens. Adverse reactions to nelarabine include neurological toxicity, the pathophysiological mechanisms of which are unknown, although the administration of intrathecal therapy at therapeutic doses given concomitantly with high-dose systemic chemotherapy that crosses the blood–brain barrier may potentiate neurotoxicity.

Case report: We report a case of a 29-year-old woman with a diagnosis of relapsed T-ALL who developed severe myelopathy and polyneuropathy of toxic origin that led to paraplegia, upper-limb paresis, and dysautonomia after the first cycle of nelarabine.

Management and outcome: Rehabilitation and pharmacological treatments were initiated early, but no evidence of a significant clinical change was obtained.

Discussion: Neurotoxicity is a dose-dependent side effect of nelarabine. It is therefore important to consider previously administered neurotoxic drugs before using nelarabine and to monitor patients closely so as to be able to act promptly in case of toxicity. In accordance with the data obtained and based on the Naranjo algorithm, the adverse reaction could be considered possible.

Keywords

Nelarabine, T-cell acute lymphoblastic leukaemia, Neurotoxicity

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Introduction

Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-*D*-arabinofuranosylguanine (ara-G) with selective cytotoxicity to T lymphoblasts.[1] It is indicated for the treatment of patients with T-cell lymphoblastic lymphoma (T-LBL) and T-cell acute lymphoblastic leukaemia (T-ALL) that have relapsed or are refractory to two previous chemotherapy regimens. Its approval was granted based on limited data from pivotal clinical studies[2] in which complete response rates were obtained.

The most common adverse reactions are anaemia, thrombocytopenia, neutropenia, infections, gastrointestinal disorders, and nervous system disorders such as somnolence, dizziness, headache, and paresthesia. In addition, during its post-marketing phase, severe dose-limiting neurological toxicities have been reported. Cases of reactions associated with demyelination or peripheral neuropathies like Guillain-Barré syndrome, not always reversible, have also been described. Thus, patients should be carefully monitored for neurological reactions and treatment should be discontinued at the first sign or symptom of grade 2 or higher neurotoxicity event.

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We report a case of a patient with relapsed T-ALL who developed a severe neuropathy after the first cycle of nelarabine.

Case presentation

A 29-year-old woman who, in November 2015, was diagnosed with T-ALL (pre-T according to the EGIL classification) based on the presentation of left postauricular, right supraclavicular, and right axillary lymphadenopathies, clinical features of hyperaesthesia of the upper trunk, upper limbs, and head, and occasional itching. The bone marrow aspirate (BMA) showed that blasts accounted for 88.3% and expressed markers of immaturity (CD34 and nTDT) as well as T-lineage highly specific markers (CyCD3), but no B-lineage markers (CyCD79a-, CD19-) or myeloid markers (CyMPO-, CD13-), except CD33. Blasts had normal cytogenetics and showed no rearrangement of *BCR/ABL* (by PCR analysis) or *MLL* (by FISH analysis) genes. There was no central nervous system involvement at the time of diagnosis.

Treatment according to the PETHEMA LAL-AR 2011 protocol[3–5] was initiated after diagnosis, but the patient failed to respond to the first induction regimen. A second induction regimen with FLAG-IDA was initiated, achieving a minimal residual disease (MRD) of 0.03% and therefore allowing the patient to proceed to consolidation therapy, reaching an MRD status <0.001%. At that point, an allogeneic hematopoietic stem cell transplantation (Allo-HSCT) was considered but finally ruled out because of the lack of an appropriate donor. Late consolidation was followed by maintenance therapy with weekly re-inductions, with a total of nine cycles. The last three cycles were given without intrathecal therapy due to post-lumbar puncture headaches without other neurological manifestations thus far. At that time, MRD remained undetectable, and maintenance therapy was continued for a second year, but no re-inductions were given.

Bone marrow relapse occurred 18 months after treatment initiation (6% blasts and MRD of 6.7%), and a donor search process was reactivated. While waiting for a donor, rescue therapy with nelarabine was started (1500 mg/m^2 IV on days +1, +3, and +5 every 21 days) together with a prophylactic dose of triple intrathecal therapy, and the patient was hospitalised for close monitoring. During the first days of treatment, the patient complained of headaches and self-limited paresthesias in feet and fingertips, with no other neurological manifestations, and the cerebrospinal fluid analysis showed no evidence of meningeal infiltration. Three weeks after the first cycle of nelarabine, a BMA was repeated providing no evidence of response (6–10% blasts), and therefore after contacting the reference transplant centre, treatment with clofarabine (40 mg/m^2 days 1–5) and citarabine (2 g/m^2 days 1–5) was started to try to achieve the required complete remission for Allo-HSCT. Detailed information of the treatment administered is provided in Figure 1.

On day +30 of nelarabine treatment (day +3 of clofarabine and citarabine treatment), the patient complained of dysesthesias in lower limbs, possibly indicative of toxic polyneuropathy, progressively ascending during the following days and leading to significant paraplegia with paresis of upper limbs in addition to dysautonomia (urine retention and constipation). The magnetic resonance imaging (MRI) performed showed a weak signal hyperintensity on T2-enhanced images in the dorsal portion of the cervical and thoracic spinal cord, and the control MRI performed 13 days later showed a more pronounced hyperintensity, evidencing progression. Once the definitive neurological diagnosis of sensory polyneuropathy associated with a posterior cord syndrome of toxic aetiology was established, rehabilitation treatment was initiated promptly together with a pharmacological treatment including vitamin B6 and vitamin B12 at high doses, dexamethasone 4 mg every 12 h for seven days followed by down-titration, and four sessions of therapeutic plasma exchange, with no improvement but with no progression of the neuropathy.

Haematologically, a complete morphological response was achieved with an MRD $\leq$0.002%, and therefore a haploidentical Allo-HSCT from maternal peripheral blood after conditioning with fludarabine and busulfan was performed. The complications that developed during this process were pharyingitis and meningitis, with no microorganisms isolated (it was aseptic given that the patient was being treated with antibiotics).

After the Allo-HSCT, in view of the absence of improvement in limb mobility, intensification of the rehabilitation treatment at a specialised local site was decided. Currently, the patient continues with paraplegia and dysautonomia that requires intermittent bladder catheterisation. With regard to the T-ALL, 17 months after the Allo-HSCT, the patient has a localised extramedullary relapse involving the orbit and is waiting for initiation of localised radiotherapy.

Discussion

Nelarabine is a purine analogue that was approved by the FDA in 2005 for the treatment of patients with refractory or relapsed T-ALL and T-LBL after treatment with at least two previous chemotherapy regimens. Its safety profile was obtained based on pivotal clinical trials, although reports of various events have been complementing its adverse reaction profile.

Chemotherapy regimens administered												
Week (0=Diagnosis)	0	1	7	16–20	25–32	35–71	75–103	104	105	108	109	
Date	11/20/2015	11/24/2015	01/04/2016	04/02/2016	07/05/2016	08/12/2016	04/27/2017 To 11/06/2017	11/15/2017	11/22/2017	12/12/2017	12/19/2017	
Treatment schedule		PETHEMA LAL/AR-2011										
		Induction -1	induction - 2	Consolidation	Late consolidation	Re-induction Maintenance	Maintenance		Nelarabine + Prophylactic ITT		Clofarabine + cytarabine	
Response		No response	RC	RC	RC	RC		Relapse		Relapse		
Drugs		mg										Total dose (mg)
Corticosteroids	Prednisone	1700										1.700
	Dexamethasone			500	475	4160						5.135
ITT	Hydrocortisone	40	20	60	60	100			20			300
	Methotrexate IT*	24	12	36	36	60			12			180
	Cytarabine IT*	60	30	90	90	150			30			450
Asparaginase IV		149.000		91.400	97.800							338.200
Clofarabine IV											320	320
Daunorubicin IV		268										268
Cytarabine IV*			15.000	12.000	13.120						3200	43.320
Fludarabine IV*			223									223
Idarubicin IV			53									53
Mercaptopurine OR						12.900	18.400					31.300
Methotrexate IV *				15.500	16.250							31.750
Methotrexate IM *						780	930					1.710
Nelarabine IV *									7.200			7.200
Vincristine IV*		8		8	8	18						34

CR: Complete Response; ITT: Intrathecal therapy;*: neurotoxic drugs; IV: intravenous; OR: oral; IM: intramuscular

Figure 1. Chemotherapy regimens administered. *Neurotoxic drugs.
CR: complete response; ITT: intrathecal therapy; IV: intravenous; OR: oral; IM: intramuscular.

The neurotoxicity of nelarabine has been described as a dose-dependent side effect, with most cases being of mild severity and with grade 3 or 4 toxicities developing exceptionally. Its incidence and severity have been associated with different factors such as age, comorbidities, dose and duration of nelarabine treatment, and concomitant administration of other cytotoxic agents.

The incidence of spinal cord involvement is based on a limited number of published cases, and the underlying pathophysiological mechanisms are unknown. The ease with which it crosses the blood–brain barrier[6] supports the hypothesis suggested by authors such as Papayannidis et al.[7] that, under certain unknown circumstances, a selective destruction of the dorsal spinal cord could occur. Other authors such as Alberti et al.[8] or Lalayanni et al.[9] postulate a potential autoimmune aetiology like Guillain-Barré syndrome, given the similarity of the signs and symptoms. Table 1 shows the 14 cases that have been published describing the neurotoxicity produced by nelarabine.

There was no involvement of the central nervous system in our patient, and this has only occurred in 2 of the 14 cases published.[11] She also received prophylactic intrathecal chemotherapy like all the other patients described. Several articles have been published suggesting that intrathecal therapy at therapeutic doses given concomitantly with high doses of systemic chemotherapy that crosses the brain–blood barrier may potentiate neurotoxicity. Dat Ngo et al.[12] described a case in which neurotoxicity from nelarabine was developed following its use with concomitant intrathecal therapy. Currently, this combination is not described in the summary of product characteristics.[2]

In our patient, neurotoxicity occurred as sensory neuropathy in both lower limbs with ascending progression and accompanied by motor impairment as well as dysautonomia. In the 14 cases published, dysesthesia occurred in seven patients, whereas dysautonomia, in the form of bladder or intestinal dysfunction or both, occurred in eight patients.

Time to onset of neurological symptoms following the administration of nelarabine is variable. In our case, it developed 30 days after nelarabine initiation. Kurtzberg et al.[13] suggest that neurological symptoms start to develop from day +12. Median time to the onset of symptoms in the cases described in Table 1 was 51 days from the first dose and 30 days from the last dose.

There is no specific regimen for the treatment of neurotoxicity, although we have noticed in the literature that a number of therapeutic approaches have been used several times with variable responses. No treatment was given or specified in five of the cases reviewed.[11,14] Among the nine patients who did receive therapy, five received corticosteroids,[7–9,15,16]

Table 1. Neurotoxicity cases in relapsed T-ALL/T-LBL patients treated with nelarabine.

Case, reference Diagnosis/CNS involvement	Received treatment (no. of cycles)/ITT	Neurological symptoms (onset time from starting nelarabine/since last dose)	Treatment for neurotoxicity	Outcome
Male 30 y/o[7] T-ALL/No	Standard CHT/nelarabine (2) // Not specified	Paresthesia in both lower extremities with cranial extension. Defect in equilibrium and walking impairment. Dysautonomia (+31/+3)	Intravenous corticosteroids Intensive rehabilitation physiotherapy	Irreversible complete paraplegia
Male 41 y/o[15] T-ALL/No	Standard CHT/nelarabine (3) //7 previous ppx doses	Hypoesthesia in lower extremities and ataxia. Ascending myelopathy with lower extremities paraplegia, hypoesthesia at T4–T6 level. Dysautonomia. Weakness of upper extremities, ataxia, and dystonia. Complete flaccid paralysis (+30/+77)	Dexamethasone (24 mg/d) VB12 + folic acid TPE × 10 d	Death (leukaemia relapse)
Male 11 y/o[14] T-ALL/No	Standard CHT/nelarabine // 1 previous ppx dose	Seizures. Guillain-Barré-like syndrome (+7)	Not specified	Death (blast crisis)
Male 53 y/o[10] T-LBL/No	Standard CHT/allo-SCT/standard CHT + nelarabine (2)/allo-SCT // not specified	Paresthesia and muscle weakness, urinary dysfunction. Complete paresis and paraplegia. Upper extremities paresis (+60/+39)	Intravenous immunoglobulins	Death (leukaemia progression)
Male 31 y/o[10] T-LBL/No	Standard CHT/nelarabine (3)/Allo-SCT // not specified	Muscle weakness and walking impairment (+88/+46)		Death (leukaemia progression)
Male 47 y/o[10] T-ALL/No	Standard CHT/nelarabine (1)/Allo-SCT // not specified	Paresthesia and lower extremities weakness, walking impairment (+95)		Death (Gastrointestinal bleeding, Graft Versus Host Disease)
Four patients[11] T-ALL/2 at relapse	Standard CHT/allo-SCT/nelarabine // not specified	1 dysautonomia/1 Paresthesia/1 peripheral sensory neuropathy / 1 Peripheral sensory neuropathy, ataxia	Not specified	Not specified
Female 37 y/o[12] T-LBL/No	Standard CHT/auto-SCT/nelarabine (2)/allo-SCT // 4 previous ppx doses, 1 concomitant	Paresthesia in both lower extremities, walking impairment, urinary incontinence (+42/+10)	Intensive rehabilitation physiotherapy	Partial recovery; progression of lymphoma
Female 41 y/o[16] T-LBL/No	Standard CHT/nelarabine (2)/allo-SCT // 1 previous ppx dose	Hipoesthesia in both lower extremities, paraparesis, ataxia. Urinary retention (+51/+30)	Dexamethasone 4 mg/12 h × 15 d Intensive rehabilitation physiotherapy	Recovery from damage; CR at 16 months after transplant
Male 28 y/o[8] T-ALL/No	Standard CHT/allo-SCT/nelarabine (2) // 1 previous ppx dose	Hipoesthesia in both lower extremities, walking impairment. Ataxia, urinary dysfunction, glove and stocking hypoesthesia (+51/+30)	Intravenous immunoglobulins 0.4 g/kg/d Dexamethasone 16 mg/d × 5 d	Damage improvement, possibility to stand up and walk. CR at three years after transplant
Male 24 y/o[9] T-LBL/No	Standard CHT/Nelarabine (2) // 5 previous ppx doses	Hipoesthesia in both lower extremities with abdominal progression. Progressive muscle weakness with walking impairment. Hypoesthesia at T8 level, seizures. Complete paraplegia with dysautonomia. Hypoesthesia at C5–C6 level. (+22/+22)	Intravenous immunoglobulins 2 g/kg/d High doses of intravenous corticosteroids (worsening) Vitamins, TPE × 5d. Intensive rehabilitation physiotherapy	Slight improvement at +105 day. Death (leukaemia progression)

T-ALL: T-cell acute lymphoblastic leukaemia; T-LBL: T-cell lymphoblastic lymphoma; CNS: central nervous system; ITT: intrathecal treatment; y/o: years old; CHT: chemotherapy; ppx: prophylactic; VB12: vitamin B12; TPE: therapeutic plasma exchange; Allo-SCT: allogenic stem cell transplant; Auto-SCT: autologous stem cell transplant; CR: complete response.

five received intravenous immunoglobulins[8–10] (leading to clinical worsening following its administration in one of the cases[9]), four underwent intensive rehabilitation,[7,9,12,16] two received vitamin supplements including vitamin B12,[9,15] and two were treated with therapeutic plasma exchange.[9,15] Our patient received corticosteroid therapy, intensive rehabilitation, therapeutic plasma exchange, and vitamin supplements with vitamins B12 and B6 for the treatment of neurotoxicity. This led to a slight improvement of paraplegia which may have been more severe as a result of the meningitis that occurred during the Allo-HSCT. With regard to the degree of response in the other cases, a single case of reversible neuropathy,[16] one case of progression to irreversible paraplegia,[7] and three cases of improvement of neurological impairment[8,9,12] have been described. In the remaining nine cases, the neurological status was not specified.

Even though our patient received neurotoxic agents as methotrexate, cytarabine, vincristine, or fludarabine, its administration was more than half year prior to the appearance of the neurological manifestations described. According to data obtained and on the basis of Naranjo probability scale, the adverse reaction for those agents was considered doubtful. Conversely, nelarabine causal relation to neurological events was determined as possible.[17]

In compliance with the Spanish Act on Guarantees and rational use of medicines and health products (Act 29/2006), which establishes the obligation of all health professionals to notify any suspected adverse drug reaction (ADR) detected during standard practice, this ADR was reported to the Pharmacovigilance Centre of the Balearic Islands using the Yellow Card form.

Conclusion

Nelarabine is a drug that has demonstrated its efficacy in the treatment of refractory or relapsed T-ALL and T-LBL. Neurological toxicity is a dose-dependent side effect which, in some cases, can be very serious. It is important to take into account the previously administered neurotoxic drugs before using nelarabine and to monitor patients closely so as to be able to act promptly in case of neurological complications.

Declaration of Conflicting Interests

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