

Ibrutinib-induced chronic demyelinating polyneuropathy in a 65-year-old man with chronic lymphoid leucosis: A clinical case

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ABSTRACT

Relevance. Most of oncological patients undergo chemotherapy, which has a wide range of various toxic reactions including polyneuropathy. Ibrutinib is a relatively new medicine with a few side effects associated with peripheral polyneuropathy. Demyelinating polyneuropathy induced by this drug is not yet defined in scientific literature.

Methods. The paper describes the first case of demyelinating polyneuropathy associated with ibrutinib in a 65-year-old man with chronic lymphoid leucosis. The authors carried out clinical assessment, laboratory and instrumental examinations.

Results. Ibrutinib administration was followed by chronic sensorimotor distal polyneuropathy. The changes measured in nerve conduction studies (NCS) corresponded to chronic inflammatory demyelinating polyneuropathy (CIDP) electrophysiological criteria (EFNS/PNS, 2010). The positive aspect of the described clinical case is that polyneuropathy regressed almost completely after a dose reduction and subsequent drug discontinuation. The second NCS made 5 months after a dose reduction showed an increase in compound motor action potential (CMAP) and nerve conduction velocities (NCV); however, normal values were not reached.

Conclusion. This report on demyelinating neuropathy associated with ibrutinib requires further study of the drug effects. The below clinical description is of great interest since most of polyneuropathies associated with chemotherapy are axonal, but not demyelinating.

Keywords: lymphoproliferative diseases, chemotherapy, chemotherapy-induced neuropathy, ibrutinib, chronic demyelinating polyneuropathy, NCV, spontaneous regress

INTRODUCTION

Chemotherapy is a uniform method of treatment for a large number of oncological diseases, which form one of the main causes of morbidity and mortality in the world. However, along with high efficiency, this type of therapy has a wide range of side effects, which significantly impair the patients' quality of life, demand correction of doses of the used drugs, delay the succession of courses or cease the treatment completely, involve additional costs for diagnostics and rehabilitation (1-3). Analysis and prevention of chemotherapy side effects is undoubtedly of great medical, social and economic importance; it is an obviously urgent problem in modern medical science.

According to the USA National Cancer Institute, neurotoxicity together with myelosuppression

and renal failure is one of the most widespread dose-dependent undesirable effects of chemotherapy. Besides, peripheral neuromotor apparatus lesion, considering hemo-neural barrier insufficiency, occurs most commonly (1-6).

This paper describes a case of demyelinating sensorimotor polyneuropathy in a patient with chronic lymphoid leucosis associated with ibrutinib administration.

CLINICAL CASE

A 65-year-old patient, a retired man, referred to the outpatient department of the Research Center of Neurology (Moscow, Russia) in July 2016 complaining of weakness in feet and awkwardness in wrists, numbness in fingers, shins and feet, and lack of confidence when walking.

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The patient's anamnesis showed that since 2008 he was followed up by oncohematologist for the diagnosis "chronic lymphocytic leukemia, stage B, the state after a course of leukeran and fludarabine (LF) therapy, 5 courses of chemotherapy with fludarabine, cyclophosphamide and rituximab (FCR), 10 courses of rituximab and bortezomib (RB) therapy, remission". In 2008-2009 within a course of chemotherapy, the patient received leukeran and fludarabine. In 2010-2011 he underwent 5 courses according to FCR scheme. This treatment was followed by a 1-year remission. A recurrence of chronic lymphocytic leukemia was detected in 2012; additional 10 courses of chemotherapy, which were carried out according to the RB treatment regimen in 2012-2014, led to stabilization. The patient had no any neurological complaints against the background of the above chemotherapeutic cycles, his state was satisfactory. At the end of 2015 (on 16.12.2015), it was decided to switch to ibrutinib 420 mg per day. In May 2016 (i.e. 5 months after the beginning of ibrutinib administration), the patient began to feel slow steady increase of polyneuritic sensitive and motor disturbances. He was diagnosed with toxic polyneuropathy at the place of his residence and prescribed neurometabolic therapy, which was ineffective. In June 2016 (6 months of ibrutinib therapy, 1 month after the beginning of neurologic disorders), the oncohematologist reduced the dose of ibrutinib to 280 mg a day, taking into account the progressive character of polyneuropathy.

The patient was examined at our site one month after the drug dose reduction, which helped to stabilize his state. The patient denied alcohol intake, aggravated hereditary anamnesis, and accompanying diabetes mellitus.

The results of the general examination were as follows: normosthenic constitution (weight – 75 kg, height – 170 cm), no symptoms of edema, no rash and other skin lesions, no bone deformations.

The neurological presentation in July 2016: the patient was alert, attentive and oriented; the speech was clear and fluent with good repetition, comprehension and naming; there were no meningeal signs. Cranial nerves were intact. Examination revealed distant symmetric peripheral quadriplegia with a decrease in strength in the ulnar group of arm muscles to Grade 4 of Medical Research Coun-

cil (MRC) scale (the right side was slightly worse), in extensors and flexors of the feet and toes – to Grade 3 of MRC scale. In other groups of muscles (the muscles of the shoulder girdle, the extensors of wrists and fingers, the median group of arm muscles, the muscles of shin flexors and extensors) the strength was sufficient. The patient stood on his toes and heels with difficulty; at the same time, he squatted down and stood up quite satisfactory. Muscle bulk was normal, muscle tone was decreased. Fasciculations were absent. Tendon reflexes were symmetric: m. biceps brachii – brisk, stylo-radial – low, knee – brisk, ankles – absent. There were no pathological reflexes and tension symptoms. Coordination tests were uncertain. In Romberg's test with open eyes, the patient stood steadily, with closed eyes – reeled (sensitive ataxia). There was a painful hyposthesia of the distal polyneuritic type. The position and vibration senses were lowered in toes. The light touch sense was reduced in the distal parts of legs. Thermoesthesia was not changed. Pelvic organ functions were not disturbed. There was symmetric steppage gait when walking, but the man walked without support. The higher cortical functions corresponded to the functions of his age.

The additional examinations and their results were the following:

- Electrophoresis of serum and urine protein with immunofixation: no pathological monoclonal secretion was revealed;

- Antibodies to GM1 gangliosides: GM2-GM3-GM4; GD1a, GD1b, GD2-GD3, GT1a, GT1b, GQ1b, sulfatides were negative;

- Electrophysiological study included needle electromyography and nerve conduction studies (NCS). NCS revealed rough generalized minimum asymmetric sensorimotor neural level of lesion of initially demyelinating character; it was much more expressed in the lower extremities. In studying the motor nerve fibers of arms, we registered conduction blocks of different degree of manifestation in the areas atypical for compression. In studying the motor and sensory nerves of legs, there were no registered responses of compound motor action potential (CMAP) and compound sensory action potential (CSAP). In studying the distal muscle of the leg (m.tibialis anterior dex.) by a needle electrode at rest, single denervation activity of muscle fibers

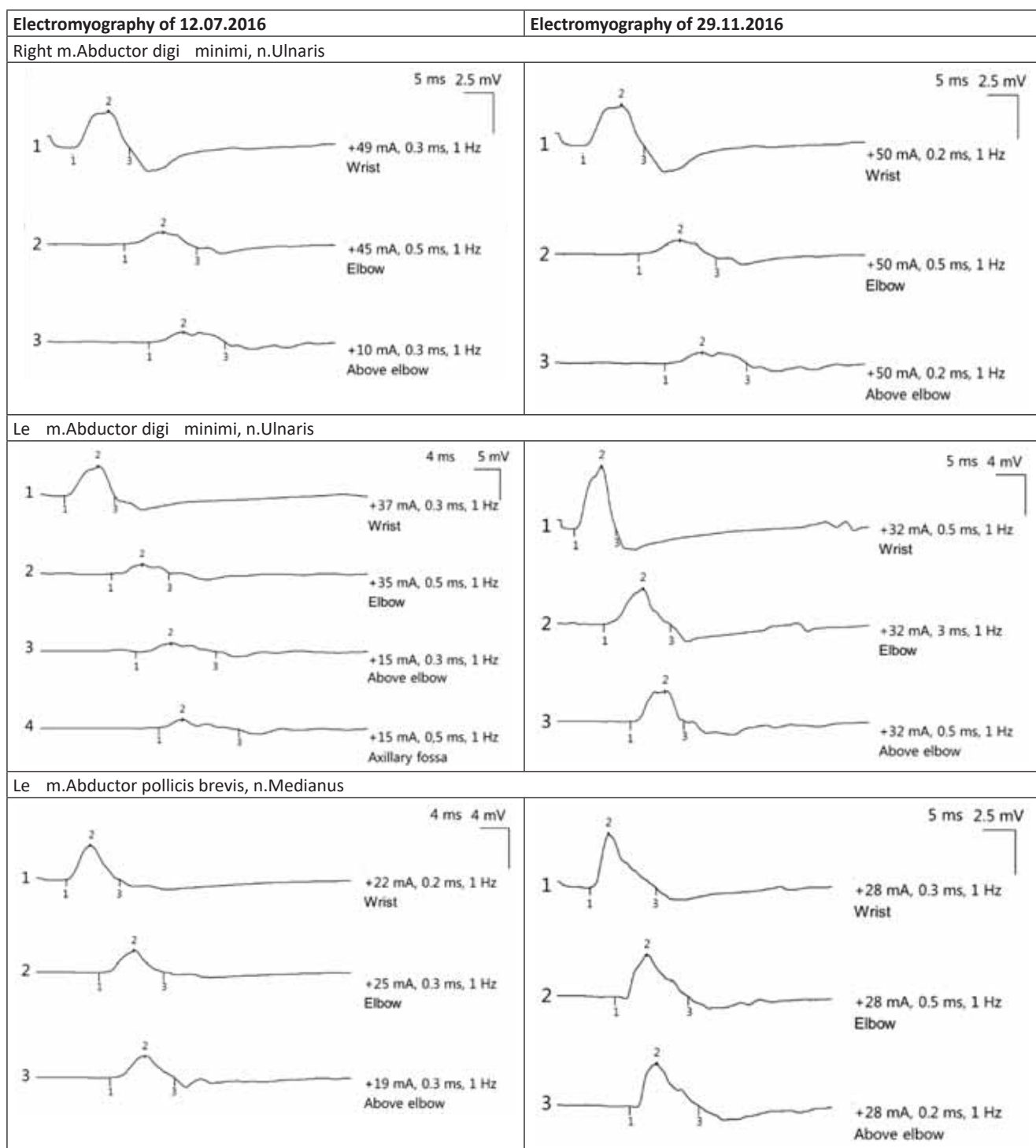


FIGURE 1. Motor responses recorded by electromyography of motor fibers of the patient's hand nerves in the initial examination (12.07.2016) and 4 months later (29.11.2016).

Note: m.Abductor digiti minimi – the muscle abducting the little finger; m.Abductor pollicis brevis – the short muscle abducting the thumb; n.Ulnaris – ulnar nerve; n.Medianus – median nerve.

was registered; the analysis of parameters of motor unit potentials showed signs of re-innervation (Fig. 1, Table 1).

The data obtained during NCS corresponded to neurophysiological criteria of chronic inflammatory demyelinating polyneuropathy (European Fed-

eration of the Neurological Societies – EFNS), 2010 (7).

– Ultrasonography of nerves (spinal C5-Th1, branches of the brachial plexus, median and elbow nerves) did not show any change of the cross-section area at all the levels of the study.

TABLE 1. Parameters of electromyography of motor and sensory nerves of the patient's upper and lower limbs (the study conducted on 12.07.2016)

a) Motor nerve conduction velocity (MNCV)

Stimulation site	Latency of M-response, ms	Amplitude of M-response, mV	Duration of M-response, ms	Area of M-response, mV×ms	MNCV, ms	Comment
Right m.Abductor digiti minimi, n.Ulnaris, C8-T1						
wrist	4.45 (N<3.0)	2.28 (N>6.0)	9.86	13.1		
4 cm below elbow joint	13.4	0.771	12.5	4.6	22.2 (N>50)	Forearm CB*, 70% of amplitude
above elbow	17.7	0.643	13.3	5.0	28.5 (N>50)	
Left m.Abductor digiti minimi, n.Ulnaris, C8-T1						
wrist	3.75 (N<3.0)	4.69 (N>6.0)	7.6	20.1		
4 cm below elbow joint	10.8	1.5	11.91	6.9	29.8 (N>50)	Forearm Mw Dispersion
Above elbow	14.6	1.45	12.1	8.2	34.1 (N>50)	
Axillary fossa	18.1	1.32	12.3	5.4	28.6 (N>50)	
Right m.Abductor pollicis brevis, n.Medianus, C8-T1						
wrist	4.95 (N<3.5)	5.66 (N>5.0)	8.3	26.1		
elbow	10.1	5.09	9.05	23.5	40.8 (N>50)	
above elbow	12.3	5.04	9.2	23.6	54.5 (N>50)	
Left m.Abductor pollicis brevis, n.Medianus, C8-T1						
wrist	4.7 (N<3.5)	4.53 (N>5.0)	8.5	18.1		
elbow	10.1	2.79	10.2	12.1	39.2 (N>50)	"Possible" forearm CB, 38% of amplitude
above elbow	11.9	2.86	10.1	13.1	72.3 (N>50)	
Right m.Tibialis anterior, n.Peroneus profundus, L4-S1						
head of fibular	2.54	1.03 (N>3.5)	13.6	4.8		
popliteal fossa	5.61	0.818	13.2	4.9	32.6 (N>40)	
Right m.Abductor hallucis, n.Tibialis, L5-S1						
medial malleolus		0				
Left m.Abductor hallucis, n.Tibialis, L5-S1						
medial malleolus		0				
Right m.Extensor digitorum brevis, n.Peroneus profundus, L4-S1						
ankle joint		0				

b) Sensor nerve conduction velocity (SNCV)

Stimulation site	Latency of S-response, ms	Amplitude of S-response, μ V	SNCV, ms
Right n. Medianus II			
wrist	3.28 (N<3.0)	0.7 (N>15.0)	50.3 (N>50)
Left n. Medianus II			
wrist	3.6 (N<3.0)	1.4 (N>15.0)	40.3 (N>50)
Right n.Peroneus superficialis, L4-S1			
Middle third of lower leg		0	
Left n.Peroneus superficialis, L4-S1			
Middle third of lower leg		0	

Note: M-response – motor response, S-response – sensor response, CB – conduction block, N – norm, n.Medianus – median nerve, n.Ulnaris – ulnar nerve, n.Peroneus profundus – deep fibular nerve, n.Tibialis – tibial nerve, n.Peroneus superficialis – superficial fibular nerve, m.Abductor digiti minimi – the muscle abducting the little finger, m.Abductor pollicis brevis – the short muscle abducting the thumb, m.Tibialis anterior – anterior tibial muscle, m.Abductor hallucis – the muscle abducting the great toe, m.Extensor digitorum brevis – the short muscle extending toes.

* Conduction block criteria are taken from previous studies (26)

Thus, the neurological examination of the patient revealed clinical signs of sensorimotor distal polyneuropathy. The neurophysiological examina-

tion confirmed the generalized sensorimotor neural level of lesion and specified the nature of the lesion as initially demyelinating. Anamnestic data showed

convincing interrelation between the beginning of ibrutinib administration and development of polyneuropathy. The patient was diagnosed “Ibrutinib-associated chronic demyelinating polyneuropathy”. Recommendations included dynamic observation and a rehabilitation course (including kinesiotherapy, wearing of orthoses).

At the re-examination conducted at the end of November 2016 (4 months after the initial examination, 5 months after ibrutinib dose reduction), the patient felt stronger in wrists, mentioned insignificant reduction of sensitive disturbances and improvement of stability when walking. The second NCS showed positive dynamics as compared with the previous examination:

– In examining the right ulnar nerve, there was a reduction of conduction block on to the forearm

and an increase in motor conduction velocity (CV) at this level from 22 to 34 m/s was noted (the norm is more than 50 m/s);

– In examining the left ulnar nerve, we registered a significant increase in distal CMAP – from 4.7 to 6.35 mV (the norm is more than 6), a reduction of conduction block from 68% to 42% (not registered in the norm), and an increase in sensor CV from 30 to 44 m/s (the norm more than 50 m/s);

– In examining the right deep fibular nerve (a branch of the tibialis anterior muscle), there was an increase in the M-response – from 1.03 to 2.24 mV, an increase in sensor CV at the level of the knee from 32 to 40 m/s (the norm is more than 40 m/s);

– Other parameters, including intensity of muscle fiber denervation activity in the distal muscle of the leg, were unchanged (Fig. 1, Table 2).

TABLE 2. Parameters of electromyography of motor and sensory nerves of the patient's upper and lower limbs (the study conducted on 29.11.2016, 4 months after the initial examination and 5 months after ibrutinib dose reduction)

a) Motor nerve conduction velocity (MNCV)

Stimulation site	Latency of M-response, ms	Amplitude of M-response, mV	Duration of M-response, ms	Area of M-response, mV×ms	MNCV, ms	Comment
Right m.Abductor digiti minimi, n.Ulnaris, C8-T1						
wrist	4.23 (N<3.0)	2.44 (N>6.0)	8.47	10.3		
4 cm below elbow joint	10.6	1.94	10.8	9.5	34.4 (N>50)	
above elbow	14.7	1.99	11.1	11.0	27.4 (N>50)	
Left m.Abductor digiti minimi, n.Ulnaris, C8-T1						
wrist	2.8 (N<3.0)	6.35 (N>6.0)	6.6	22.5		
4 cm below elbow joint	7.54	3.68	10.6	16.5	44.3 (N>50)	Forearm Mw Dispersion
Above elbow	11.7	3.08	8.6	14.2	26.1 (N>50)	
Left m.Abductor pollicis brevis, n.Medianus, C8-T1						
wrist	6.03 (N<3.5)	3.02 (N>5.0)	11.9	14.9		
elbow	10.7	2.39	13.2	13.3	45.1 (N>50)	
above elbow	13.3	2.41	12.4	13.5	45.4 (N>50)	
Right m.Tibialis anterior, n.Peroneus profundus, L4-S1						
head of fibular	5.08	2.24 (N>3.5)	12.1	14.7		
popliteal fossa	6.56	1.79	11.4	11.0	81.0 (N>40)	
Right m.Abductor hallucis, n.Tibialis, L5-S1						
medial malleolus		0				
Right m.Extensor digitorum brevis, n.Peroneus profundus, L4-S1						
ankle joint		0				

b) Sensor nerve conduction velocity (SNCV)

Stimulation site	Latency of S-response, ms	Amplitude of S-response, μV	SNCV, ms
Right n. Medianus II			
wrist	3.28 (N<3.0)	0.7 (N>15.0)	50.3 (N>50)
Right n.Peroneus superficialis, L4-S1			
Middle third of lower leg		0	

Note: M-response – motor response, S-response – sensor response, CB – conduction block, N – norm, n.Medianus – median nerve, n.Ulnaris – ulnar nerve, n.Peroneus profundus – deep fibular nerve, n.Tibialis – tibial nerve, n.Peroneus superficialis – superficial fibular nerve, m.Abductor digiti minimi – the muscle abducting the little finger, m.Abductor pollicis brevis – the short muscle abducting the thumb, m.Tibialis anterior – anterior tibial muscle, m.Abductor hallucis – the muscle abducting the great toe, m.Extensor digitorum brevis – the short muscle extending toes. Due to the positive clinical-neurophysiological dynamics, it was decided to continue the observation.

DISCUSSION

Chemotherapy-induced polyneuropathy is a subacute (within 4-8 weeks) or chronic (for more than 8 weeks) polyneuritic disorders that develop during or 3-6 months after a chemotherapy course with predominance of symptoms reflecting involvement of sensory and autonomic fibers (Table 3). Their specific feature is dose- and chemotherapeutic agent-dependence, alleviation of symptoms after discontinuation of the drug that induces the disease (2,3).

The group of chemotherapeutic agents with high and moderate degree of neurotoxicity is currently defined (Table 4) (4).

The exact mechanism of chemotherapy-induced types of polyneuropathy is still unclear. Nevertheless, considering various action spectrums of drugs and results of a number of pilot studies, scientists suggest the following main pathogenic drivers: disturbance of DNA cellular structure, mitochondrion and microtubules damage, axonal transport disturbance, oxidizing processes and apoptosis activation, neurotransmitter ion channel function change, etc. The result of these processes is formation of vicious mutually activating pathophysiological circles. The specified changes inevitably lead to dorsal ganglia damage, development of neuropathy

and disturbance of axon microtubular architectonics, which finally results in axonal nerve fibers degeneration (Fig. 2) (5,6).

Chemotherapy-induced sensory, autonomic and sensorimotor polyneuropathies are common in the practice of clinical neurologists; the great majority of them are axonal (2-4,20). The demyelinating pattern of changes is much less often revealed in the NCS of this category of patients.

Scientific literature covers few cases of development of demyelinating polyneuropathies caused by chemotherapy. In all the described cases, the cause of the complication is bortezomib (Table 4) (8-12). It is assumed that demyelinating polyneuropathies associated with bortezomib are caused by immune-mediated mechanisms. That was confirmed by morphological, neuroimaging and neurophysiological studies, as well as by clear neurologic improvement after administration of high-dosage intravenous immunoglobulin (9,10,13). Development of demyelinating polyneuropathy after ibrutinib administration has not been described in scientific literature.

Ibrutinib (Imbruvica, PCI-32765) is a new-generation drug in the treatment of malignant B-lymphoproliferative diseases. It is a covalent selective inhibitor of Bruton tyrosine kinase, which plays an

TABLE 3. The main clinical manifestations of chemotherapy-induced polyneuropathies, depending on the type of fibers involved (3).

Injured structure	Clinical manifestations
Peripheral ganglion	<ul style="list-style-type: none"> • Loss of proprioception and vibration sense • Sensory ataxia • Pain, temperature and tactile hypoesthesia • Dysesthesias • Neuropathic pain • Autonomic dysfunction
Small-diameter sensory fibers	<ul style="list-style-type: none"> • Dysesthesias • Allodynia • Neuropathic pain • Burning • Paresthesias
Small-diameter autonomic fibers	<ul style="list-style-type: none"> • Intestinal motility disorders (constipation, diarrhea) • Urinary retention • Blood pressure instability (including orthostatic hypotension) • Sexual dysfunction • Impaired sweating, etc.
Large-diameter sensory fibers of superficial sensitivity	<ul style="list-style-type: none"> • Numbness of hands and feet • Paresthesias • Pain and temperature hypoesthesia
Large-diameter sensory fibers of deep sensitivity	<ul style="list-style-type: none"> • Impaired proprioception and vibration sense • Impaired coordination of movements, stairs and gait – sensory ataxia
Motor fibers	<ul style="list-style-type: none"> • Muscle weakness • Awkward movements • Walking disorder

TABLE 4. Characteristics of chemotherapeutic agents with high and moderate degree of neurotoxicity (according to Banach M. et al. 2016 (4), with alterations).

Preparation	Cases of administration	Mechanism of action	Neurotoxicity
Platinum-based drugs: cisplatin, carboplatin, oxaliplatin	Lung, ovarian, bladder, colorectal cancer, etc.	The preparations bifunctionally alkylate DNA strands, inhibit biosynthesis of nucleic acids, and cause cell death. At the first stage, they inhibit the synthesis of DNA, RNA and protein; on the second stage, they form metabolic products, which affect only DNA synthesis.	Very High 70-100%
Taxane-containing drugs: paclitaxel, Abraxane, docetaxel	Breast, ovarian, prostate, lung, pancreas cancer, etc.	These drugs have a cytotoxic and mitotic effect, induce anomalous bundle-like arrangement of microtubules throughout the entire cell cycle.	High 11-87%
Thalidomide and its analogues: lenalidomide, Revlimid, Methotrexate	Multiple myeloma	This anti-angiogenic immunomodulatory drug inhibits secretion of proinflammatory cytokines (TNF- α , IL-1 β , IL-6 and IL-12), induces proliferation of T-cells and intensifies the synthesis of IL-2 and interferon- γ , активность собственных клеток-киллеров. It also increases the cytotoxic activity of natural killer cells.	High 20-60%
Ixabepilone, Ixempra	Breast cancer	The drug stabilizes the microtubule dynamics, which leads to blockade of tumor cell mitosis, and, finally, to their apoptosis and death.	High 60-65%
Bortezomib	Multiple myeloma	Bortezomib is a proteasome inhibitor; it reversibly inhibits the chymotrypsin-like activity of the 26S proteasome – a large protein complex, which catalyzes cleavage of the main proteins and regulates their intracellular concentrations. That impedes proteolysis, causing a complex signaling cascade inside the cell and disturbance of its homeostasis, which ultimately leads to apoptosis.	Moderate 20-30%
Vinca alkaloids: vincristine, vinblastine, vinorelbine, vindesine	Lung, brain, bladder, testicular cancer, etc.	These preparations bind to tubulin, inhibit formation of mitotic spindle and stop mitotic cell division at the metaphase stage. Its large doses also inhibit the synthesis of nucleic acids and protein.	Moderate Up to 20%

important role in maintenance of malignant cells viability. In 2014, it was approved by the U.S. Food and Drug Administration for treatment of patients with chronic lymphocytic leucosis (14). The official instruction to the drug (the part concerning side effects) mentions development of sensory axonal neuropathy in up to 40% of cases (15).

The interrelation between ibrutinib administration and polyneuritic disturbances in our patient was evident; it was also confirmed by spontaneous improvement after the daily dose reduction. This case was characterized by the presence of the motor disturbances, which were not described previously. There were also interesting electrophysiological

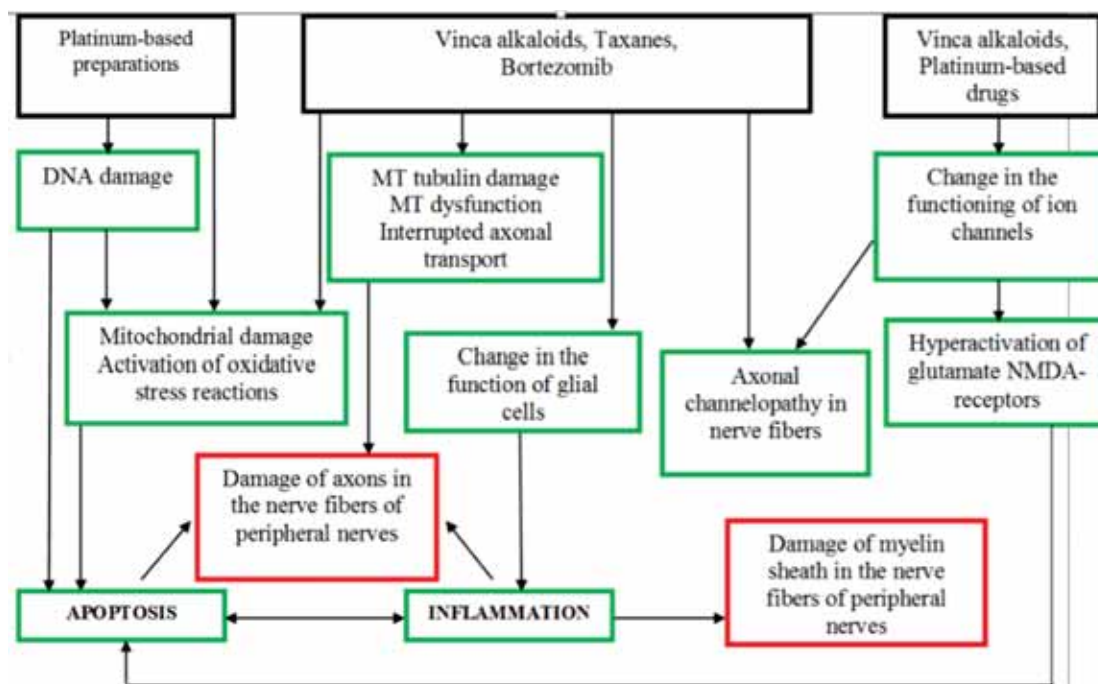


FIGURE 2. Probable pathogenic mechanism of chemotherapy-induced polyneuropathy development (5,6).

Note: DNA – deoxyribonucleic acid, MT – microtubules.

findings, requiring specification of the disease etiology: either toxic or dysimmune.

As other causes of demyelinating polyneuropathy (idiopathic, hereditary, paraproteinemic ones) were excluded in the course of examination and the ultrasonography of peripheral nerves did not reveal any changes in their structure that could be typical for an inflammatory process (16-18), toxic genesis was obvious. This allowed choosing the best tactics for the patient managing (dynamic observation after the permissible ibrutinib dose reduction) and proved the refusal from immunotherapy by intravenous immunoglobulins.

The main tactics for managing the patients with the polyneuropathies of **toxic genesis** after chemotherapy consists in the most possible reduction in the dose of the chemotherapeutic drug and symptomatic therapy: correction of autonomic disturbances, treatment of neuropathic pain syndrome by drugs and methods with a proved efficiency (tricyclic antidepressants, duloxetine/venlafaxine, pregabalin/gabapentin, cognitive behavioural therapy, transcranial magnetic stimulation, etc.), prescription of non-drug treatment-and-rehabilitation actions (kinesiotherapy, transdermal electroneuro- and myostimulation) (21-23). Persistence or increase of neurologic disorders and considerable motor deficiency limiting self-care may require

complete cancellation of chemotherapy. There is no pathogenic treatment for toxic polyneuropathies, and neurometabolic drugs showed no convincing efficiency in test trials (4,21,22).

Another tactics should be used in the cases of progressing demyelinating chemotherapy-induced polyneuropathies with proven dysimmune genesis, in which it is possible to conduct a disease-modifying treatment with steroid drugs or intravenous immunoglobulin (9,10,24,25). Dysimmune genesis of polyneuropathy can be clarified by means of laboratory tests (blood test for antibodies to gangliosides, electrophoresis of serum proteins and urine with immunofixation, liquor analysis for oligoclonal antibodies, etc.), instrumental examination (ultrasonography of nerves, magnetic resonance imaging of plexus with a contrast intensifier) and morphological examinations (sural nerve biopsy) tests (16-19).

CONCLUSION

The present paper is the first description of chronic demyelinating polyneuropathy developed after ibrutinib administration. It shows the differentiated approach to specify the causes of neurologic disorders in the patients undergoing chemotherapy.

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