ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

DOI: 10.21802/artm.2026.1.37.55
UDC 616.833-009.17-092.9:615.277

MORPHOLOGICAL CHANGES IN THE RAT CEREBELLUM AFTER PACLITAXEL-INDUCED NEUROTOXICITY AND THERAPEUTIC VORTIOXETINE TREATMENT

H.B. Kulynych

Ivano-Frankivsk National Medical University, Department of Histology, Cytology and Embryology, Ivano-Frankivsk, Ukraine
ORCID ID: 0000-0002-0233-2282, Scopus ID: 57388983100, e-mail: galija1979@ukr.net

Abstract. Paclitaxel is a widely used taxane antineoplastic agent, and its administration is frequently associated with neurotoxic complications affecting both the peripheral and central nervous systems. While chemotherapy-induced peripheral neuropathy has been extensively characterized, central morphological alterations particularly in the cerebellum remain insufficiently investigated. The cerebellum is a functionally critical structure involved in motor coordination and sensorimotor integration; it is especially vulnerable to toxic injury due to the high metabolic demands of its neurons (primarily Purkinje cells) and the structural and functional dependence on intact neurogliovascular units.

The aim of this study was to evaluate morphological and morphometric changes in the rat cerebellum following paclitaxel-induced neurotoxicity and to assess the corrective potential of therapeutic vortioxetine administration.

The study was conducted on adult male white rats. Neurotoxicity was induced by intraperitoneal administration of paclitaxel at a dose of 2 mg/kg (four injections every other day), resulting in a cumulative dose of 8 mg/kg. Therapeutic correction was performed via intragastric vortioxetine at a dose of 5 mg/kg once daily for 14 days, starting immediately after completion of paclitaxel treatment. Cerebellar morphology was examined on days 14, 28, 60, 90, and 120 using light microscopy after hematoxylin and eosin staining, followed by digital morphometric analysis of cortical layer thickness and Purkinje cell parameters. Motor function was assessed through behavioral tests evaluating locomotor activity and coordination.

Paclitaxel exposure led to time-dependent structural alterations in the cerebellar cortex. Early changes included moderate neuropil edema and focal chromatin condensation in Purkinje cells. At the peak of toxic load (day 28), partial disorganization of the Purkinje cell layer, reduced cortical thickness, and focal neuropil homogenization were observed. Morphometric analysis revealed significant reductions in the thickness of the molecular, Purkinje, and granular layers, decreased Purkinje cell density, and reduced soma and nuclear areas. At later time points, gradual spontaneous recovery occurred but remained incomplete in untreated animals.

Therapeutic vortioxetine administration attenuated the severity of cerebellar damage, limited disorganization of the Purkinje cell layer, and promoted preservation of neuronal morphology. From days 60 to 120, reparative changes predominated, with partial restoration of laminar organization and normalization of morphometric indices toward control values. Behavioral assessments demonstrated persistent motor impairment following paclitaxel administration, whereas vortioxetine contributed to partial functional compensation, as evidenced by improved locomotor activity and motor coordination.

These findings indicate that therapeutic vortioxetine administration mitigates paclitaxel-induced cerebellar structural damage and supports reparative processes, highlighting its potential role in the post-toxic correction of central nervous system involvement.

Keywords: paclitaxel-induced neurotoxicity, cerebellum, Purkinje cells, vortioxetine, morphological changes.

Introduction. Chemotherapy-induced neurotoxicity is one of the most clinically significant complications of anticancer treatment, substantially limiting therapeutic efficacy and negatively affecting patients' quality of life [4, 5, 11, 23]. Paclitaxel, a widely used taxane-based chemotherapeutic agent for the treatment of solid tumors, is associated with a high incidence of neurotoxic disorders, traditionally linked to damage of the peripheral nervous system [8, 17, 24].

However, accumulating experimental and clinical evidence indicates that the toxic effects of paclitaxel are not restricted to peripheral structures and may involve central nervous system regions [2, 3]. One of the potentially vulnerable structures is the cerebellum, which plays a key role in motor coordination, muscle tone regulation, and sensorimotor integration [16, 22]. The high metabolic activity of cerebellar neurons, particularly Purkinje cells, as well as their functional dependence on the integrity of neuroglio-vascular units, determines the increased sensitivity of this structure to cytotoxic insults [7, 10, 18].

Paclitaxel has been shown to disrupt microtubule stability, impair axonal transport and mitochondrial function, and induce neuroinflammation and reactive gliosis [15, 24, 27]. Within the cerebellum, these mechanisms may lead to degeneration of the dendritic arbor of Purkinje cells, disorganization of the granular layer, and impairment of neuron–glia interactions [10, 12, 14]. Nevertheless, the temporal morphological patterns of these alterations following completion of paclitaxel treatment remain insufficiently characterized.

Vortioxetine is a multimodal serotonergic modulator with documented effects on neuroplasticity, glial reactivity, and neurotrophic signaling pathways [1, 21, 25]. Its administration in a therapeutic regimen, that is, after the establishment of toxic injury, is clinically relevant; however, its influence on cerebellar morphology under

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

conditions of paclitaxel-induced neurotoxicity has not yet been adequately investigated.

The aim of the study. To evaluate morphological and morphometric cerebellar alterations, associated motor dysfunction, and the corrective effect of therapeutic vortioxetine in paclitaxel-induced neurotoxicity.

Object and methods of research. The experimental study was conducted on adult male inbred white rats weighing 180–220 g. Animals were housed in the vivarium under standard conditions, including a controlled temperature regime, regulated light–dark cycle, and free access to water and standard laboratory chow. Prior to the experiment, all rats underwent a seven-day acclimatization period.

All animal manipulations were performed in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), as well as in compliance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Bioethics Committee of Ivano-Frankivsk National Medical University (Protocol No. 146/24, September 26, 2024). All animals survived until the predetermined time points of euthanasia.

Neurotoxicity was induced by intraperitoneal administration of paclitaxel at a dose of 2 mg/kg, administered four times every other day, resulting in a cumulative dose of 8 mg/kg. This regimen corresponds to commonly used experimental models of paclitaxel-induced neurotoxicity and is consistent with dose translation principles applied in preclinical studies [20].

Pharmacological correction was performed using therapeutic administration of vortioxetine. The drug was administered intragastrically via a metal gavage needle with a rounded tip at a dose of 5 mg/kg once daily. Treatment was initiated on the third day after completion of the paclitaxel course and continued for 14 days. The selected dose and administration regimen were based on preclinical studies demonstrating the central activity and neuroprotective potential of vortioxetine without evidence of toxicity in experimental animals.

Animals were withdrawn from the experiment on days 14, 28, 60, 90, and 120. The cerebellum was fixed in 10 % neutral buffered formalin, followed by preparation of paraffin blocks and serial histological sections. Sections were stained with hematoxylin and eosin and examined using light microscopy.

Morphological analysis of the cerebellar cortex included assessment of Purkinje cell integrity, neuropil condition, and preservation of laminar organization. The analysis was performed on a series of histological sections using quantitative and semi-quantitative evaluation of morphological changes. For each animal, at least ten fields of view selected from three non-consecutive sections were analyzed to ensure representativeness of the obtained data.

Morphometric measurements were performed in a digital mode using a calibrated microscopy system and ImageJ software.

Statistical analysis was conducted using Python programming language with the SciPy library. For intergroup comparisons, parametric one-way analysis of variance (ANOVA) or the non-parametric Mann–Whitney U test was applied, depending on data distribution. Results are presented as mean ± standard deviation (M ± SD). Differences were considered statistically significant at $p < 0.05$.

Research results and their discussion. Morphological features of the cerebellar cortex after paclitaxel-induced neurotoxicity under therapeutic vortioxetine treatment (Fig. 1).

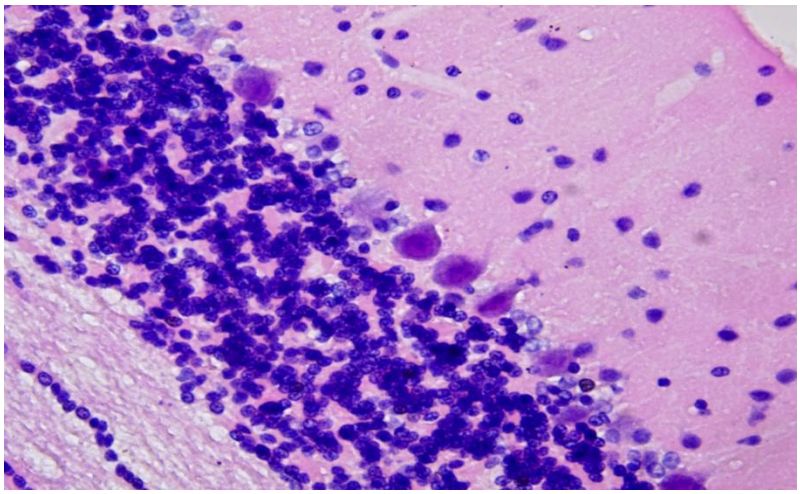

Fig. 1. Cerebellar cortex of rats on day 14 after completion of paclitaxel administration under therapeutic vortioxetine treatment. Preserved laminar organization of the cortex with a continuous Purkinje cell layer. Moderate neuropil edema in the molecular layer. Hematoxylin and eosin staining, ×400

On day 14 after completion of paclitaxel administration under therapeutic vortioxetine treatment, the overall architectonics of the cerebellar cortex preserved a clearly defined laminar organization. The Purkinje cell layer remained continuous, with no signs of massive neuronal loss. In the molecular layer, moderate neuropil edema with expansion of intercellular spaces was observed, reflecting residual manifestations of toxic exposure. Isolated Purkinje cells exhibited moderate chromatin condensation without pronounced pyknosis or nuclear fragmentation, indicating a limited degree of neuronal injury.

At the peak phase of toxic load, structural alterations of the cerebellar cortex were observed, including partial disorganization of the Purkinje cell layer and focal neuropil homogenization (Fig. 2).

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

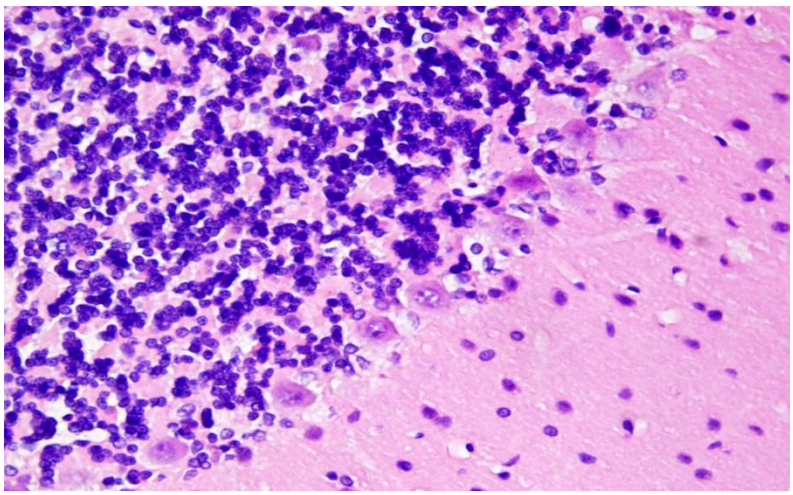

Fig. 2. Cerebellar cortex on day 28 of the experiment (peak phase of toxic load) under therapeutic vortioxetine treatment. Partial disorganization of the Purkinje cell layer and focal areas of neuropil homogenization with preservation of a substantial number of morphologically intact neurons. Hematoxylin and eosin staining, ×400

On day 28 of the experiment, corresponding to the peak phase of toxic load, partial disorganization of the Purkinje cell layer was detected in the cerebellar cortex, accompanied by reduced optical density of the cytoplasm and focal areas of neuropil homogenization. Some neurons lost their typical pear-shaped morphology, reflecting an active phase of degenerative changes. At the same time, in animals treated with vortioxetine, the severity of structural alterations was less pronounced: a greater number of morphologically intact Purkinje cells were preserved, and the extent of neuropil disorganization remained limited compared with the untreated toxic group.

At later time points (days 60–90), the cerebellar cortex exhibited a predominance of reparative changes, including improved Purkinje cell morphology and reduced neuropil alterations (Fig. 3).

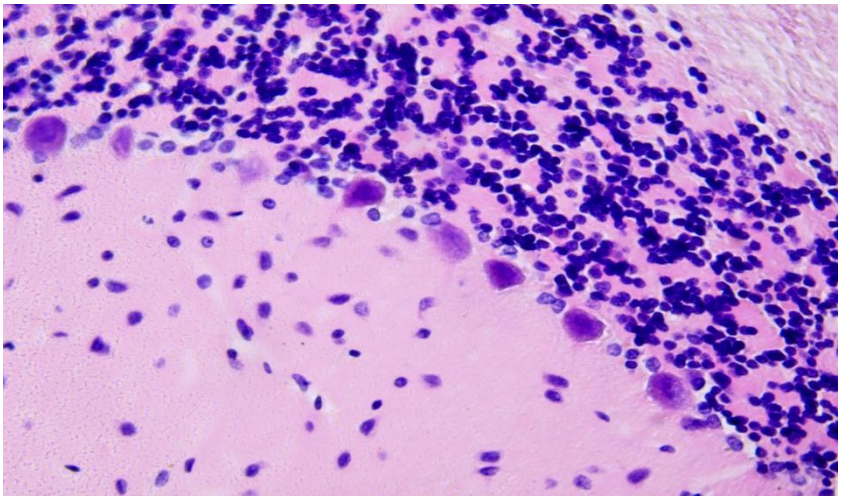

Fig. 3. Reparative changes in the cerebellar cortex on days 60–90 after paclitaxel-induced neurotoxicity under vortioxetine treatment. More distinct Purkinje cell contours, reduced tissue edema, and stabilization of the glial microenvironment. Hematoxylin and eosin staining, ×400

On days 60 and 90 of the experiment, reparative processes predominated in the cerebellar cortex. The contours of Purkinje cells became more distinct, soma shape normalized, and tissue edema and the degree of neuropil vacuolization decreased. Stabilization of the glial microenvironment was observed, manifested by attenuation of reactive changes and restoration of structural organization of interneuronal connections. The granular layer acquired a more ordered architecture with a uniform distribution of neurons.

At the long-term stage of observation, the cerebellar cortex demonstrated near-complete restoration of structural organization with only isolated residual alterations (Fig. 4).

On day 120 after completion of toxic exposure, near-complete restoration of the laminar organization of the cerebellar cortex was observed. Most Purkinje cells retained typical morphology with clearly defined nuclear–cytoplasmic boundaries, whereas residual dystrophic changes were isolated in nature. The combination of morphological features indicated completion of the active phase of injury and stabilization of cerebellar structures under therapeutic vortioxetine administration.

Morphometric analysis of Purkinje cells demonstrated that, in the therapeutic vortioxetine group, no abrupt shifts in quantitative parameters characteristic of massive neuronal damage were detected.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

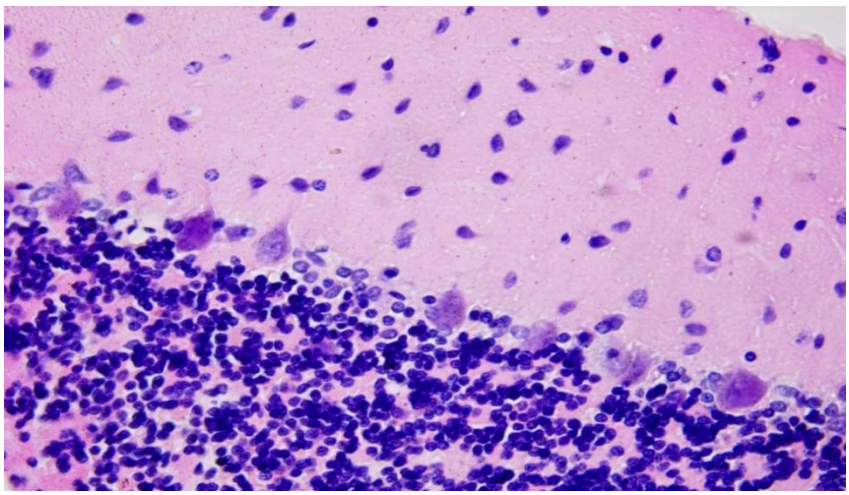

Fig. 4. Cerebellar cortex on day 120 of the experiment under therapeutic vortioxetine administration. Restoration of laminar organization with only isolated residual dystrophic changes in Purkinje cells. Hematoxylin and eosin staining, ×400

On day 14, morphometric indices remained close to control values, consistent with preservation of a continuous Purkinje cell layer. During the peak phase (day 28), only moderate deviations in morphometric parameters were recorded, corresponding to localized degenerative changes in the neuropil. At later time points (days 60–120), morphometric values gradually normalized, in accordance with morphological signs of reparative processes.

Paclitaxel-induced neurotoxicity was accompanied by persistent motor dysfunction, manifested by reduced locomotor activity and impaired motor coordination in behavioral tests. In untreated animals, the open field test revealed a significant decrease in total distance traveled and the number of rearings, which developed from early time points after paclitaxel administration and persisted throughout the entire observation period, reflecting sustained motor deficit and suppression of exploratory activity.

In the rotarod test, rats with paclitaxel-induced neurotoxicity demonstrated a reduced latency to fall, indicating impaired motor coordination and decreased muscular endurance. The most pronounced deficits were observed at later stages of the experiment, consistent with the chronic nature of the neurotoxic effect.

Under therapeutic vortioxetine administration, indices of motor activity and coordination were higher compared with the untreated toxic group. In the open field test, a greater distance traveled and a higher number of rearings were preserved, while in the rotarod test, animals demonstrated a longer retention time on the rotating rod. Although functional parameters did not reach the level of intact animals, the observed positive dynamics indicated partial functional compensation of motor impairments.

The functional findings were consistent with the morphological picture of the cerebellar cortex: in the absence of massive Purkinje cell loss and under conditions of gradual stabilization of the neuropil at later time points, even moderate structural alterations were associated with clinically relevant impairments of motor coordination.

Quantitative morphometric parameters of the cerebellar cortex in control animals, paclitaxel-treated rats, and animals receiving therapeutic vortioxetine are summarized in Table 1.

Table 1

Morphometric parameters of the rat cerebellar cortex

Parameter	Control (M ± SD)	Paclitaxel 2 mg/kg (M ± SD)	Paclitaxel + vortioxetine (M ± SD)
Molecular layer thickness, μm	185 ± 6	172 ± 5*	178 ± 5#
Purkinje cell layer thickness, μm	32 ± 2	29 ± 2*	31 ± 2#
Granular layer thickness, μm	210 ± 7	192 ± 6*	202 ± 6#
Total cortical thickness, μm	427 ± 10	393 ± 9*	415 ± 9#
Purkinje cell density, cells/mm	12.4 ± 0.6	10.6 ± 0.5*	11.8 ± 0.5#
Purkinje cell soma area, μm²	420 ± 18	378 ± 16*	402 ± 17#
Purkinje cell nuclear area, μm²	96 ± 5	84 ± 4*	91 ± 4#
Nuclear–cytoplasmic ratio	0.30 ± 0.02	0.29 ± 0.02	0.30 ± 0.02
Granule cell density, cells/mm²	$4.8\times10^5 \pm 0.2\times10^5$	$4.3\times10^5 \pm 0.2\times10^5$*	$4.6\times10^5 \pm 0.2\times10^5$#

Notes: 1. * $p < 0.05$ vs control, 2. $p < 0.05$ vs paclitaxel group.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Morphometric analysis revealed significant reductions in cortical layer thickness and Purkinje cell parameters in the paclitaxel group, whereas therapeutic vortioxetine administration partially restored these indices toward control values.

Discussion. Paclitaxel-induced neurotoxicity in the present study was associated with sustained, phase-dependent morphological remodeling of the cerebellar cortex. Although chemotherapy-induced neuropathy is traditionally considered predominantly a peripheral nervous system disorder, contemporary clinical and experimental evidence indicates involvement of central nervous system structures, including the cerebellum, in the development of motor and, in some cases, cognitive dysfunction [4, 5, 11, 16, 17, 22–24, 26].

Paclitaxel exerts neurotoxic effects through microtubule stabilization, impairment of axonal transport, cytoskeletal destabilization, and mitochondrial dysfunction, mechanisms that are particularly critical for large, metabolically active projection neurons [8, 15, 27]. Although most mechanistic evidence has been obtained in peripheral models, the same microtubule- and mitochondria-dependent vulnerability provides a plausible substrate for central nervous system involvement, including cerebellar structures and Purkinje cell susceptibility [15, 18, 27]. Preclinical studies further demonstrate that paclitaxel can induce not only peripheral but also central neurotoxicity, manifested by electrophysiological, behavioral, and histological alterations within nervous system structures [3, 19]. In addition, the contribution of ion channels and neuroglial interactions to paclitaxel-related neurotoxicity has been supported by studies showing that TRPV4 inhibition attenuates neurotoxic manifestations in preclinical settings [2].

Our morphological analysis indicates that the Purkinje cell layer represents the most vulnerable component of the cerebellar cortex under paclitaxel exposure. This observation is consistent with established concepts of cerebellar cortical cytology and organization, according to which Purkinje cells function as key integrative neurons characterized by high metabolic demands, extensive dendritic arborization, and dependence on intact neuron–glia interactions [18]. Their susceptibility is further supported by broader evidence of cerebellar involvement across diverse neurological and toxic conditions [10]. Given that Purkinje cells constitute the sole output of the cerebellar cortex, even moderate structural alterations at this level may translate into functionally meaningful consequences for cerebellar network activity and motor coordination [7, 16].

At early time points after completion of paclitaxel administration under therapeutic vortioxetine treatment, the general cerebellar cortical architecture remained largely preserved, without signs of massive neuronal loss. This finding is in line with the concept that central neurotoxicity related to taxanes often evolves progressively and does not necessarily manifest as acute neuronal destruction [4, 11, 24]. The moderate neuropil edema observed in the molecular layer likely reflects reactive microenvironmental changes involving glial and neurovascular components that may precede more pronounced structural impairment.

The peak phase of toxic load (day 28) was characterized by partial disorganization of the Purkinje cell layer and focal neuropil homogenization. Such mosaic degenerative patterns have been described in experimental models of neurotoxicity and are thought to reflect disrupted neuron–glia interactions, altered synaptic microenvironment, and impaired cerebellar plasticity [7, 12, 14]. The absence of total neuronal loss at this stage is compatible with the high compensatory capacity of cerebellar circuits and their ability to reorganize under injury conditions [12, 16]. The morphometric decline in cortical thickness and Purkinje cell parameters observed at this time point is therefore more consistent with functional decompensation than with irreversible neuronal elimination, in agreement with current concepts of progressive taxane-related neurotoxicity [11, 23, 24].

At later stages of observation (days 60–90), reparative processes predominated in the cerebellar cortex, manifested by normalization of Purkinje cell soma morphology, reduction of neuropil edema, and stabilization of the glial microenvironment. From a neurobiological perspective, these changes may reflect restoration of synaptic organization and engagement of intrinsic plasticity mechanisms, including long-term depression (LTD), which represents a fundamental adaptive process within cerebellar circuitry [14]. By day 120, near-complete restoration of laminar organization suggested completion of the active injury phase and stabilization of cerebellar morphology.

A key finding of this study is the influence of vortioxetine on the temporal dynamics of cerebellar morphological changes. Given the post-toxic treatment design, vortioxetine could not prevent the initial injury; however, it appeared to limit further progression of structural deterioration and promote an earlier transition toward the reparative phase. This interpretation is consistent with the pharmacological profile of vortioxetine as a multimodal agent capable of modulating serotonergic neurotransmission and interacting with glutamatergic networks and neuroplasticity-related pathways [1, 21]. In preclinical pain models, vortioxetine has also been shown to influence neuroinflammatory and neuromediator mechanisms through catecholaminergic and cholinergic systems [9, 25], which may be relevant for the broader neurobiological context of chemotherapy-associated neurotoxicity.

In a wider context, chemotherapy-induced neuropathy represents a multifactorial process, with severity and temporal profile determined by the specific agent, cumulative dose, and administration schedule [17, 26], including considerations of dose translation in preclinical experimental designs [20]. The high prevalence of CIPN and the limited options for effective prevention and treatment underscore the importance of exploring strategies aimed at post-toxic correction, including central manifestations of neurotoxicity [23, 24]. Systematic analyses of animal models further emphasize the necessity of combining morphological and functional endpoints to adequately evaluate neuroprotective and corrective interventions [6, 13].

Taken together, the present findings support the cerebellum as an important target of paclitaxel-induced neurotoxicity and suggest that therapeutic vortioxetine administration may limit structural deterioration and promote morphological prerequisites for recovery of integrative cerebellar functions. These data expand current understanding of the central aspects of taxane neurotoxicity and provide a rationale for further investigation of multimodal neuromodulation as a strategy for post-toxic correction of

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

chemotherapy-related central nervous system involvement [4, 11, 21, 24].

Conclusions. Paclitaxel administration results in persistent morphological alterations of the cerebellar cortex, characterized by progressive Purkinje cell damage, disruption of their spatial organization, and neuropil disintegration, indicating the development of long-lasting central neurotoxicity. Therapeutic vortioxetine administration after completion of chemotherapeutic exposure reduces the severity of cerebellar structural damage, limits the extent of neuronal degeneration, and modifies the temporal profile of injury progression by attenuating late degenerative changes. At extended observation periods, vortioxetine promotes activation of reparative processes in the cerebellar cortex, manifested by stabilization of the glial microenvironment, reduction of reactive alterations, and partial restoration of the structural integrity of neuronal networks. Collectively, these morphological findings support the potential applicability of vortioxetine as a post-toxic pharmacological approach for correcting central manifestations of paclitaxel-induced neurotoxicity, particularly at the level of cerebellar structures.

Funding. This study was conducted within the framework of the institutional fundamental research project of Ivano-Frankivsk National Medical University (State Registration No. 0125U004275).

Conflict of interest: absent.

Study limitations and future directions.

The study has several limitations that should be considered. First, the obtained results are based on an experimental animal model which, despite its wide application and pathophysiological relevance, does not fully reproduce the complexity of chemotherapy-induced neurotoxicity in humans. Second, the exclusive use of morphological methods without the inclusion of immunohistochemical markers did not allow a detailed assessment of glial activation, synaptic remodeling processes, or apoptotic pathways.

In future studies, it would be advisable to expand the morphological approach by incorporating immunohistochemical techniques targeting neuronal, glial, and neuroinflammatory markers, as well as ultrastructural analysis using electron microscopy. Such an integrated approach would enable a deeper characterization of neuron–glia interactions, subcellular alterations, and the pathogenetic mechanisms underlying cerebellar involvement in paclitaxel-induced neurotoxicity and its pharmacological correction.

References:

1. Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, et al. Discovery of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Med Chem.* 2011;54(9): 3206-21. doi.10.1021/jm101459g
2. Boehmerle W, Huehnchen P, Balkaya M, Endres M. TRPV4 inhibition prevents paclitaxel-induced neurotoxicity in preclinical models. *Exp Neurol.* 2018; 306:64-75. https://doi.org/10.1016/j.expneurol.2018.04.014
3. Boehmerle W, Huehnchen P, Peruzzaro S, Balkaya M, Endres M. Electrophysiological, behavioral and histological characterization of paclitaxel, cisplatin, vincristine and bortezomib-induced neuropathy in C57Bl/6 mice. *Sci Rep.* 2014; 4:6370. https://doi.org/10.1038/srep06370
4. Boyette-Davis JA, Walters ET, Dougherty PM. Mechanisms involved in the development of chemotherapy-induced neuropathy. *Pain Manag.* 2015; 5(4):285-296. https://doi.org/10.2217/pmt.15.19
5. Cioroiu C, Weimer LH. Update on chemotherapy-induced peripheral neuropathy. *Curr Neurol Neurosci Rep.* 2017; 17(6):47. https://doi.org/10.1007/s11910-017-0757-7
6. Currie GL, Angel-Scott HN, Colvin LA, Cramond F, Hair K, Khandoker L, et al. Animal models of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *PLoS Biol.* 2019; 17(5):e3000243. https://doi.org/10.1371/journal.pbio.3000243
7. D'Angelo E, Casali S. Seeking a unified framework for cerebellar function and dysfunction: from circuit operations to cognition. *Front Neural Circuits.* 2013 Jan 10; 6:116. https://doi.org/10.3389/fncir.2012.00116
8. Duggett NA, Griffiths LA, Flatters SJL. Paclitaxel-induced painful neuropathy is associated with changes in mitochondrial bioenergetics, glycolysis, and an energy deficit in dorsal root ganglia neurons. *Pain.* 2017 Aug; 158(8):1499-508. https://doi.org/10.1097/j.pain.0000000000000939
9. Saini A, Sharma S, Rana P, Khanna B, Kaur T, Dhingra N. Amelioration of chemotherapy induced neuropathic pain using novel nicotinic acid derivatives with possible HCN channel binding ability. *Mol Neurobiol.* 2025 Oct; 62(10):13318-37. https://doi.org/10.1007/s12035-025-05088-w
10. Liu G, Yang C, Wang X, Chen X, Cai H, Le W. Cerebellum in neurodegenerative diseases: Advances, challenges, and prospects. *iScience.* 2024 Oct 18; 27(11):111194. https://doi.org/10.1016/j.isci.2024.111194
11. Flatters SJL, Dougherty PM, Colvin LA. Clinical and preclinical perspectives on chemotherapy-induced peripheral neuropathy. *Br J Anaesth.* 2017; 119(4):737-49. https://doi.org/10.1093/bja/aex229
12. Gao Z, van Beugen BJ, De Zeeuw CI. Distributed synergistic plasticity and cerebellar learning. *Nat Rev Neurosci.* 2012; 13(9):619-35.
13. Griffiths LA, Duggett NA, Pitcher AL, Flatters SJL. Evoked and ongoing pain-like behaviours in a rat model of paclitaxel-induced peripheral neuropathy. *Pain Res Manag.* 2018; 2018:8217613. https://doi.org/10.1155/2018/8217613
14. Ito M. Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol Rev.* 2001; 81(3):1143-95. https://doi.org/10.1152/physrev.2001.81.3.1143
15. Malacrida A, Meregalli C, Rodriguez-Menendez V, Nicolini G. Chemotherapy-induced peripheral neuropathy and changes in cytoskeleton. *Int J Mol Sci.* 2019; 20(9):2287. https://doi.org/10.3390/ijms20092287
16. Manto M, Bower JM, Conforto AB, Delgado-García JM, da Guarda SNF, Gerwig M, et al. Consensus paper: roles of the cerebellum in motor control.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

*Cerebellum.*2012;11(2):457-87. https://doi.org/10.1007/s12311-011-0331-9
17. Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: a comprehensive survey. *Cancer Treat Rev.*2014;40(8):872-82. https://doi.org/10.1016/j.ctrv.2014.04.004
18. Apps R, Hawkes R, Aoki S, Bengtsson F, Brown AM, Chen G, et al. Cerebellar modules and their role as operational units of motor and cognitive function. Cerebellum.2018;17(5):654-82. https://doi.org/10.1007/s12311-018-0952-3
19. Polomano RC, Mannes AJ, Clark US, Bennett GJ. A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug paclitaxel. *Pain.* 2001; 94(3):293-304. https://doi.org/10.1016/S0304-3959(01)00363-3
20. Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. *FASEB J.* 2008; 22(3):659-61. https://doi.org/10.1096/fj.07-9574LSF
21. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol Ther.* 2015; 145:43-57. https://doi.org/10.1016/j.pharmthera.2014.07.001
22. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain.* 1998; 121(4):561-79. https://doi.org/10.1093/brain/121.4.561
23. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, Macleod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy. *Pain.* 2014; 155(12):2461-70. https://doi.org/10.1016/j.pain.2014.09.020
24. Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. *Front Mol Neurosci.* 2017; 10:174. https://doi.org/10.3389/fnmol.2017.00174
25. Turan Yücel N, Kandemir Ü, Üçel Uİ, Demir Özkay Ü, Can ÖD. Catecholaminergic and cholinergic systems mediate beneficial effect of vortioxetine on diabetes-induced neuropathic pain. *Biomedicines.* 2023; 11(4):1137. https://doi.org/10.3390/biomedicines11041137
26. Valentin VM. Toxic peripheral neuropathies: agents and mechanisms. *Toxicol Pathol.* 2019; 48(1):152-173. https://doi.org/10.1177/0192623319854326
27. Xiao WH, Zheng H, Zheng FY, Nuydens R, Meert TF, Bennett GJ. Mitochondrial abnormality in sensory axons in paclitaxel-evoked neuropathy. *Neuroscience.* 2011;199:461-9. https://doi.org/10.1016/j.neuroscience.2011.10.010

УДК 616.833-009.17-092.9:615.277

МОРФОЛОГІЧНІ ЗМІНИ МОЗОЧКА ЩУРІВ ЗА УМОВ ПАКЛІТАКСЕЛ-ІНДУКОВАНОЇ НЕЙРОТОКСИЧНОСТІ ТА ЛІКУВАЛЬНОГО ЗАСТОСУВАННЯ ВОРТІОКСЕТИНУ

Г.Б. Кулинич

Івано-Франківський національний медичний університет, кафедра гістології, цитології та ембріології, м. Івано-Франківськ, Україна
ORCID ID: 0000-0002-0233-2282,
Scopus ID: 57388983100,
e-mail: galija1979@ukr.net

Резюме. Паклітаксел є одним із ключових протипухлинних препаратів таксанового ряду, застосування якого супроводжується розвитком нейротоксичних ускладнень з боку периферичної і центральної нервової системи. Попри детальний опис периферичної нейропатії, морфологічні зміни центральних структур, зокрема мозочка, залишаються недостатньо вивченими. Мозочок характеризується високою метаболічною активністю нейронів, передусім клітин Пуркіньє, та складною організацією нейрогліо-судинних комплексів, що зумовлює його підвищену чутливість до токсичних впливів.

Метою дослідження було оцінити морфологічні й морфометричні зміни мозочка щурів за умов паклітаксел-індукованої нейротоксичності та визначити коригувальний ефект лікувального введення вортіоксетину.

Дослідження виконано на статевозрілих самцях білих щурів. Нейротоксичність моделювали внутрішньоочеревинним введенням паклітакселу в дозі 2 мг/кг чотири рази через добу. Лікувальну корекцію проводили шляхом внутрішньошлункового введення вортіоксетину в дозі 5 мг/кг один раз на добу протягом 14 діб після завершення курсу паклітакселу. Морфологічне дослідження мозочка здійснювали на 14, 28, 60, 90 і 120 добу з використанням світлової мікроскопії та цифрового морфометричного аналізу.

Паклітаксел спричиняв часово залежні структурні порушення кори мозочка, що проявлялися дезорганізацією шару клітин Пуркіньє, набряком нейропілю та зменшенням товщини кортикальних шарів із максимумом змін на 28 добу. Лікувальне введення вортіоксетину зменшувало вираженість ушкоджень, сприяло збереженню клітин Пуркіньє та поступовому відновленню організації мозочка на пізніх етапах експерименту. Морфометричні показники демонстрували тенденцію до нормалізації, що узгоджувалося з частковим відновленням рухової координації.

Отримані результати свідчать про коригувальний вплив вортіоксетину на центральні прояви паклітаксел-індукованої нейротоксичності.

Ключові слова: паклітаксел-індукована нейротоксичність, мозочок, клітини Пуркіньє, вортіоксетин, морфологічні зміни.

Конфлікт інтересів: відсутній.

Copyright © H.B. Kulynych, 2026

Дата першого надходження статті до видання 30.12.2025 р.
Дата прийняття статті до друку після рецензування 27.02.2026 р.