

doi: 10.3978/j.issn.2095-6959.2021.

View this article at: <http://dx.doi.org/10.3978/j.issn.2095-6959.2021>.

长春新碱诱发周围神经病变治疗的研究进展

姜嘉悦 综述 崔晓光 审校

(哈尔滨医科大学附属第二医院麻醉科, 哈尔滨 150000)

[摘要] 长春新碱作为一种抗肿瘤药物, 是许多化学药物治疗方案的重要组成部分, 但其诱发的周围神经病变可严重影响患者的生活质量, 是目前临床减量甚至停药的原因之一。长春新碱可以通过增加离子通道活性、激活胶质细胞等方式诱发周围神经病变。本文主要从瞬时感受器电位通道蛋白、T型钙通道、丝裂原活化蛋白激酶/核因子信号通路、趋化因子/趋化因子受体、N-甲基-D-天冬氨酸受体等对靶向治疗长春新碱诱发周围神经病变的研究进展作一综述, 同时总结丹参酮IIA等中药和脊髓刺激疗法在此方面的研究成果, 以期对长春新碱诱发周围神经病变的治疗提供新思路。

[关键词] 长春新碱; 周围神经病变; 治疗

Research advances in the treatment of vincristine-induced peripheral neuropathy

JIANG Jiayue, CUI Xiaoguang

(Department of Anesthesiology, The Second Affiliated Hospital of Harbin Medical University, Harbin 150000, China)

Abstract Vincristine, as an anti-tumor drug, is an integral part of many chemotherapy regimens. However, the peripheral neuropathy induced by vincristine can seriously affect the quality of life of patients, which is one of the reasons for the clinical reduction or withdrawal of the drug. Vincristine can induce peripheral neuropathy by increasing the activity of ion channels and activating glial cells. This article mainly reviews the research progress of targeted therapy of vincristine-induced peripheral neuropathy from the perspectives of transient receptor potential channel protein, T-type calcium channel, mitogen-activated protein kinase/nuclear factor-kappa B signaling pathway, Chemokine(C-X3-C motif)ligand1/Chemokine(C-X3-C motif)receptor1, N-methyl-D-aspartate receptor. At the same time, it summarizes the research results of traditional Chinese medicine(such as Tanshinone IIA) and spinal cord stimulation in this area, in order to provide new ideas for the treatment of vincristine-induced peripheral neuropathy.

Keywords vincristine; peripheral neuropathy; treatment

收稿日期 (Date of reception): 2020-08-25

通信作者 (Corresponding author): 崔晓光, Email: cuixiaoguang1018@126.com

长春新碱是临床常用的化学治疗药物,用于治疗淋巴瘤、急性淋巴细胞白血病等多种癌症。剂量依赖性的周围神经病变是长春新碱的主要毒副作用,显著降低患者的生活质量和治愈率^[1-2]。因此,防治长春新碱诱发的周围神经病变一直是国内外学者的研究热点,本文总结了近年来治疗长春新碱诱发周围神经病变的研究进展,以期望为临床有效缓解长春新碱所致周围神经病变提供新靶点、新思路。

1 长春新碱

长春新碱是从夹竹桃科植物长春花中提取出的一种双吲哚型生物碱,可溶于氯仿、丙酮和乙醇,是目前广泛应用的天然抗癌药物之一。它通过与 β -微管蛋白结合,抑制微管形成,阻断细胞分裂,使癌细胞生长停滞^[3],对淋巴瘤、肾母细胞瘤、小细胞肺癌、乳腺癌等都有很好的治疗作用,尤其对儿童急性淋巴细胞白血病效果显著^[4-8]。但长春新碱可引起剂量依赖性的周围神经病变,主要表现为感觉、运动、自主神经的紊乱^[9]。长春新碱抗癌效果明确,国内外学者研究制备了长春新碱脂质体,以提高药物治疗指数,减轻毒副作用,但其在临床的疗效和安全性有待进一步观察^[10-11]。

2 长春新碱诱发的周围神经病变

长春新碱具有神经毒性,引起周围神经病变,损伤的神经纤维向疼痛中枢传递不正确的信号,导致神经病理性疼痛^[12-13]。多数长春新碱治疗的患者会出现周围神经病变,具体表现为早期麻木、手脚刺痛和脚踝痉挛等感觉运动功能障碍,神经性疼痛、肌肉疼痛也经常出现,少数患者会出现直立性低血压、便秘、麻痹性肠梗阻、膀胱功能障碍等自主神经紊乱症状^[14]。不良反应的发生降低患者生活质量,限制长春新碱的使用剂量,影响治疗效果^[15]。长春新碱所致的周围神经病变停药后仍可持续,Lieber等^[16]对46名急性淋巴细胞白血病已治愈的患儿进行随访测试,发现长春新碱停药至少3个月后,2/3的患者存在大纤维神经病变,1/3的患者存在小纤维神经病变和疼痛敏感。动物研究^[17]发现:在小鼠出生后的第11天和21天给予大剂量的长春新碱(60 $\mu\text{g}/\text{kg}$),

从第26天开始出现机械性痛觉过敏,并持续到成年,提示早期暴露于长春新碱所致的异常感觉传入对疼痛处理的长期影响。因此,预防和治疗长春新碱诱发的周围神经病变在癌症治疗中具有重要意义。

长春新碱诱发的周围神经病变机制复杂,它可以与 β -微管蛋白高度结合,导致细胞分裂中断和细胞死亡,轴突微管的改变引起有髓纤维和无髓纤维轴突肿胀以及神经纤维损伤^[18]。长春新碱增加了配体门控离子通道和电压门控离子通道的活性,促进活性氧产生,破坏线粒体电子传递链并可能导致感觉神经元的ATP产生异常^[19]。同时,长春新碱通过激活脊髓胶质细胞及免疫细胞,促进丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)磷酸化,合成并释放胶质介质(如趋化因子、炎症因子、蛋白酶等)^[20-21]。这些离子通道、通路、细胞因子等为长春新碱诱发周围神经病变的防治提供靶点。

3 长春新碱诱发周围神经病变的治疗进展

临床能缓解长春新碱所致周围神经病变的药物包括抗焦虑药、抗癫痫药等。度洛西汀被证实能够减轻患者由长春新碱引起的周围神经病变^[22]。Tsavaris等^[23]研究表明,加巴喷丁能缓解化疗所致的神经病理性疼痛,且患者对加巴喷丁的反应与神经毒性的严重程度相关。而Angheliescu等^[24]发现加巴喷丁不能预防长春新碱所致神经病理性疼痛的复发,有待进一步探究。口服B组维生素虽然不能预防长春新碱所致的周围神经病变,但在患者的神经毒性问卷中表现出周围感觉神经病变减轻^[25]。目前,针对长春新碱诱发周围神经病变靶向治疗的研究越来越多,离子通道、通路、细胞因子等在其中发挥了重要作用。

3.1 阻断瞬时感受器电位

3.1.1 瞬时感受器电位锚蛋白-1

孤立的感觉神经元暴露于长春花生物碱后,去极化内向电流被快速激活导致神经元放电,该电流对瞬时感受器电位锚蛋白-1(transient receptor potential ankyrin-1, TRPA1)拮抗剂敏感,在TRPA1突变神经元中消失^[26]。此外,对TRPA1有阻断作用的柴胡皂苷能够减轻长春新碱诱发的机械性痛觉超敏^[27],说明在长春新碱所致周围神经

病变中, TRPA1发挥重要作用。Amirkhanloo等^[28]研究发现, 长春新碱诱发的周围神经病变大鼠出现机械性和热痛觉过敏, 运动神经传导速度减慢, TRPA1、肿瘤坏死因子- α (tumor necrosis factor, TNF- α)和白细胞介素-1 β (interleukin, IL)水平升高, 神经兴奋药莫达非尼预处理可以改善上述症状, 表明莫达非尼可能是预防长春新碱诱发周围神经病变的神经保护剂。

3.1.2 瞬时感受器电位香草酸受体 1

瞬时感受器电位香草酸受体 1(transient receptor potential vanilloid 1, TRPV1)参与了长春新碱诱发的周围神经病变, TRP拮抗剂钉红和TRPV1拮抗剂capsazepine可显著抑制长春新碱诱发的大鼠机械性痛觉超敏。长春新碱可引起大鼠背根神经节(dorsal root ganglion, DRG)TNF- α 上调, TNF- α 通过促进TRPV1的表达使其敏化, 导致长春新碱治疗的大鼠出现机械性异常疼痛和热痛觉过敏。沙利度胺通过抑制TNF- α 的合成减少TRPV1的表达, 缓解大鼠由长春新碱引起的异常疼痛^[29-30]。

3.2 阻断 T 型钙通道

T型钙通道的激活促进伤害性感受信号的传递, Ca_v3.2是主要的T型钙通道亚型, 在初级感觉传入神经元和脊髓均有表达, T型钙通道阻滞剂ABT-639选择性阻断Ca_v3.2, 增加了长春新碱诱发神经病理性疼痛小鼠的触觉异常性疼痛阈值^[31]。Sharma等^[32]研究发现, 大鼠接受10 μ g/kg长春新碱预处理5 d后, 其致痛剂量的长春新碱(50 μ g/kg)引起的足部冷痛觉超敏、机械和热痛觉过敏明显缓解, T型钙通道阻滞剂乙磺酰亚胺能抵消长春新碱预处理产生的保护作用, 该研究认为, 长春新碱预处理过程中, T型钙通道可能被激活, 这些通道的瞬时开放触发信号级联, 阻止大剂量长春新碱诱发的神经元兴奋和疼痛的发生发展。

3.3 抑制丝裂原活化蛋白激酶 / 核因子信号通路

长春新碱诱发神经病理性疼痛的机制之一是丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)/核因子(nuclear factor-kappa B, NF- κ B)信号通路的参与。研究^[33]表明: p38MAPK主要在小胶质细胞中表达, 炎症刺激导致p38MAPK磷酸化和激活, 活化的MAPK通过NF- κ B易位促进NF- κ B活化, 增加TNF- α 和IL-1 β 合成, 并激活细胞凋亡的下游信号通路, 促进疼

痛的发生和维持。Jaggi等^[34]研究发现, Ras(一种小鸟嘌呤核苷酸)是MAPK家族细胞内信号传导通路的重要组成部分, 可激活MAPK信号级联通路, 鞘内注射Ras抑制剂法尼基硫代水杨酸显著减轻长春新碱引起的痛觉过敏和痛觉超敏。同时, Khalilzadeh等^[35]发现阿立哌唑通过抑制NF- κ B过度激活, 有效预防长春新碱诱发的周围神经病变。

3.4 抑制趋化因子/趋化因子受体

趋化因子[chemokine (C-X3-C motif) ligand 1, CX3CL1], 又称fractalkine(FKN), 是刺激脊髓小胶质细胞释放疼痛介质并维持慢性疼痛的重要分子。可溶性CX3CL1激活小胶质细胞特异性受体趋化因子受体[chemokine (C-X3-C motif) receptor 1, CX3CR1], 导致p38MAPK磷酸化, 促进IL-1, TNF- α 等促炎细胞因子的分泌和释放^[36]。天麻素通过CX3CL1/CX3CR1抑制脊髓小胶质细胞激活, 在不影响长春新碱抗肿瘤作用的同时减轻周围神经病变^[2]。同时, 研究发现长春新碱治疗导致内皮细胞黏附性上调, 循环中的CX3CR1⁺单核细胞浸润到坐骨神经。在内皮-神经界面, 趋化因子CX3CL1激活CX3CR1⁺单核细胞, 促进活性氧产生, 激活感觉神经元中的TRPA1引起疼痛, CX3CR1拮抗剂的应用可能成为防治长春新碱诱发神经病理性疼痛的有效途径^[37]。

3.5 阻滞 NMDA 受体

研究^[38]发现长春新碱诱发的神经病理性疼痛大鼠伴有脊髓星形胶质细胞激活, 活化的星形胶质细胞增加IL-1 β 的表达, 诱导脊髓神经元N-甲基-D-天冬氨酸(N-methyl-D-aspartate, NMDA)受体磷酸化, 增加疼痛信号传递。Bujalska等^[39]研究表明, 连续5 d单独使用阿片受体激动剂, 如吗啡、芬太尼, 以及部分激动剂丁丙诺啡, 并不能改善长春新碱大鼠的痛觉过敏, 而低剂量的硫酸镁预处理后(镁离子是生理状态下的NMDA受体阻滞剂), 3种阿片类药物的镇痛作用逐渐增强, 停止给药后, 效果持续数天。提示镁离子增强阿片类药物的镇痛效应在化疗所致神经病理性疼痛的治疗中可能具有重要临床意义。

3.6 诱导脊髓血红素加氧酶 1 合成

Shen等^[40]研究发现, 小鼠注射长春新碱2周后, 脊髓血红素加氧酶1(heme oxygenase 1, HO-1)

mRNA和蛋白质表达增加,腹腔注射HO-1诱导剂增加了脊髓中的HO-1,缓解长春新碱引起的疼痛,此外,鞘内注射HO-1诱导剂,可以减少长春新碱导致的神经胶质细胞(星形胶质细胞和小胶质细胞)活化,MAPKs磷酸化以及脊髓中TNF- α 和单核细胞趋化蛋白1的产生,说明外源性诱导的HO-1在长春新碱所致周围神经病变中的潜在治疗作用。

3.7 其他

中医中药可用于治疗长春新碱诱发的周围神经病变。付宝军等^[41]研究表明,腹腔注射丹参酮IIA可以抑制星形胶质细胞c-Jun N-末端激酶(MAPK家族主要成员之一)通路激活和炎症反应,缓解长春新碱诱发神经病理性疼痛大鼠的痛觉过敏。蒺藜皂苷被证实能够抑制中枢和外周的细胞因子和白细胞介素,缓解长春新碱诱发的周围神经病变,同时通过减低大脑TNF- α 和谷氨酸水平修复神经元损伤,恢复突触活动^[42]。Jiang等^[20]研究认为无花果提取物桑色素能缓解长春新碱大鼠的疼痛,修复坐骨神经组织学和功能上的损伤,抑制IL-6和NF- κ B的表达。菖蒲、夜香牛、罗勒等可通过抗氧化、抑制钙通道等方式缓解长春新碱诱发的周围神经病变^[43-45]。

脊髓刺激是治疗化疗诱发神经病理性疼痛的一种有效方法。Youn等^[46]研究发现,对长春新碱大鼠的DRG行高强度聚焦超声治疗可提高长春新碱大鼠的机械和热痛阈值。DRG行外部非侵入式低强度聚焦超声治疗5 d,同样可以改善疼痛且无组织损伤^[47],提供药物之外的潜在有效治疗途径。

4 结语

综上所述,长春新碱诱发的周围神经病变是影响癌症患者生活质量和治疗效果的重要因素之一,本文主要从离子通道、通路、细胞因子等角度回顾了靶向治疗长春新碱所致周围神经病变的研究成果。值得注意的是,上述提到的治疗药物及方法大多局限在动物实验阶段,临床疗效和安全性有待进一步观察。另外,长春新碱所致周围神经病变机制复杂,多种细胞因子、通路的参与提示我们,联合用药、预防性用药效果可能更好。希望未来能够更加系统、全面的治疗长春新碱诱发的周围神经病变。

参考文献

- Hu C, Zhao YT, Cui YB, et al. Wnt/beta-catenin signaling contributes to vincristine-induced neuropathic pain[J]. *Physiol Res*, 2020, 69(4): 701-710.
- Qin B, Luo N, Li Y, et al. Protective effect of gastrodin on peripheral neuropathy induced by anti-tumor treatment with vincristine in rat models[J]. *Drug Chem Toxicol*, 2021, 44(1): 84-91.
- Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy[J]. *Front Mol Neurosci*, 2017, 10: 174.
- Lewis WD, Lilly S, Jones K. Lymphoma: diagnosis and treatment[J]. *Am Fam Physician*, 2020, 101(1): 34-41.
- Ehrlich P, Chi Y, Chintagumpala M, et al. Results of the first prospective multi-institutional treatment study in children with bilateral Wilms tumor (AREN0534): a report from the Children's Oncology Group[J]. *Ann Surg*, 2017, 266(3): 470-478.
- Waqar SD, Morgensztern D. Treatment advances in small cell lung cancer (SCLC)[J]. *Pharmacol Ther*, 2017, 180: 16-23.
- Zeng F, Ju R, Liu L, et al. Efficacy in treating lung metastasis of invasive breast cancer with functional vincristine plus dasatinib liposomes[J]. *Pharmacology*, 2018, 101(1/2): 43-53.
- Kato M, Manabe A. Treatment and biology of pediatric acute lymphoblastic leukemia[J]. *Pediatr Int*, 2018, 60(1): 4-12.
- Starobova H, Mueller A, Allavena R, et al. Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy[J]. *Front Neurosci*, 2019, 13: 653.
- 张雪冰, 李文静, 王杏林, 等. 硫酸长春新碱脂质体的质量评价研究[J]. *现代药物与临床*, 2015, 30(6): 658-662.
ZHANG Xuebing, LI Wenjing, WANG Xinglin, et al. Quality evaluation of vincristine sulphate liposomes[J]. *Drugs & Clinic*, 2015, 30(6): 658-662.
- Douer D. Efficacy and safety of vincristine sulfate liposome injection in the treatment of adult acute lymphocytic leukemia[J]. *Oncologist*, 2016, 21(7): 840-847.
- Chiba T, Kambe T, Yamamoto K, et al. Vincristine increased spinal cord substance P levels in a peripheral neuropathy rat model[J]. *Drug Chem Toxicol*, 2020. [Epub ahead of print].
- Singh G, Singh A, Singh P, et al. Bergapten ameliorates vincristine-induced peripheral neuropathy by inhibition of inflammatory cytokines and NF κ B signaling[J]. *ACS Chem Neurosci*, 2019, 10(6): 3008-3017.
- Canta A, Pozzi E, Carozzi V. Mitochondrial dysfunction in chemotherapy-induced peripheral neuropathy (CIPN)[J]. *Toxics*, 2015, 3(2): 198-223.
- Jaggi AS, Singh N. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy[J]. *Toxicology*, 2012, 291(1/3): 1-9.
- Lieber S, Blankenburg M, Apel K, et al. Small-fiber neuropathy and pain

- sensitization in survivors of pediatric acute lymphoblastic leukemia[J]. *Eur J Paediatr Neurol*, 2018, 22(3): 457-469.
17. Schappacher KA, Styczynski L, Baccei M. Early life vincristine exposure evokes mechanical pain hypersensitivity in the developing rat[J]. *Pain*, 2017, 158(9): 1647-1655.
18. Carozzi VA, Canta A, Chiorazzi A. Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms?[J]. *Neurosci Lett*, 2015, 596: 90-107.
19. Sisignano M, Baron R, Scholich K, et al. Mechanism-based treatment for chemotherapy-induced peripheral neuropathic pain[J]. *Nat Rev Neurol*, 2014, 10(12): 694-707.
20. Jiang K, Shi J, Shi J. Morin alleviates vincristine-induced neuropathic pain via nerve protective effect and inhibition of NF- κ B pathway in rats[J]. *Cell Mol Neurobiol*, 2019, 39(6): 799-808.
21. Ji R, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy?[J]. *Pain*, 2013, 154 Suppl 1(0 1): S10-S28.
22. Hirayama Y, Ishitani K, Sato Y, et al. Effect of duloxetine in Japanese patients with chemotherapy-induced peripheral neuropathy: a pilot randomized trial[J]. *Int J Clin Oncol*, 2015, 20(5): 866-871.
23. Tsavaris N, Kopterides P, Kosmas C, et al. Gabapentin monotherapy for the treatment of chemotherapy-induced neuropathic pain: a pilot study[J]. *Pain Med*, 2008, 9(8): 1209-1216.
24. Anghelescu DL, Faughnan L, Jeha S, et al. Neuropathic pain during treatment for childhood acute lymphoblastic leukemia[J]. *Pediatr Blood Cancer*, 2011, 57(7): 1147-1153.
25. Schloss JM, Colosimo M, Airey C, et al. A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN)[J]. *Support Care Cancer*, 2017, 25(1): 195-204.
26. Boiko N, Medrano G, Montano E, et al. TrpA1 activation in peripheral sensory neurons underlies the ionic basis of pain hypersensitivity in response to vinca alkaloids[J]. *PLoS One*, 2017, 12(10): e0186888.
27. Lee G, Choi J, Nam Y, et al. Identification and characterization of saikosaponins as antagonists of transient receptor potential A1 channel[J]. *Phytother Res*, 2020, 34(4): 788-795.
28. Amir Khanloo F, Karimi G, Yousefi-Manesh H, et al. The protective effect of modafinil on vincristine-induced peripheral neuropathy in rats: A possible role for TRPA1 receptors[J]. *Basic Clin Pharmacol Toxicol*, 2020, 127(5): 405-418.
29. Chiba T, Oka Y, Sashida H, et al. Vincristine-induced peripheral neuropathic pain and expression of transient receptor potential vanilloid 1 in rat[J]. *J Pharmacol Sci*, 2017, 133(4): 254-260.
30. Wang Y, Feng C, He H, et al. Sensitization of TRPV1 receptors by TNF- α orchestrates the development of vincristine-induced pain[J]. *Oncol Lett*, 2018, 15(4): 5013-5019.
31. Jarvis ME, Scott V, McGaraughty S, et al. A peripherally acting, selective T-type calcium channel blocker, ABT-639, effectively reduces nociceptive and neuropathic pain in rats[J]. *Biochem Pharmacol*, 2014, 89(4): 536-544.
32. Sharma J, Maslov L, Singh N, et al. Pain attenuating actions of vincristine-preconditioning in chemotherapeutic agent-induced neuropathic pain: key involvement of T-type calcium channels[J]. *Fundam Clin Pharmacol*, 2020, 34(3): 336-344.
33. Dai WL, Bao Y, Fan J, et al. -Levocorydalmine attenuates microglia activation and neuropathic pain by suppressing ASK1-p38 MAPK/NF- κ B signaling pathways in rat spinal cord[J]. *Reg Anesth Pain Med*, 2020, 45(3): 219-229.
34. Jaggi AS, Singh N. Analgesic potential of intrathecal farnesyl thiosalicylic acid and GW 5074 in vincristine-induced neuropathic pain in rats[J]. *Food Chem Toxicol*, 2012, 50(5): 1295-1301.
35. Khalilzadeh M, Hassanzadeh F, Aghamiri H, et al. Aripiprazole prevents from development of vincristine-induced neuropathic nociception by limiting neural NOS overexpression and NF- κ B hyperactivation[J]. *Cancer Chemother Pharmacol*, 2020, 86(3): 393-404.
36. Qin B, Li Y, Liu X, et al. Notch activation enhances microglial CX3CR1/P38 MAPK pathway in rats model of vincristine-induced peripheral neuropathy[J]. *Neurosci Lett*, 2020, 715: 134624.
37. Old EA, Nadkarni S, Grist J, et al. Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain[J]. *J Clin Invest*, 2014, 124(5): 2023-2036.
38. Ji XT, Qian N, Zhang T, et al. Spinal astrocytic activation contributes to mechanical allodynia in a rat chemotherapy-induced neuropathic pain model[J]. *PLoS One*, 2013, 8(4): e60733.
39. Bujalska M, Makulska-Nowak H, Gumulka S. Magnesium ions and opioid agonists in vincristine-induced neuropathy[J]. *Pharmacol Rep*, 2009, 61(6): 1096-1104.
40. Shen Y, Zhang Z, Zhu M, et al. Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice[J]. *Neurobiol Dis*, 2015, 79: 100-110.
41. 付宝军, 姜静静, 黄玉琼, 等. 丹参酮 II A 对长春新碱诱导神经病理痛大鼠痛觉过敏的影响及其机制[J]. *河北医学*, 2020, 26(7): 1057-1062.
- FU Baojun, JIANG Jingjing, HUANG Yuqiong, et al. Effect of Tanshinone II A on hyperalgesia induced by vincristine in rats with neuropathic pain and its mechanism[J]. *Hebei Medicine*, 2020, 26(07):1057-62.
42. Gautam M, Ramanathan M. Saponins of *Tribulus terrestris* attenuated neuropathic pain induced with vincristine through central and peripheral mechanism[J]. *Inflammopharmacology*, 2019, 27(4): 761-772.
43. Muthuraman A, Singh N, Jaggi A. Protective effect of *Acorus calamus* L. in rat model of vincristine induced painful neuropathy: an evidence of

- anti-inflammatory and anti-oxidative activity[J]. Food Chem Toxicol, 2011, 49(10): 2557-2563.
44. Thiagarajan VR, Shanmugam P, Krishnan U, et al. Ameliorative effect of Vernonia cinerea in vincristine-induced painful neuropathy in rats[J]. Toxicol Ind Health, 2014, 30(9): 794-805.
45. Kaur G, Jaggi A, Singh N. Exploring the potential effect of Ocimum sanctum in vincristine-induced neuropathic pain in rats[J]. J Brachial Plex Peripher Nerve Inj, 2010, 5: 3.
46. Youn Y, Hellman A, Walling I, et al. High-intensity ultrasound treatment for vincristine-induced neuropathic pain[J]. Neurosurgery, 2018, 83(5): 1068-1075.
47. Hellman A, Maietta T, Byraju K, et al. Low intensity focused ultrasound modulation of vincristine induced neuropathy[J]. Neuroscience, 2020, 430: 82-93.

本文引用: 姜嘉悦, 崔晓光. 长春新碱诱发周围神经病变治疗的研究进展[J]. 临床与病理杂志, 2021. doi: 10.3978/j.issn.2095-6959.2021.

Cite this article as: JIANG Jiayue, CUI Xiaoguang. Research advances in the treatment of vincristine-induced peripheral neuropathy[J]. Journal of Clinical and Pathological Research, 2021. doi: 10.3978/j.issn.2095-6959.2021.