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长春新碱诱发周围神经病变治疗的研究进展

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[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，以期为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 progress in the treatment of vincristine-induced peripheral neuropathy

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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 patients' life, 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, etc. 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, and 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, which is in order to provide new ideas for the treatment of vincristine-induced peripheral neuropathy.

Keywords vincristine; peripheral neuropathy; treatment

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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不良反应，显著降低了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治疗效果显著[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，减轻不良反应，但其在临床的疗效和安全性有待进一步研究阐明[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功能紊乱症状[14]。不良反应的发生降低患者生活质量，限制了长春新碱的使用剂量，影响了治疗效果[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，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 μg/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的周围神经病变的防治提供了靶点。

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]的研究表明：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Anghelescu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族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 α，TNF-α)和白细胞介素-1β(interleukin 1β，IL-1β)水平升高，神经兴奋药莫达菲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拮抗剂钌红和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 μg/kg长春新碱预处理5 d后，其致痛剂量的长春新碱(50 μg/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和发展。

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-κB)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磷酸化激活，活化的MAPK通过NF-κB易位促进NF-κB活化，增加TNF-α和IL-1β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家族细胞内信号转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-κB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方法[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-1β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生成，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致大鼠的疼痛，修复坐骨神经组织学和功能上的损伤，抑制IL-6和NF-κB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、全面地治疗长春新碱诱发的周围神经病变。

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