Advances in Clinical Medicine 临床医学进展, 2022, 12(7), 6377-6383
Published Online July 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.127919

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乳腺癌患者使用紫杉类化疗药物后引起周围神经病变的相关预防和治疗措施

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收稿日期：2022年6月11日；录用日期：2022年7月3日；发布日期：2022年7月13日

摘　要

乳腺癌是全球女性发病率第一的癌种，严重影响女性健康。化学治疗作为其重要的治疗方式之一，占据着不可撼动的地位；其中，紫杉类药物作为乳腺癌化学治疗的基石之一，其诱导的周围神经病变可导致化疗中止，影响疗效，甚至影响患者日后的生活质量。目前临床上尚未有明确的预防或治疗标准，是该领域一直难以攻克的问题。本文就目前紫杉类药物导致乳腺癌患者周围神经毒性的预防和治疗方法做一综述，以期为今后的临床研究提供一定的依据。

关键词

乳腺癌，紫杉类药物，化疗导致的周围神经病变

Prevention and Treatment Measures Related to Peripheral Neuropathy Caused by Paclitaxel-Based Chemotherapy Drugs in Breast Cancer Patients

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Received: Jun. 11th, 2022; accepted: Jul. 3rd, 2022; published: Jul. 13th, 2022

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文章引用: 张瑾, 达梦婷, 袁明雪, 沈国双. 乳腺癌患者使用紫杉类化疗药物后引起周围神经病变的相关预防和治疗措施[J]. 临床医学进展, 2022, 12(7): 6377-6383. DOI: 10.12677/acm.2022.127919

Abstract

Breast cancer is the most prevalent cancer among women worldwide and seriously affects women's health. Chemotherapy occupies an unassailable position as one of its important treatment modalities. Peripheral neuropathy induced by paclitaxel, one of the cornerstones of chemotherapy for breast cancer, can lead to discontinuation of chemotherapy, affecting the efficacy and even the quality of life of patients later in life. There is no clear clinical standard for prevention or treatment, and it is a problem that has been difficult to overcome in this field. This article reviews the current methods of prevention and treatment of peripheral neurotoxicity caused by paclitaxel in breast cancer patients, with the aim of providing some basis for future clinical studies.

Keywords

Breast Cancer, Paclitaxel-Based, Chemotherapy-Induced Peripheral Neuropathy

1. 引言

2020 年国际癌症研究机构(International Agency for Research on cancer)对全球癌症发病率的调查表明，女性乳腺癌现已超越肺癌成为世界肿瘤发病率第一的癌种，约有 230 万新发病例，占全球所有癌症患者数的 11.7% [1]。目前乳腺癌治疗方式诸多，包括：外科手术、新辅助化学治疗、化学治疗、内分泌治疗、靶向治疗及放射治疗等[2] [3]。全身化疗治疗癌症往往伴随着很多副作用，化疗引起的周围神经病变(Chemotherapy-induced peripheral neuropathy, CIPN)是多种抗癌药物诱发(包括紫杉烷类、铂类、长春花生物碱类)的潜在剂量限制性不良事件，大约 30%~40%的化疗患者会出现这种情况，个体差异较大[4]。紫杉烷类药物作为国内外临床指南均推荐的一线治疗药物[5]，可能通过紊乱微管结构[6]，损伤神经元和非神经元的线粒体[7] [8]，使轴索变性[9] [10]，进而使内环境中钙离子失衡[11]等机制导致 CIPN 发生、发展，发生率在 30%~97%之间不等[12] [13] [14] [15] [16]，涉及对周围神经、感觉和自主神经结构和功能的损伤[5]。CIPN 通常在化疗结束后得到一定的缓解，但相关研究发现[17] [18] [19]，部分患者在紫杉类药物治疗结束后会存在持续的麻木，时间长短因个人而异，这将严重影响机体功能和生活质量。本文将概述目前已有的关于紫杉类药物引起乳腺癌患者 CIPN 的预防策略和治疗手段，为日后临床研究和治疗提供参考。

2. 紫杉类药物引起乳腺癌患者 CIPN 的预防和治疗措施

2.1. 加冰手套/加压

丹麦一项研究对多西他赛导致周围神经病变的乳腺癌患者进行干预，发现在 1725 名患者中，佩戴冷冻手套和袜子罹患周围神经毒性的发生率显著降低(OR = 0.56; 95%CI: 0.38~0.81)，这可能与冰冻的袜子和手套可以收缩区域的血管而降低药物运输对手脚轴突的损伤有关[20]。一项 II 期多中心的研究也表明，外科手套压迫对治疗白蛋白结合型紫杉醇导致的周围神经病变有预防作用，与对照组相比，外科手套保护的患者 CTCAE 2 级或更高级别感觉和运动周围神经病变的发生率明显下降(76.1%: 21.4%; 57.1%: 26.2) [21]。一

项关于白蛋白紫杉醇导致周围神经病变的小型试验也证明，使用长袜和袖子的压迫疗法联合 goshajinkigan 在内的预防药物，使用四个周期后试验组的神经毒性评分显著低于对照组($P < 0.001$) [22]，目前认为加压治疗可能增加了流向动静脉吻合口的小动脉流量，促使血液回流到静脉，同时使通过毛细血管的流量最小，从而潜在的抑制了 CIPN，但对于这种方式的有效性还需要更深入的研究。

2.2. 药物干预

美国临床肿瘤学会临床实践指南唯一推荐用于治疗 CIPN 的药物是度洛西汀[19] [23]，此药能够在一定程度上减轻麻木和刺痛的神经毒性症状，我国的一项前瞻性研究也证实，在预防 CIPN 方面度洛西汀具备很好的效果(OR = 5.426; $P = 0.002$) [24]。其他常用的药物可能对 CIPN 有一定的帮助，如：抗抑郁药(如阿米替林)、抗惊厥药(如加巴喷丁)、文拉法辛、卡马西平等，但目前证据并不充足[25]。各种物质如：氨磷汀，谷胱甘肽，维生素 E，谷氨酸，静脉注射钙和镁，以及神经营养生长因子等，也进行了与预防 CIPN 相关的临床研究，可能有一定的效果，但存在证据不充分、样本量较小、缺乏对照组、非随机对照组以及不同临床试验之间结果矛盾等问题[26] [27]。目前也有其他具有发展前景的临床试验，如：乙氧基鸟苷可以通过调节 HSP90 防止紫杉醇和顺铂诱导的周围神经毒性，从而具备作为化疗方案佐剂的潜力以防止 CIPN [28]，但需要进一步的研究来探讨对其他类型化疗药物神经毒性的疗效。此外，张振等人[29]发现中药补阳还五汤膏剂(黄芪、红花、川芎、赤芍、桃仁、当归、地龙等)可在一定程度上减轻紫杉醇类化疗药物导致的外周神经毒性，突出了中医治疗在 CIPN 中的作用及潜力。

2.3. 调整剂量

化疗过程中出现严重 CIPN 或不可耐受的患者，则需调整使用剂量甚至停用化疗药物。2020 紫杉类药物相关周围神经病变规范化管理专家共识[30]指出：癌症患者(包括乳腺癌)使用紫杉类药物治疗期间出现 1 级或 2 级 CIPN 时通常不需要调整剂量，但如果出现 3 级以上 CIPN，则建议临床医生根据患者个体情况决定是否需要减量或停止治疗，直至该症状恢复至 2 级或低于 2 级。使用紫杉醇出现严重外周神经毒性症状，建议后续给药剂量下降约 20%；使用多西他赛治疗期间出现重度外周神经症状，剂量可由 100 mg/m^2 减至 75 mg/m^2 和/或由 75 mg/m^2 减至 60 mg/m^2；若在给予 60mg/m^2 剂量时仍出现严重 CIPN，则应该停止治疗；使用 3 周方案白蛋白紫杉醇(260 mg/m^2)初次出现严重外周神经毒性症状，药物用量可减至 220 mg/m^2，若 CIPN 再次出现可考虑将剂量继续减至 180 mg/m^2。

2.4. 中医

2.4.1. 中医针刺

中医针刺被证明可以有效减轻化疗引起的毒副反应[31] [32] [33]，已在癌症患者的临床试验中崭露头角。国外已有研究证明针刺可以改善神经传导并缓解 CIPN 症状[34] [35]。Ting Bao [36]等人在评估针刺治疗 2 级 CIPN 或中度患者的疗效中发现，在化疗治疗的最后 1 周期，只有 1 名患者进展至 4 级 CIPN (4%)，9 名(33%)仍在 2 级 CIPN，11 名(41%降级至 1 级 CIPN)，6 名(22%降级至 0 级 CIPN)，达到了他们预期的成功标准，证实了针刺在 CIPN 中的意义，相关机制值得进一步研究。Jeong YJ 等人[27]对 10 名使用紫杉类化疗药后周围神经病变的乳腺癌患者进行了针刺治疗后的可行性和安全性评估，结果所有参与者的总(神经病理性疼痛症状量表)NPIS 评分在治疗结束时显著降低($P = 0.003$)，亚组分析中，自发性压迫性疼痛、自发性阵发性疼痛、诱发性疼痛和感觉异常显著改善($P = 0.014$、$P = 0.015$、$P < 0.001$ 和 $P = 0.003$)，提示针刺是缓解乳腺癌 CIPN 症状的一种有效替代方法。刘柏[37]等发现，与对照组相比，针刺治疗 CIPN 具有统计学意义($P < 0.05$)，缩短了 CIPN 的自愈时间。简黄晨等人[23]为了评估手法针刺对 CIPN 的影响，

选取 20 例接受紫杉类化疗方案的乳腺癌患者，结果显示针刺组第 9 周的平均疼痛严重程度较最初显著降低($P = 0.031$)，表明针刺处理在癌症患者的神经性疼痛方面发挥了一定的效果。

2.4.2. 电针

电针疗法属中医的一种治疗方式，其中“针”指通过针刺入穴位获取“得气”感，“电”指与人体生物电相似的电流，这种双重刺激可以通过舒筋通络而起到治疗疾病的作用。韩国一项个案报道表示[38]，电针治疗可能对使用多西紫杉醇的乳腺癌 CIPN 患者具有显著影响。韦海霞等人[39]选择使用紫杉醇的 60 例恶性肿瘤患者(包括乳腺癌)后随机分成治疗组及对照组，结果电针艾箱灸组中 CIPN 的发生率明显低于对照组(50%: 90%, $P < 0.01$)。同样，一项大鼠的体外实验表明[40]电针可通过调节 Nrf2-ARE 和氧化机制改善紫杉醇类药物化疗后引起的神经性疼痛，说明电针镇痛的潜在分子机制在 CIPN 的治疗中存在潜在的临床意义，除动物实验外，还需要其他类型更可靠的实验验证。

2.4.3. 其他

Nur Izgu 等人[41]在一项随机对照试验中发现，经典按摩对女性乳腺癌患者使用紫杉醇药物后导致的周围神经病理性疼痛有益($P < 0.05$)，生活质量中的感觉和运动子量表得分也显示出经典按摩获益的统计学差异($P < 0.05$)。杨志峥等人[42]用中医三联疗法(包括中医汤药、针灸治疗、中药外洗)治疗化疗引起的手足麻木(包括紫杉醇类药物)，发现与西医组相比疗效有显著的意义(93.75%: 76.74%, $P < 0.05$)，这种针药合用相比于传统营养神经的治疗具有疗效高，疗程短的优势。还有一些中医研究[43] [44]认为化疗药物性阴寒，其导致 CIPN 的机制可以认为是血脉不通，经络闭阻，可通过中药外洗的方法治疗 CIPN，以益气养血，活血通络的方法起到疏通经络、解毒化瘀的作用，体现了内病外治的观点。

3. CIPN 的研究意义

紫杉类药物的临床研究和应用已经历了 20 余年，广泛并成功应用于乳腺癌多个治疗阶段[45]，无论是原有药物还是新型药物都具有诱发 CIPN 的毒副作用。CIPN 作为重要的临床难题一直有待解决，其可能成为一种慢性疾病，使患者产生长期影响，包括麻木、残疾和神经性疼痛，影响了患者的治疗、日常生活和总体生活质量[4]。尽管一些研究表明了其在 CIPN 中的作用并展示了一定的潜力，但并没有指南为临床提供统一的关于预防或治疗 CIPN 的方法[19]。另外，现有预防和治疗 CIPN 的研究思路及方法层次不穷，但研究出更科学的方式才是目前直至未来更关键的一步。

4. 展望

上述处理方式在一定程度上体现了对 CIPN 的疗效性，但 CIPN 本身就缺乏毒副作用机制及评估的统一标准，所以存在或多或少的局限性，如研究样本量不足、临床随访率低、实验设计、对照设计、疗效评估、干预方式时间节点缺乏统一的标准等问题。国内外对于 CIPN 研究的关注度一直只增不减，值得关注的是，中医在这方面也展现了一定的潜力。为了日后更好地管理紫杉类药物导致周围神经病变的患者，改善其对患者治疗及生活质量的影响，临床医生应做好对单一恶性肿瘤患者使用同一类化疗方案后发生不良反应的归类，尽量扩大样本的数量，科学合理、客观地设计实验，并且应该注重预测个体患者的易感性或治疗反应，以便更好地用于建模和疾病相关基础和临床的研究。

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