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常见化疗药物诱导口周神经病变的相关探讨

李婉茹，陈　军*

浙江大学医学院附属第二医院口腔颌面外科，浙江　杭州

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摘　要

化疗诱导的周围神经病变(CIPN)作为细胞毒性化疗药物的常见并发症，其影响范围广泛，包括口腔及口周区域，这一现象虽报道较少，但不容忽视。本综述旨在系统梳理并分析排除由头颈部肿瘤、放疗、口咽黏膜炎、感染或术后疼痛等直接引起的口腔及口周化疗诱发周围神经病变(OCIPN)的相关数据，细胞毒性化疗药物在此区域神经毒性作用，包括颌骨疼痛或麻木。通过检索PubMed和Cochrane数据库至2025年6月，并遵循严格的文献筛选标准，我们汇总了铂类、紫杉烷类、长春花生物碱、免疫调节剂及烷基化剂等药物在OCIPN方面的表现，为临床医生提供有价值的参考。

关键词

口腔化疗所致周围神经病变，舌部麻木，舌痛，口腔麻木感，牙齿敏感，化疗药物

Related Discussion on Common Chemotherapy Drugs Inducing Perioral Neuropathy

Wanru Li, Jun Chen*

Department of Oral and Maxillofacial Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou Zhejiang

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent complication of cytotoxic chemotherapeutic agents; its incidence largely varies, depending on type, dose, agent and preexisting risk factors. Oral-and-peri-oral-CIPN (OCIPN) is underreported. A narrative literature review, following

*通讯作者。

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SANRA guidelines was conducted. PubMed and Cochrane databases were searched until now. Articles referring to neuropathy or neuropathic pain due to head and neck cancer, head and neck radiotherapy, oropharyngeal mucositis, infection or post-surgical pain were excluded. Platinum-based chemotherapeutics, taxanes, vinca alkaloids, immunomodulatory and alkylating agents can cause OCIPN.

Keywords

Oral Chemotherapy-Induced Peripheral Neuropathy, Tongue Numbness, Tongue Tingling, Oral Cavity Numbness, Teeth Hypersensitivity, Chemotherapeutic Agents

1. 引言

化疗作为癌症治疗的重要手段，其疗效显著，但伴随的并发症亦不容忽视。其中，化疗诱导的周围神经病变(CIPN)是铂类、紫杉烷类、长春花生物碱等细胞毒性药物常见的并发症之一。CIPN 不仅限于四肢，口腔及口周区域同样可能受累，表现为疼痛、麻木、刺痛及感觉过敏等症状，严重影响患者的生活质量。同时 CIPN 也可导致化疗药物治疗剂量减少或停药从而加重病症。其症状表现主要取决于受累及的感觉神经纤维包括 Aβ 神经纤维，Aδ 神经纤维及无髓鞘 C 神经纤维[1] [2]。其中 Aδ 神经纤维及无髓鞘 C 神经纤维等细小神经纤维损伤更易导致温度及疼痛感知异常[3]。

化疗药物在治疗后不同时间点可诱发神经病理性症状。顺铂所致神经病变可能在治疗后约 1 个月发生。奥沙利铂相关症状可能在输注后 30~60 分钟内出现，而长春碱类药物相关的神经病变可能在给药数日后发生[4]。

口腔及口周神经毒性症状主要表现为持续性深部、弥漫性、搏动性颌面部疼痛或麻木。三叉神经支配的多个部位可能受累，包括下颌骨、上颌骨、牙齿及舌部[5] [6]。然而，相较于四肢 CIPN，OCIPN 的研究报道相对匮乏[2] [7]-[12]，本综述旨在填补这一空白，深入探讨化疗药物对口腔及口周神经的毒性作用。

2. 材料与方法

2.1. 文献检索策略

我们通过电子数据库 PubMed 和 Cochrane 进行系统性文献检索，检索时间范围截至 2025 年 6 月。使用化疗药物的通用名称(包括铂类化疗药物、紫杉烷类、长春花生物碱、免疫调节剂和烷基化剂)结合“口腔神经病变”、“牙齿敏感”、“口腔毒性”、“口腔麻木”及“舌痛”等关键词进行筛选。同时，对相关文献的参考文献部分进行了人工复核，以确保检索的全面性。

2.2. 纳入与排除标准

2.2.1. 纳入标准

以英文发表，聚焦于口腔及口周化疗药物诱导神经病变的研究，包括回顾性研究、前瞻性调查、病例报告及临床试验等。

2.2.2. 排除标准

涉及头颈部肿瘤、头颈部放疗、口咽黏膜炎、感染或术后神经病理性疼痛所致的神经病变及神经病

理性疼痛的研究。

2.3. 评估方法

遵循叙事性综述文章评估量表(SANRA)指南[13]，对纳入的文献进行质量评估，确保综述的科学性和可靠性。本研究基于已发表数据，未涉及受试者入组，故无需伦理委员会批准。

3. 结果

3.1. 检索结果

检索显示在 17 篇文献[12] [14]-[29]中，奥沙利铂在五篇文献中被引用[12] [17] [21]-[24]，顺铂单药治疗仅一篇[18]，紫杉醇两篇[12] [20]，两篇多西他赛[12] [20]，六篇维甲酸酯[12] [17] [21]-[24]，两篇文献涉及沙利度胺[27] [28]，环磷酰胺在两篇文献中被提及[12] [29]。七篇文献为病例报告[19] [20] [23] [24] [27]-[29]，1 个病例系列[18]，一项临床试验[21]其中一项为回顾性研究[12]以及 7 项前瞻性研究[14]-[17] [22] [25] [26]具体见(图 1)。

Author, Year [Ref. no]	Chemotherapy	Study type
Hino et al., 2021 [12]	oxaliplatin, pacli- taxel, docetaxel, vincristine, cyclophosphamide	retrospective
Leonard et al., 2005 [14]	oxaliplatin	prospective study
de Albuquerque Ribeiro Gondinho et al., 2020 [15]	oxaliplatin	prospective study
Macquart-Moulin et al. 2000 [16]	oxaliplatin	prospective study
McCarthy et al., 1992 [17]	oxaliplatin, vincristine	prospective study
Gupta et al., 2022 [18]	cisplain, vinblastine	case series
Lee et al. 1999 [19]	paclitaxel	case report
Fujita et al. 2018 [20]	docetaxel	case report
Levine et al. 1990 [21]	vincristine	clinical tria
Sandler et al. 1969 [22]	vincristine	prospective study
Dixit et al. 2012 [23]	vincristine	case report
Valenzuela et al. 2019 [24]	vincristine	case report
Spigel et al. 1978 [25]	vincristine	prospective study
Samuels et al. 1970 [26]	vincristine	prospective study
Anyanwu et al. 2014 [27]	Thalidomide	case report
Elad et al. 1997 [28]	Thalidomide	case report
Zadik et al. 2010 [29]	Cyclophosphamide	case report

Figure 1. Articles sorted by author, chemotherapy agent and study type
图 1. 按作者、化疗药物及研究类型分类的文献

3.2. 化疗药物与 OCIPN 的关联

3.2.1. 铂类药物

铂类药物，如顺铂和奥沙利铂，通过作用于 DNA 后诱导程序性细胞死亡，通常应用于肠道膀胱睾丸卵巢及头颈部恶性肿瘤[30]，是引起 OCIPN 的常见药物。铂类药物诱发的神经病变通常在数日内消退，但重复给药可能导致复发并加重或在停药后症状加重，需要较长的治疗后恢复期症状才能改善，有时甚至无法完全缓解[31]。铂类药物诱导的神经病变被认为通过与线粒体 DNA (mtDNA)形成加合物导致线粒体损伤并破坏其复制过程[32] [33]。其常积蓄于脊背神经节和三叉神经节神经元中[34]。患者常报告口腔面部冷敏感、口腔及颌部疼痛、口腔刺痛及牙齿敏感等症状[14] [35]-[37]。这些症状可能在治疗后不同时间点出现，如顺铂所致神经病变可能在治疗后约 1 个月发生，而奥沙利铂相关症状则可能在输注后 30~60 分钟内迅速显现。

奥沙利铂治疗患者中最常报告的神经病理性症状是“初咬”时的口面部冷敏感及颌部疼痛，该症状通常持续时间较短，且在进食和饮水时出现，面部受冷风刺激或饮用冷饮也可能引发剧烈疼痛[14]。阿尔布开克·里贝罗·贡迪尼奥等人[15]有研究报道了颌骨疼痛、咽喉不适以及口腔内刺痛感，Hino 等[12]。报告了舌尖触痛、口腔黏膜热敏感及牙齿冷敏感。研究发现，奥沙利铂治疗期间的口面部疼痛发生率为 45%~56% [16] [17]。

顺铂给药通过 TRPA1 在口腔黏膜组织和舌下腺(TG)的敏化作用导致口腔周围神经病变[38]。它与外周运动神经元上钾通道(VGKC)相互作用，表现出神经兴奋性增高、去极化延长和神经传递增强[39]。Ta 等[40]据报道，在接受顺铂治疗的小鼠三叉神经节(TG)神经元中，瞬时受体电位或 TRPV1 及 TRPA1 mRNA 表达增加，且该现象与热觉和机械敏感性增强相关。其亦有报道双侧颌骨疼痛[18]。

3.2.2. 紫杉烷类药物

紫杉烷类药物，包括紫杉醇和多西他赛，可能诱发口腔及舌部麻木刺痛、热敏感等感觉异常[41] [42]这些症状通常与药物对神经纤维的直接毒性作用有关，影响患者的进食和言语功能。外周神经元的敏化及随后的神经元兴奋性改变会导致机械性高敏感性和异位自发性活动，从而促进周围神经病变的发生[10]此类症状在紫杉醇(pacli-taxel)治疗中最为严重；而多西他赛(docetaxel)给药时症状强度较轻[30]。Lee 等人的病例报告中一名 62 岁乳腺癌女性患者单次接受紫杉醇给药后，出现口周感觉异常，18 天后因口腔麻木及双侧面神经麻痹导致进食困难。该并发症在 23 个月后完全缓解[19]。亦有报道显示舌背出现刺痛感及口腔黏膜热敏感性增高[12]。多西他赛可能引起三叉神经功能障碍。Hino 等人[12]报告了舌尖刺痛感。而 Fujita 等[20]报告了涉及舌神经、颊神经及下牙槽神经的三叉神经病变，表现为颊黏膜、舌及下唇(包括皮肤表面)的麻木感。

3.2.3. 长春花生物碱

长春碱类药物，如长春新碱和长春碱，可导致颌部、牙齿及唇部疼痛，以及口腔黏膜痛觉过敏[10]。接受长春新碱治疗的患者最常见的症状为颌骨疼痛[17] [21]-[23]。在 McCarthy 等人的研究中[17]据报道，该分布中存在多个位点三叉神经可受累，其发生率与上颌牙和下颌牙相当(分别为 33%和 28%)，同时可累及舌、唇及牙槽嵴(较少见)。疼痛发作于给药后 3 天，平均持续时间为 2 天；22%的患者报告为剧烈疼痛，12%为中度疼痛[17]。Valenzuela 等[24]另有报告指出，约 30%的患者出现上颌牙和下颌牙疼痛，以及下颌疼痛(表现为进食时单侧颌部疼痛)、上颌、舌、口腔黏膜及唇部疼痛。

3.2.4. 免疫调节剂与烷基化剂

免疫调节药物，如沙利度胺，可引起唇、舌及口周麻木，而烷基化剂，如环磷酰胺，则可能导致舌唇

刺痛及牙齿冷敏感。已有报道表明环磷酰胺具有神经毒性作用[41]-[44]。有病例报告提示环磷酰胺与牙神经病变之间存在关联，表现为一名 54 岁非霍奇金淋巴瘤男性患者出现严重牙痛(疼痛评分量表为 9 分和 10 分) [29]。疼痛最初位于右侧下颌磨牙区，随后转移至左侧上颌磨牙区，由呼吸及饮用冷饮诱发，且无口外神经病理性疼痛。此外，Hino 等人报告了接受环磷酰胺联合长春新碱治疗的患者出现舌唇刺痛及牙齿冷敏感[12]。在皮肤红斑狼疮(CLE)的治疗病例中，患者主诉嘴唇、舌部及口周区域麻木[27]症状最初表现为上下唇的刺痛感，逐渐扩展至舌尖及口周区域，继而发展为麻木；未出现运动功能缺损，亦未累及其他部位。停用沙利度胺后，所有症状均消失。此外，在一例异基因外周血干细胞移植后发生的慢性移植排异病例中，患者出现口周区域、手指及脚趾麻木[28]。

4. 讨论

化疗可能引发口腔及口周神经病变，因其药物作用会引发细胞结构与功能的多重改变，具体表现为：膜受体、代谢、细胞内信号传导、神经传递及兴奋性等机制的异常。三叉神经(第五对脑神经)可受累，其病程中不同部位可能出现神经病变；例如，下颌神经受累时，可能表现为持续性深部弥漫性跳动性疼痛或麻木；舌、唇、上颌骨及无牙槽嵴受累则较为少见[5]。

同时化疗可能影响牙髓组织，导致患者在化疗后数周或数月出现牙痛敏感症状；此类症状被定义为无临床或影像学病理学表现的严重、搏动性局部疼痛[29]。其需进行详细检查(如口内检查和 X 线检查)以区分神经病变与牙髓病变引起的疼痛。

OCIPN 的患病率受以下因素影响：使用的药物、剂量(每日剂量和累积计量)、年龄、原有疾病风险因素(如糖尿病或神经系统综合征)。头颈部癌症患者在放射治疗期间的神经病理性疼痛可能因手术引起的疼痛或放射性口腔黏膜炎加重引发[3] [11]。Hino 等[12]对 180 例癌症患者末次化疗后 1 个月随访调查中，15 例患者(约 8.0%)主诉口腔感觉异常(13 例)其中牙痛(4 例)，其中 13 人还患有 CIPN (86.7%, P = 0.0037)。12 例患者使用了已知可产生 CIPN 的药物：4 种紫杉烷类(多西他赛和紫杉醇各 2 例)、4 种奥沙利铂、3 种长春新碱和 1 种阿糖胞苷。

文献记载的化疗最常见口腔不良事件包括口腔黏膜炎、味觉障碍和口干[11]。化疗引发的口腔及口周神经毒性作为癌症治疗的并发症鲜有文献记载，且可能仅有少数接受化疗的患者因颌面部疼痛而转诊至牙科就诊。由于症状的短暂性，加之化疗期间的神经毒性有时可模拟牙源性或牙周性疼痛，牙科医师可能无法识别神经毒性的症状。这可能导致对健康牙齿进行不必要的牙科治疗，从而损害患者的生活质量。因此接受细胞毒性药物治疗的患者需进行详细的牙科检查。

临床医师应首先明确 OCIPN 的临床特征，并将其与更常见的常于四肢末端“手套－袜套”样分布 CIPN 进行对比，并逐步排除其他可能导致口周症状的常见原因，如口腔黏膜炎、病毒感染(如疱疹)、药物性口干、或营养缺乏等，以确保诊断的准确性。

OCIPN 通常在停止化疗后缓解。然而，在某些情况下，疼痛可能引发感觉和运动功能改变，并演变为慢性状态。因为对于 OCIPN 的治疗研究较少，目前多数还是借鉴 CIPN 治疗方案。临床常见的药物主要包括钙通道调节剂(如普瑞巴林，加巴喷丁，美洛加巴林、克利加巴林)，抗抑郁药(如度洛西汀)，局部利多卡因贴剂等。钙通道调节剂可能降低三叉神经等感觉神经元的高反应性，缓解口周区域的异常疼痛。但缺乏在 OCIPN 人群中的直接临床试验，同时全身用药可能引起头晕、嗜睡等中枢副作用。度洛西汀是多个指南推荐用于治疗糖尿病周围神经病变疼痛的一线药物但其口干等副作用可能加重口腔不适感。局部利多卡因贴剂或者凝胶理论上适合局部给药治疗神经病理性疼痛，但受限于口腔湿润环境，可能影响药物附着和渗透。除了药物治疗以外，目前也有部分临床尝试一些非药物方法如冷冻疗法。理论上，口含冰水或冰棒是口周区域的“冷冻疗法”，在临床上已被许多患者自发采用。然而，温度与时长控制欠

缺精准并难以均匀覆盖整个口腔复杂环境。

本研究存在若干局限性。由于 OCIPN 很少在大型科学研究中得到记录，因此，近半数文章为病例报告或病例系列。专科医师与牙科医师应参与药物临床试验的多学科团队，以记录此类毒性反应。为了提高癌症患者的生活质量，肿瘤科医师、疼痛科医师和专科牙科医师需要了解 OCIPN。

5. 结论

化疗药物在口腔及口周区域的神经毒性作用是一个值得关注的问题。本综述通过汇总和分析现有数据，为临床医生提供了关于 OCIPN 的全面认识。未来研究应进一步探索 OCIPN 的发病机制、预防措施及有效治疗方法，以改善癌症患者的生活质量。同时，加强多学科合作，促进口腔医生、肿瘤科医生及疼痛管理专家的沟通与协作，共同应对化疗药物带来的挑战。

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