

免疫检查点抑制剂相关性肺炎的研究进展

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摘要: 免疫检查点抑制剂(ICIs)被广泛应用于多种恶性肿瘤的治疗,但由ICIs诱导的免疫系统过度激活也会导致T细胞对自身抗原进行攻击,临床上出现一系列免疫相关不良事件(IRAEs)。免疫检查点抑制剂相关性肺炎(CIP)是一类少见但有潜在致命危险的免疫相关不良反应,发生在肿瘤免疫治疗任何时间。临床医生应了解CIP的机制及特征,及早识别并正确处理。本文就CIP的流行病学、生物学机制、临床特征、诊断及治疗等进行综述。

关键词: 免疫检查点抑制剂; 免疫系统; 免疫检查点抑制剂相关性肺炎; 流行病学; 生物学机制

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Research progress of immune checkpoint inhibitors associated pneumonia

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Abstract: Immune checkpoint inhibitors (ICIS) are widely used in the treatment of a variety of malignant tumors, but the over activation of the immune system induced by ICIS will also lead to T cells attacking their own antigens, and cause a series of immune related adverse events (IRAEs) in clinic. Immune checkpoint inhibitor associated pneumonia (CIP) is a rare but potentially fatal immune related adverse reaction that occurs at any time of tumor immunotherapy. Clinicians should understand the mechanism and characteristics of CIP, and identify and deal with it correctly as soon as possible. This paper reviewed the epidemiology, biological mechanism, clinical characteristics, diagnosis and treatment of CIP.

Key words: immune checkpoint inhibitors; immune system; immune checkpoint inhibitor associated pneumonia; epidemiology; biological mechanism

近年来,免疫检查点抑制剂(ICIs)在非小细胞肺癌、黑色素瘤、肾透明细胞癌等多种肿瘤治疗中取得显著疗效^[1]。免疫检查点是T细胞和其他免疫细胞表面上参与免疫应答调节的分子,而ICIs是针对某些免疫检查点的单克隆抗体,例如细胞毒性T淋巴细胞相关抗原4(CTLA-4)阻断剂、程序性死亡分子1(PD-1)阻断剂及其配体(PD-L1)阻断剂等。ICIs主要通过阻断T细胞的抑制性信号通路,诱导T细胞活化增殖来恢复其特异性识别和杀伤肿瘤细胞的能力^[2]。然而,免疫系统过度激活可能使得免疫耐受失衡而引起

多系统的免疫相关不良反应(IRAEs)^[3]。随着癌症免疫治疗领域的迅速发展,有关各种器官系统毒性的免疫相关不良事件逐渐增多并引起临床重视^[4]。其中免疫检查点抑制剂相关性肺炎(CIP)发生率为2%~5%,虽少见却是一种致命性的免疫相关不良反应。本文就CIP发展的流行病学、生物学机制、临床特征、诊断及治疗等进行综述。

1 定义

CIP是指由ICIs治疗引起的胸部影像学上出现新发浸润影,和在临床上没有检测到新的肺部

感染或肿瘤进展等情况下,出现呼吸困难和/或其他呼吸体征/症状(包括咳嗽和活动后气短等)^[5]。

2 CIP 的流行病学及危险因素

CIP 的发生率取决于肿瘤类型和 ICI 的类型^[6-7]。研究显示 CIP 在非小细胞肺癌中的发生率为 7%~13%^[5,8-10],远高于在黑色素瘤患者中的发病率^[11],由此推断 CIP 的发生率可能与瘤种相关。此外,不同 ICI 类型所致 CIP 发生率也不同。与应用抗 CTLA-4 药物相比,接受抗 PD-1/PD-L1 抗体治疗的患者 CIP 发生率更高。据报道^[12-13],在应用伊匹单抗治疗的患者中,肺炎发生率约为 1%,而使用 PD-1 和 PD-L1 抑制剂单药治疗的发生率约为 5%,PD-1 或 PD-L1 抑制剂和 CTLA-4 抑制剂的联合用药可致肺炎发生率高达 10%^[14]。目前临床所知 CIP 的发病率为 2%~5%,然而有研究称在真实世界中 CIP 发生率可高达 19%^[15-16],病死率甚至可达 12.8%~22.7%^[16-18]。

CIP 大多发生在免疫治疗的早期,其中位发病时间约为 3 个月^[9,19-21]。但在免疫治疗的任何时间甚至治疗结束后都有可能出现,因此临床医生应时刻警惕 CIP 的发生。根据目前已有的研究和病例报告评估了 CIP 的多个潜在危险因素。这些因素包括患者特征、疾病特征和治疗方法。具体因素包括年龄、性别、吸烟史、季节、既往肺部疾病(间质性肺病、慢性阻塞性肺疾病)、肿瘤组织学类型、表皮生长因子受体(EGFR)-酪氨酸激酶抑制剂与 ICI 联合治疗和既往胸部放疗史^[15]。

3 CIP 的发病机制

CIP 的具体发病机制目前尚未完全清楚,可能机制有以下 4 种:① T 细胞活性增强会同时针对肿瘤和其他健康组织中存在的交叉抗原进行攻击;② 先前所存在自身抗体水平的增高;③ 炎性细胞因子特别是 IL-17 的过度分泌;④ CTLA-4 抗体与正常组织中所表达的 CTLA-4 抗原直接结合而导致的补体介导的炎症反应增加^[22]。其中,最主要的原因是效应 T 细胞的活性增强而直接攻击靶器官抗原。CIP 中 T 细胞的过度活化与 PD-L2 和排斥性导向分子 b(RGMb)相互作用有关^[23]。PD-L2 可在抗原呈递细胞(例如巨噬细胞和树突状细胞)中检测到^[24],由于其可负性调节 T 细胞表达,在机体免疫耐受方面起重要作用,

RGMb 可表达于肺间质巨噬细胞和肺泡上皮细胞中。PD-L1 与 RGMb 同为 PD-L2 的配体,使用 PD-L1 抑制剂之后会阻断 PD-L1 和 PD-L2 之间的结合,从而使 PD-L2 与 RGMb 之间作用增加,此时可诱导大量 T 细胞增殖。与此同时,由于 PD-L1 阻滞,打破了 PD-L1 介导维持的自身抗原免疫耐受状态,局部增加的 T 细胞会损害肺泡上皮等细胞而导致 CIP 的发生^[23]。另外还有研究^[22]表明,CIP 的发生与肺部本身的炎症状态与肿瘤炎症微环境有关。

4 CIP 的诊断及鉴别诊断

CIP 的诊断依据^[25]为:① 既往接受过 ICI 治疗;② 新出现症状或原症状加重,包括呼吸困难、咳嗽、胸痛、发热、缺氧等;③ 影像学表现:新出现的肺部阴影(如磨玻璃影、斑片影或实变影、网格状影、小叶间隔增厚、纤维条索影、结节影等);④ 需排除肺部感染、肿瘤进展、其他原因引起的肺间质性疾病、肺栓塞、心功能不全引起的肺水肿等;⑤ 抗菌药物无效,而激素有效,再次使用 ICI 或停用激素可复发。

疑似 CIP 患者的鉴别诊断主要包括:肺部感染、肿瘤进展(癌性淋巴管病、肺肿瘤栓塞)、放射性肺炎、心力衰竭引起的肺水肿/心肌炎、药物相关间质性肺炎和 ICI 相关神经肌肉疾病引起的呼吸衰竭。此外,区分新发 CIP 和先前存在的自身免疫性疾病急性加重相关的肺炎也是一项挑战,因为两者都具有自身免疫现象。而在新型冠状病毒肺炎(COVID-19)病毒大流行期间,COVID-19 可能与 CIP 的表现相似,两者间的诊断也具有挑战性。这是最近对接受 ICI 治疗的急性呼吸道症状患者进行鉴别诊断的重要补充。

5 CIP 的临床表现及特点

CIP 的临床症状具有相对非特异性,在 CIP 有症状的患者中症状常有呼吸困难、持续性刺激性干咳、发烧和胸痛^[26],咯血、低血压、心动过速/心悸、腹泻和关节痛较少见。多达 1/3 的 CIP 患者是无症状的^[27],主要靠影像学检查发现。临床上也有少数患者仅出现呼吸困难但无影像学表现。

胸部 CT 扫描对于评估 CIP 至关重要,在胸部 CT 成像中可以发现肺炎的多种放射学特征,表现为 4 种主要类型:隐匿性机化性肺炎(OP)、非特异性间质性肺炎(NSIP)、过敏性肺炎(HP)

和急性间质性肺炎(AIP)与急性呼吸窘迫综合征(ARDS)相关^[9, 27]。最常见的模式是OP,其次是HP和NSIP。一般情况下,病灶累及下叶较累及中上叶更常见^[28],最常见的影像学以靠外周的磨玻璃阴影为主,也可发展为实变区^[29]。

支气管镜检查在CIP中可用于诊断和排除其他疾病,例如感染或肿瘤进展。CIP患者在支气管镜下肺泡灌洗液(BALF)多以淋巴细胞炎症为主^[30-35],而肺部细菌感染则多以中性粒细胞浸润为主。此外研究^[30]显示,来自BALF的T细胞的免疫检查点谱可用于区分CIP和其他肺部疾病,且有助于预测疾病的严重程度。

实验室检查方面目前同样缺乏特异性,然而在CIP发展过程中可表现出显著升高的中性粒细胞与淋巴细胞的比率(NLR)。NLR反映了全身免疫状况,被称为ICIs治疗的预后标志物。研究^[36]表明对NLR以及KL-6持续监测能更准确地预测CIP的发作和严重程度。还有研究^[37]提出乳酸脱氢酶(LDH)、血清 α -羟丁酸脱氢酶(HBDH)升高可能有助于重症CIP的早期诊断,且这2项指标对于预测疗效和判断预后有一定价值。

由于CIP的活检标本样本量较少,病理结果同样也缺乏代表性,但多数病理报告常表现为淋巴细胞浸润、弥漫性肺泡损伤、肉芽肿性炎症、机化性肺炎等^[27, 31]。

6 CIP的分级

美国国立癌症研究所常见不良反应评价标准(CTCAE),将CIP按严重程度分为5级^[37]。G1,无症状,炎症仅限于单叶或<25%的肺实质;G2,新症状或症状加重,包括呼吸急促、咳嗽、胸痛、发烧或缺氧,炎症累及多个肺叶或达肺实质的25%~50%,影响日常生活,需药物干预;G3,症状严重,中度缺氧,累及全部肺叶或>50%肺实质,个人自理能力有限,需吸氧住院;G4,危及生命的呼吸困难、ARDS需紧急干预,如插管;G5,死亡。

7 CIP的治疗

迄今尚无前瞻性试验来评价CIP的最佳管理方法,各大指南已发布的关于CIP的管理均基于肺炎的临床严重程度。根据CIP的临床严重程度对其进行以全身糖皮质激素为基础,必要时辅以经验性抗生素和免疫抑制剂的分级治疗。糖皮质激素是CIP治疗的基础用药,可控制70%~80%

的CIP^[5]。对于G1患者指南未推荐糖皮质激素治疗,建议停止ICIs治疗并应密切监测患者病情,包括体格检查、血氧饱和度监测、肺功能等,3~4周后复查CT,如果显示影像学进展则需按G2方案治疗。G2患者需通过静脉滴注给予泼尼松1~2 mg/(kg·d)或口服等效剂量糖皮质激素。如评估到症状改善,则在4~6周内将糖皮质激素用量逐渐减少到5~10 mg/周,患者激素减量的依据在临床中需参考影像学表现;如无改善,按G3~G4级肺炎治疗。当怀疑感染时,建议进行支气管镜检查 and/或支气管肺泡灌洗(BAL)加上经验性抗生素治疗^[38]。G3、G4患者需要永久停止ICI治疗,需住院并密切监测病情。在开始治疗前,应进行适当的诊断检查来排除感染或其他病因。药物治疗给予静滴甲泼尼龙2 mg/(kg·d)。类固醇治疗48 h后,如果观察到改善,则继续治疗直至改善至G1或更低,并在4~6周内逐渐减少糖皮质激素用量;如果临床症状未得到改善,应考虑额外的免疫抑制剂或免疫调节剂,包括静脉注射免疫球蛋白(IVIG)、英夫利昔单抗、环磷酰胺、他克莫司和吗替麦考酚酯。考虑到长期使用高剂量类固醇的可能性,临床上需要进行感染性预防,如甲氧苄氨嘧啶和磺胺甲恶唑可用于耶氏肺孢子的预防。

然而激素的初始剂量通常现实需要大于指南,临床医生需在1周之内控制患者病情以防止病情继续恶化。此外,免疫抑制剂通常不联合使用,但对于重症CIP患者在临床中联合使用免疫抑制剂效果更佳,比如静脉注射丙球蛋白。

8 预后及再挑战

大部分CIP可通过治疗后缓解或治愈,少数对于激素治疗不敏感、激素免疫抑制治疗后继发感染或癌症恶化的患者可能预后不良。此外在CIP好转后,ICIs再挑战治疗后再次发生肺炎的概率较高,因此需谨慎评估^[39]。G2患者一旦恢复到1级或更低,就可以恢复ICIs。对于G3患者,应慎重选择ICIs再挑战治疗,而对于G4患者,根据指南推荐应永久停用ICIs^[40]。ICIs再挑战用药方面,一般选择原药,若初始使用双免疫检查点抑制剂治疗,一般不建议继续联合治疗,可考虑选择其中一种再挑战。再挑战后复发性肺炎的模式、受累部位和严重程度可能有所不同。ICIs再挑战是否能使患者受益取决于具体情况。临床医生应

考虑患者的癌症状态、合并症和体能状态,并应告知患者这些发生率,以确定是否再次使用 ICIs。

9 小结与展望

CIP 的发生可贯穿免疫治疗的全过程,及早发现诊断,积极正确治疗,多学科合作诊治是关键。目前迫切需要前瞻性、多学科、多机构的临床试验研究,来阐明现实世界中 CIP 的病理生理学和危险因素,并找寻可以明确预测肺损伤的生物标志物。临床医生应了解 CIP 的各种临床、病理和影像学表现,能更准确地为患者管理提供策略并改善患者的预后。

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