

·述评·

免疫检查点抑制剂相关消化系统不良事件:从发病机制到临床管理

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【摘要】 免疫检查点抑制剂(immune checkpoint inhibitor, ICI)的广泛应用革新了肿瘤治疗范式,但随之而来的免疫相关不良事件(immune-related adverse events, irAEs),尤其是消化系统不良事件,已成为临床实践中亟待解决的重大挑战。本文系统阐述了消化系统 irAEs 的发病机制,其核心在于 ICI 诱导的机体自身免疫耐受失衡。该过程涉及由分子模拟与抗原交叉反应、免疫细胞异常激活及肠道微生态紊乱等多因素介导的炎症级联反应。本文详细归纳了 ICI 治疗过程中上/下消化道、肝胆及胰腺受累的流行病学特征与关键风险因素,并结合最新临床指南,全面梳理了基于不良事件分级的规范化评估与分层管理策略。未来研究应聚焦于深层的免疫学机制挖掘,探索靶向特定免疫细胞亚群、关键信号通路及调节肠道微生态等新型精准干预手段,旨在优化免疫治疗的安全性及有效性。

【关键词】 免疫检查点抑制剂; 免疫相关不良事件; 消化系统免疫相关不良事件; 不良事件分级

Digestive system adverse events associated with immune checkpoint inhibitors: from pathogenesis to clinical management

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【Abstract】 The advent of immune checkpoint inhibitor (ICI) has fundamentally reshaped the paradigm of oncology treatment. However, the emergence of immune-related adverse events (irAEs), particularly digestive system adverse events, presents a formidable clinical challenge. This review systematically elucidates the multifaceted pathogenesis of digestive system irAEs, which primarily stems from the disruption of immunological self-tolerance following ICI therapy. The underlying mechanisms involve complex inflammatory cascades driven by factors such as molecular mimicry and antigen cross-reactivity, dysregulated immune cell activation, and gut microbiota dysbiosis. This article provides a comprehensive overview of the epidemiology and risk factors associated with ICI therapy across the upper/lower gastrointestinal tract, hepatobiliary system, and pancreas. Furthermore, integrated with the latest clinical practice guidelines, this article delineates standardized assessment and stratified management protocols based on severity grading. In conclusion, future research should prioritize decoding the intricate immunological orchestrations of irAEs and exploring precision interventions—including targeting specific immune cell subsets, modulating inflammatory signaling pathways, and leveraging the gut microbiome—to ultimately optimize the therapeutic index of ICI.

【Key words】 Immune checkpoint inhibitor; Immune-related adverse events; Digestive system adverse events associated with immune checkpoint inhibitor; Adverse event grading

免疫治疗的出现标志着肿瘤治疗范式发生了根本性转变^[1]。以免疫检查点抑制剂(immune

checkpoint inhibitor, ICI)为代表的免疫治疗,通过特异性阻断 T 细胞负性调控通路,突破部分晚期恶性肿瘤的治疗瓶颈^[2]。目前,已有多种靶向免疫检查点的单克隆抗体获美国食品药品监督管理局

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及中国国家药品监督管理局批准使用^[3-5]。

目前ICI在消化系统恶性肿瘤中的应用日益广泛,包括胃癌、结直肠癌、肝癌、食管癌、胰腺癌、胆管癌等^[6-12]。然而,异常免疫应答所导致的免疫相关不良事件(immune-related adverse events, irAEs)已成为消化系统恶性肿瘤临床实践中不得不面对的挑战^[13]。消化系统irAEs的临床表现各异,严重程度不一。鉴于临床表现的复杂性和临床治疗的紧迫性,本文旨在解析驱动消化系统irAEs发生的分子与细胞机制,系统性分析消化系统irAEs的流行病学和临床特征,并基于国际指南总结此类irAEs的管理策略和未来研究方向。

1 发病机制

目前获批的ICI主要针对3个核心靶点:细胞毒性T淋巴细胞相关蛋白4(cytotoxic T lymphocyte-associated protein-4, CTLA-4)、程序性死亡受体1(programmed death-1, PD-1)/程序性死亡受体配体1(programmed death-ligand 1, PD-L1)以及新近发现的淋巴细胞激活基因3(lymphocyte activation gene-3, LAG-3)^[14]。这些靶点均是T细胞功能的负向调节因子,可维持免疫耐受,避免免疫过度激活,而肿瘤细胞往往通过细胞表面表达免疫检查点相应配受体分子,抑制T细胞功能,从而逃避体内免疫监视^[15-16]。ICI可单独使用,也可联合其他疗法(如其他ICI、化学治疗或放射治疗),用于新辅助、辅助或晚期肿瘤的姑息性治疗阶段。

尽管ICI在临床试验中取得了成功,但ICI可导致机体自身耐受性丧失,引发针对非肿瘤细胞的免疫应答,因此患者易发生ICI介导的不良事件,即irAEs^[1]。irAEs具体机制尚未完全阐明,以抗PD-1/PD-L1单克隆抗体治疗为例,目前认为,抑制T细胞负性调控通路后,包括自身反应性T细胞激活和克隆性扩增,髓系细胞活化和浆细胞功能失调,以及自身抗体产生等在内的多种因素参与了irAEs的发生过程^[17-19]。T细胞对组织免疫监视具有空间特性,其中循环记忆T细胞负责监视次级淋巴器官,而组织驻留记忆T细胞则在屏障组织如肠道中充当“哨兵”,其功能受到PD-1和CTLA-4等抑制性受体的负性调控。然而在ICI治疗过程中,组织驻留记忆T细胞免疫“刹车”信号解除,功能异常活化,最终导致肠道炎症^[20]。研

究揭示在免疫治疗相关结肠炎(尤其ICI含抗CTLA-4单克隆抗体治疗)中,活化的组织驻留记忆T细胞及其克隆来源且高度增殖性的杀伤性CD8⁺T细胞扮演着关键角色,它们共同介导了辅助性T细胞(helper T cell, Th细胞)和杀伤性T细胞极化的炎症反应^[21-22]。研究者利用高分辨率核成像和高度多重成像质谱流式技术,鉴定出肠道固有层-上皮交界处异常活化、高度增殖的CD8⁺组织驻留记忆T细胞,且在抗PD-1和抗CTLA-4单克隆抗体联合治疗诱导的免疫治疗相关结肠炎患者组织和血清中,颗粒酶B表达水平均显著升高,提示CD8⁺组织驻留记忆T细胞是免疫治疗相关结肠炎的重要驱动因素^[21]。另一项研究利用空间组学技术,发现免疫治疗相关结肠炎患者肠道中存在一类能产生细胞因子 γ 干扰素和肿瘤坏死因子(tumor necrosis factor, TNF) α 、具备组织驻留特性的CD8⁺T细胞,直观展示了这些细胞在病变组织局部被异常激活并产生炎症因子,从而直接参与irAEs发生的过程^[23]。T细胞受体测序研究支持抗原交叉反应性的假设,即肿瘤抗原与受irAEs影响的炎症组织之间存在表位共享,新抗原或与自身抗原存在分子模拟的微生物组分可促进T细胞过度激活,导致异常免疫炎症反应^[24-26]。通过筛查健康肺组织与肺腺癌的共有抗原,研究人员鉴定出肿瘤相关自身抗原,可在部分患者中诱发T细胞反应,并在ICI介导的肺炎组织中发现相应抗原特异性T细胞受体克隆^[27]。Th17细胞是一类促炎性的CD4⁺T细胞亚群,在irAEs发生过程中发挥着重要作用。此类细胞分泌的白介素(interleukin, IL)-17是介导irAEs的关键介质。研究发现,接受新辅助ICI治疗的黑色素瘤患者血清IL-17浓度越高,严重免疫治疗相关结肠炎的发生率越高^[28]。IL-17可促进角质细胞增殖并激活信号转导与转录激活因子3(signal transducer and activator of transcription 3, STAT3)分子,从而加重皮肤炎症^[29],通过中和抗体对IL-17通路进行靶向治疗,已被证实能够有效改善免疫治疗相关银屑病样皮损^[30]。需要注意的是,IL-17阻断治疗也可抑制抗PD-1单克隆抗体的抗肿瘤疗效,影响肿瘤患者长期获益^[31]。IL-6是由活化的髓系细胞分泌、参与irAEs发生的又一重要炎症因子。研究发现,IL-6、IL-6受体与gp130组装形成异源六聚体复合物,通过募集Janus激酶和STAT3等下

游信号通路分子发挥作用^[32]。IL-6可促进Th17细胞分化,同时募集中性粒细胞,加重组织炎症和损伤,介导免疫治疗相关结肠炎的发生^[33]。阻断IL-6可在预防irAEs的同时不影响ICI疗效^[34]。此外,一项系统综述发现,近50%接受抗PD-1单克隆抗体和/或抗CTLA-4单克隆抗体治疗的肿瘤患者,包括黑色素瘤、非小细胞肺癌、肾/尿路上皮癌等,可检测到自身抗体^[35]。基线期升高的抗BP180 IgG滴度与皮肤irAEs的发生显著相关^[36]。出现免疫治疗相关肌炎/肌无力/心肌炎的患者常常合并抗横纹肌抗体、抗乙酰胆碱受体抗体和肌炎特异性抗体阳性;免疫治疗相关肝炎或结肠炎患者可出现抗核抗体和p型抗中性粒细胞胞浆抗体^[35]。因此,分泌自身抗体的B细胞可能参与了某些特定表型irAEs的发生,靶向清除B细胞可能是一种精准治疗自身抗体谱阳性irAEs的潜在方法。

肠道微生物-免疫轴已被证实对调节肿瘤免疫微环境具有关键作用。越来越多研究表明,肠道菌群组成改变如厚壁菌门、拟杆菌门和放线菌门等,与irAEs风险密切相关,尤其是免疫治疗相关结肠炎^[37]。一项涉及抗PD-L1单克隆抗体单药或联合抗CTLA-4单克隆抗体治疗晚期胃肠癌患者的前瞻性研究发现,未发生严重irAEs的患者基线期解木聚糖拟杆菌(拟杆菌门)和瘤胃球菌(厚壁菌门)更为富集^[38]。另一项研究发现,在接受抗PD-L1单克隆抗体联合抗CTLA-4单克隆抗体治疗后发生irAEs的黑色素瘤患者中,肠道拟杆菌在基线期显著富集,其高丰度与严重免疫治疗相关结肠炎患者的结肠活检样本以及小鼠模型中黏膜IL-1 β mRNA表达水平呈正相关^[39]。双歧杆菌属是放线菌门的重要成员,在肠道免疫稳态中发挥着重要作用。在一项接受抗PD-1单克隆抗体治疗的晚期胸部肿瘤患者的临床队列研究中,发生irAEs或免疫治疗相关结肠炎患者的双歧杆菌丰度显著降低^[40]。在抗CTLA-4单克隆抗体诱导的结肠炎小鼠模型中,双歧杆菌具有肠道保护功能,且不会削弱抗肿瘤活性^[41]。肠道菌群可被视为一个“代谢器官”,研究表明微生物代谢物在调节局部与全身免疫中发挥着重要作用^[37]。以短链脂肪酸为例,这类脂肪酸是肠道微生物通过发酵膳食纤维产生的,对维持肠道屏障完整性、肠道氧化应激平衡以及免疫稳态至关重要^[42-44]。通过膳食补充短链脂肪酸,特别是丁酸盐,可显著改善葡聚糖

硫酸钠诱导的小鼠结肠炎^[45]。此外,与非结肠irAEs患者相比,出现结肠irAEs的患者肠道产丁酸盐细菌丰度显著降低^[40]。宏基因组测序研究表明后续发生irAEs的患者治疗前肠道丁酸盐分泌水平显著下降^[46]。现阶段研究发现,肠道微生物通过抗原交叉反应直接或者通过其代谢物间接影响免疫细胞如T细胞、髓系细胞等的功能,促进炎症因子如TNF- α 、IL-1 β 、IL-6等的分泌,调控组织免疫微环境,进而调控irAEs发生^[37]。

2 流行病学与风险因素

由于ICI所引发的免疫激活具有非特异性,irAEs常常影响消化道、肝脏、胰腺和皮肤等多个器官及系统。大多数irAEs临床表现不严重,但少数患者可出现不可逆的器官功能衰竭,甚至死亡^[47]。ICI引发的消化系统irAEs,根据受累部位的不同,具有以下不同的临床特征。

2.1 上消化道不良事件

ICI引起的胃与食管炎症相对少见,发生率为3.0%~5.4%^[48-49]。45%的患者伴有十二指肠受累,70%的患者同时合并结肠炎^[50-51];若患者存在某些风险因素,例如既往使用非甾体抗炎药以及同时接受化学治疗或放射治疗,累及邻近器官的情况则更为常见^[50]。食管炎症状通常比较轻微,如恶心、呕吐,可伴有吞咽困难或吞咽疼痛、呕血、消化不良和黑便;胃肠炎主要表现为厌食、体重下降、消化不良、恶心呕吐、早饱、腹胀和黑便,偶见缺铁性贫血。若患者同时合并结肠炎,则可出现腹痛和血便症状。

2.2 下消化道不良事件

免疫治疗相关结肠炎在所有irAEs中发生率仅次于皮肤,临床表现通常最为严重^[52]。腹泻是其首要症状,13%~37%接受免疫治疗的患者会出现腹泻,9%的患者会出现其他相关症状,包括腹痛、发热、便中带血或黏液以及直肠出血^[53-54]。不同治疗方案的下消化道不良事件发生率存在差异:以腹泻的发生率为例,抗PD-1/PD-L1单克隆抗体单药治疗最低(11%),抗CTLA-4单克隆抗体单药治疗次之(36%),抗CTLA-4和抗PD-1/PD-L1单克隆抗体联合治疗最高(44%)^[55]。与酪氨酸激酶抑制剂联合应用可增加结肠炎风险^[56]。少数患者以结肠炎并发症为首发症状,如肠梗阻、穿孔、中毒性巨结肠或严重电解质紊乱^[57-60]。若患者既往

曾使用质子泵抑制剂($OR=5.4, 95\%CI\ 1.18\sim50.55, P=0.024$)^[61]、使用非甾体抗炎药(31%比5%, $P=0.003$)^[62]、肥胖(体重指数 $\geq 30\ kg/m^2$ 比 $\leq 25\ kg/m^2$: 11.4%比7.9%, $P=0.029$)^[63]以及既往炎症性肠病史($HR=7.59, 95\%CI\ 3.00\sim19.15, P<0.0001$)^[64], 发生免疫治疗相关结肠炎的概率均升高。

2.3 肝胆不良事件

免疫治疗相关肝炎的典型临床表现为无症状性血清肝酶水平升高,平均发病时间为51~63 d^[65-67]。免疫治疗相关肝炎发生率在接受抗PD-1单克隆抗体单药治疗的患者中最低(0.7%~2.1%),抗PD-L1单克隆抗体或标准剂量抗CTLA-4单克隆抗体单药治疗次之(0.9%~12%),抗CTLA-4和抗PD-1单克隆抗体联合治疗及高剂量抗CTLA-4单克隆抗体单药治疗的发生率则较高,分别为13%及16%^[68]。患者可出现非特异性“流感样”症状,如肌痛、疲劳、厌食或恶心^[65]。极少数患者会出现黄疸等症状^[65]。免疫治疗相关胆管炎几乎仅见于接受抗PD-1/PD-L1单克隆抗体治疗的患者,但也有1例病例报道与抗CTLA-4单克隆抗体单药治疗相关^[69]。其典型表现为胆汁淤积性肝功能异常。大多数患者(约65%)无临床症状,其他常见临床表现包括黄疸、发热和腹痛,从接受ICI治疗到起病的中位发病时间为5.7个月^[70]。高达40%的患者合并免疫治疗相关结肠炎^[70]。

2.4 胰腺不良事件

在接受ICI治疗的患者中,有1.1%~3.7%会发生胰腺损伤^[71-72],临床上表现为无症状性胰酶升高(2.7%)^[73]、糖尿病(0.9%)^[74]、急性或慢性胰腺炎(0.9%~1.9%)^[73]。极少数情况下可出现不伴胰腺炎症的孤立性外分泌胰腺功能不全^[75]。约2/3免疫治疗相关胰腺炎患者无明显临床症状,而是通过影像学检查确诊^[76]。显性症状表现则与胰腺炎相类似,包括腹痛和/或背痛、恶心呕吐、发热及腹泻^[77]。既往胰腺炎病史是免疫治疗相关胰腺炎

的重要风险因素^[76]。

2.5 其他消化系统不良事件

据报道,有1.5%~6.3%接受ICI治疗的患者会出现口腔黏膜炎,其中约0.2%的患者表现为重症^[78-79]。既往研究还报道其他罕见的消化系统irAEs,如乳糜泻、胃排空延迟、憩室炎、胆囊炎、阑尾炎、肠系膜炎和肠壁囊样积气症^[80-86]等。

3 消化系统 irAEs 严重程度分级和处理

不良事件通用术语评价标准(common terminology criteria for adverse events, CTCAE)5.0版是美国国家癌症研究所制定的一套标准化、系统化的不良事件分级体系,用于对肿瘤治疗中出现的所有类型不良事件进行评估^[87]。CTCAE 5.0版的核心是根据临床表现和检验检查结果,将不良事件(包括irAEs)划分为1~5级严重程度:1级,轻度不良事件;2级,中度不良事件;3级,重度不良事件;4级,危及生命的不良事件;5级,与不良事件相关的死亡。下面将对2024年发布的美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南中有关不良事件的分级和管理框架进行解读。

3.1 上消化道不良事件

在上消化道不良事件的评估中,应筛查可能导致症状的风险因素,例如阿片类药物、胃肠动力抑制剂、非甾体抗炎药的使用,某些癌症治疗药物和方案,乳糜泻。若症状为中度至重度,应考虑完善:胃镜检查,以排除感染(念珠菌、巨细胞病毒、单纯疱疹病毒、幽门螺杆菌等)或食管、胃及十二指肠炎症;胃肠动力评估。

不同严重程度的上消化道不良事件有不同的处理流程,需根据具体的分级情况采取合适的应对方案(表1)。

3.2 下消化道不良事件(腹泻/结肠炎)

基于下消化道不良事件的严重程度,可采取

表1 上消化道不良事件的分级和处理方案

分级	处理
1级:有症状,但可正常进食或维持体重及容量状态,无需积极干预	继续免疫治疗;支持性措施,包括补液、止吐、饮食调整;考虑使用硫糖铝、质子泵抑制剂、口服镇痛药;尽可能消除风险因素
2~4级:有症状,无法正常进食,出现脱水、体重下降、血流动力学不稳定,需要积极干预	考虑暂停免疫治疗;采取与1级不良事件相同的支持性措施;考虑住院治疗;胃肠科会诊;口服泼尼松/静脉注射甲泼尼龙[1 mg/(kg·d)]或口服布地奈德;若无改善,考虑生物制剂治疗(如英夫利昔单抗或维得利珠单抗) 对于持续性腹泻,若上述治疗无效,需考虑其他病因(如胰腺外分泌功能不全、乳糜泻)

以下评估措施。1级不良事件考虑进行粪便检测以排除感染性病因:艰难梭菌;胃肠道病原体的核酸扩增试验(针对其他细菌、病毒);必要时检测虫卵,或进行针对蓝氏贾第鞭毛虫、隐孢子虫、溶组织内阿米巴、微孢子虫和环孢子虫等的分子检测;条件允许时可考虑检测粪便乳铁蛋白/钙卫蛋白。2~4级不良事件除了完善与1级不良事件一致的粪便检测外,还应考虑完善腹部/盆腔增强计算机断层扫描(computed tomography, CT),考虑胃肠科会诊,以及完善结肠镜或乙状结肠镜检查±食管胃镜检查和组织活检。不同分级的下消化道不良事件处理方案见表2。

3.3 肝胆不良事件

对于以转氨酶升高为主的肝胆不良事件,应排除病毒、疾病相关肝功能不全和其他药物性肝损伤引起的肝酶升高;限制/停用肝毒性药物(评估对乙酰氨基酚、膳食补充剂使用情况和饮酒情况);考虑进行肌酸激酶、醛缩酶和铁蛋白检测,排除丙氨酸转氨酶(alanine transaminase, ALT)/天冬氨酸转氨酶(aspartate transaminase, AST)升高的其他病因(如肌炎、心肌炎和噬血细胞性淋巴瘤细胞增多症);考虑腹部超声;若治疗无反应或检验结果

提示胆汁淤积,考虑增强CT/磁共振成像(magnetic resonance imaging, MRI)检查。其分级和处理方案见表3。

若肝胆不良事件以碱性磷酸酶升高伴或不伴转氨酶升高/胆红素升高为主;需排除其他药物性肝损伤;需排除胆道梗阻或肿瘤肝浸润,考虑进行磁共振胰胆管成像(magnetic resonance cholangiopancreatography, MRCP)或腹部增强CT/MRI(若存在增强造影剂禁忌,则考虑超声);考虑检测碱性磷酸酶分型、检测 γ -谷氨酰转氨酶或5'-核苷酸酶,以明确碱性磷酸酶来源于肝脏;对于混合型肝损伤(ALT/AST和碱性磷酸酶均升高)或经验性治疗无应答的情况,可考虑肝活检。此类型肝胆不良事件的分级和处理方案见表4。

3.4 胰腺不良事件

胰腺不良事件的评估应涵盖是否存在胰腺炎的症状/体征。若临床上怀疑胰腺炎,需进行腹部增强CT检查;若CT检查未发现急性胰腺炎影像学证据,可考虑进行MRCP;需鉴别其他原因(例如饮酒、胆道疾病);评估胰腺外分泌功能不足和/或糖尿病的迹象/症状。无症状性淀粉酶/脂肪酶升高的胰腺不良事件与急性胰腺炎分别对应不同的

表2 下消化道不良事件的分级和处理方案

分级	处理
1级:每日较基线增加的排便次数少于4次,且无结肠炎症状	补液;密切监测病情;饮食调整;考虑暂停免疫治疗;可考虑将洛哌丁胺或地芬诺酯/阿托品作为缓解症状的辅助用药,使用2~3d;若无改善,进行感染性病因排查;需避免掩盖症状;若腹泻持续,应适当停用止泻药,以评估后续可能升级的免疫抑制治疗的效果;若症状持续或进展,完善乳铁蛋白/钙卫蛋白检测,若阳性,按2级处理,若阴性且无感染,继续1级管理,必要时加用美沙拉嗪和/或考来烯胺
2级:每日较基线增加的排便次数为4~6次,伴有结肠炎症状,但不影响日常生活活动能力	暂停免疫治疗;对于病理确诊的镜下结肠炎,首选口服布地奈德9mg/d治疗6周,之后3周逐渐减停;若无法进行布地奈德治疗,可口服泼尼松/静脉注射甲泼尼龙[1~2mg/(kg·d)];若口服激素3d后无应答,考虑转为静脉注射激素;若结肠镜或乙状结肠镜检查显示明显溃疡或广泛非溃疡性炎症,考虑加用英夫利昔单抗或维得利珠单抗 ^a ;对于英夫利昔单抗和/或维得利珠单抗难治性结肠炎,可考虑托法替布或乌司奴单抗
3~4级:每日较基线增加的排便次数超过6次,伴有结肠炎症状,影响日常生活活动能力,出现血流动力学不稳定、需要住院、发生严重并发症(如缺血性肠病、穿孔、中毒性巨结肠)或其他危及生命的情况	3级:若使用的是联合免疫治疗,停止当前治疗方案 4级:停用导致不良事件的免疫治疗药物 考虑住院治疗以提供支持性护理;静脉注射甲泼尼龙[1~2mg/(kg·d)];若1~2d内无应答或无法过渡到口服激素,且结肠镜/乙状结肠镜检查显示明显溃疡或广泛非溃疡性炎症,则需在使用激素的同时,考虑加用英夫利昔单抗或维得利珠单抗 ^a ;对于英夫利昔单抗和/或维得利珠单抗难治性结肠炎,可考虑托法替布或乌司奴单抗 若经上述管理后腹泻仍持续不缓解,需考虑其他病因(如胰腺外分泌功能不全、乳糜泻)

注:^a 英夫利昔单抗起效快但系统感染风险高,而维得利珠单抗靶向 $\alpha 4\beta 7$ 整合素,具有高度肠道选择性;最新指南强调,对于英夫利昔单抗难治性,或存在英夫利昔单抗使用禁忌的患者,可考虑使用维得利珠单抗。

表3 肝胆不良事件(转氨酶升高)的分级和处理方案

分级	处理
1级: ALT/AST<3倍正常值上限	考虑根据实验室指标的变化趋势,暂停免疫治疗;增加肝脏相关检验的频率
2级: ALT/AST为3~5倍正常值上限	暂停免疫治疗;每3~5天复查肝脏相关检验;定期监测凝血酶原时间/国际标准化比值;考虑使用泼尼松0.5~1 mg/(kg·d);若3~7 d后肝脏相关检验结果无改善甚至恶化,按3级处理
3级: ALT/AST>5~20倍正常值上限	暂停免疫治疗;启动口服泼尼松/静脉注射甲泼尼龙1 mg/(kg·d);如果1~2 d后无改善,考虑加用吗替麦考酚酯或其他类固醇替代免疫抑制治疗;如果治疗7 d后无改善,或使用2种免疫抑制剂后7 d内仍无充分应答,需紧急转诊至胃肠科/肝病科;考虑住院治疗,特别是肝脏合成功能障碍时;根据指标变化的幅度和速度,每1~5天复查肝脏相关检验 ^a
4级: ALT/AST>20倍正常值上限	停用免疫治疗;启动口服泼尼松/静脉注射甲泼尼龙1 mg/(kg·d);如果1~2 d后无改善,考虑加用吗替麦考酚酯或其他类固醇替代免疫抑制治疗;如果治疗7 d后无改善,或使用2种免疫抑制剂后7 d内仍无充分应答,需紧急转诊至胃肠科/肝病科;需要住院治疗,特别是肝脏合成功能障碍时;每1~3天复查肝脏相关检验 ^a

注:ALT,丙氨酸转氨酶;AST,天冬氨酸转氨酶。^a针对3~4级不良事件,还应定期监测凝血酶原时间/国际标准化比值;如果没有禁忌证,可考虑进行诊断性肝活检,通常用于临床表现或生化指标不典型(胆汁淤积型)或对标准治疗无反应的患者;若患者同时合并胆红素升高(>2 mg/dl),则肝功能衰竭风险增加。

表4 肝胆不良事件(碱性磷酸酶升高伴或不伴转氨酶升高/胆红素升高)的分级和处理方案

分级	处理
1级: 碱性磷酸酶<2.5倍正常值上限(或基线值)	考虑暂停免疫治疗;增加肝脏相关检验的频率
2级: 碱性磷酸酶为2.5~5倍正常值上限(或基线值)	暂停免疫治疗;开始泼尼松治疗0.5~1 mg/(kg·d);考虑加用熊去氧胆酸 ^a 13~15 mg/(kg·d);每3~5天复查肝脏相关检验;如果治疗3 d后碱性磷酸酶恶化或无改善,按3级处理;考虑胃肠科会诊
3级: 碱性磷酸酶>5~20倍正常值上限(或基线值)	停用免疫治疗;监测国际标准化比值;启动口服泼尼松/静脉注射甲泼尼龙1 mg/(kg·d);如果1~2 d后无改善,考虑加用类固醇以外的免疫抑制剂治疗,或考虑加用熊去氧胆酸 ^a 13~15 mg/(kg·d);每1~3天复查肝脏相关检验;胃肠科会诊;根据临床情况考虑住院监测
4级: 碱性磷酸酶>20倍正常值上限(或基线值)	处理方案同3级

注:^a此类型不良事件对激素治疗往往不敏感,必要时尽早采用熊去氧胆酸及介入治疗。

分级标准和处理方案,见表5和表6。

TNF抑制剂是一类广泛用于阻断TNF在自身免疫性疾病中促炎效应的药物^[88]。英夫利昔单抗是一种抗TNF- α 单克隆抗体,它通过阻断TNF- α 与其受体的相互作用,抑制促炎性细胞因子的分

泌,并调节免疫效应细胞的活性^[89]。该药已用于治疗ICI引起的严重、激素难治性的免疫治疗相关结肠炎^[90]。维得利珠单抗是一种整合素拮抗剂,它能与 $\alpha 4\beta 7$ 整合素结合,阻断其与黏膜地址素细胞黏附分子-1的相互作用,从而抑制T细胞穿过内皮

表5 胰腺不良事件(无症状性淀粉酶/脂肪酶升高)的分级和处理方案

分级	处理
1级: 淀粉酶 $\leq$ 3倍正常值上限和/或脂肪酶 $\leq$ 3倍正常值上限	如果仅单纯性胰酶升高而无胰腺炎证据,可继续免疫治疗;评估是否存在胰腺炎;若存在胰腺炎证据,参考急性胰腺炎处理流程;鉴别淀粉酶/脂肪酶升高的其他原因
2级: 淀粉酶>3~5倍正常值上限和/或脂肪酶>3~5倍正常值上限	如果单纯性胰酶升高而无胰腺炎证据,可考虑继续免疫治疗;评估是否存在胰腺炎;进行临床评估;若2~4级的淀粉酶和/或脂肪酶升高持续存在,完善腹部增强CT或MRCP检查;鉴别淀粉酶/脂肪酶升高的其他原因;若存在胰腺炎证据,参考急性胰腺炎处理流程
3~4级: 淀粉酶>5倍正常值上限和/或脂肪酶>5倍正常值上限	

注:CT,计算机断层扫描;MRCP,磁共振胰胆管成像。

表6 胰腺不良事件(急性胰腺炎)的分级和处理方案

分级	处理
1~2级:无症状的淀粉酶/脂肪酶升高或CT影像学特征或临床发现提示胰腺炎	若淀粉酶/脂肪酶>3倍正常值上限,或CT影像学表现突出,考虑暂停免疫治疗;考虑转入胃肠科;静脉补液;无症状时,参考淀粉酶/脂肪酶升高的处理流程进行管理
3级:有症状性疼痛或呕吐,且伴有任何程度的淀粉酶/脂肪酶升高或CT提示胰腺炎	暂停免疫治疗;考虑转入胃肠科;静脉补液;仅当补液和疼痛控制无改善时,考虑泼尼松/甲泼尼龙治疗[0.5~1 mg/(kg·d)]
4级:淀粉酶/脂肪酶升高或CT提示胰腺炎危及生命或血流动力学不稳定或需要紧急干预的情况	永久停用免疫治疗;考虑转入胃肠科;静脉补液;仅当补液和疼痛控制无改善时,考虑泼尼松/甲泼尼龙治疗[1~2 mg/(kg·d)]

注:CT,计算机断层扫描。

迁移至胃肠道炎症组织,发挥靶向性的胃肠道免疫抑制作用^[91]。目前,临床上维得利珠单抗可用于治疗激素依赖性或非激素难治性免疫治疗相关结肠炎^[92]。一项双中心、回顾性、观察性队列研究结果表明,对于免疫治疗相关腹泻和结肠炎的患者,采用维得利珠单抗相较于英夫利昔单抗,可缩短激素使用疗程(35 d比50 d, $P<0.001$),降低疾病复发率,减少住院治疗需求(住院率16%比28%, $P=0.005$;平均住院时间10.5 d比13.5 d, $P=0.043$)^[93]。此外,近期一项国际多中心研究证实,维得利珠单抗可用于英夫利昔单抗耐药的免疫治疗相关胃肠道不良事件患者,相较于其他药物,接受维得利珠单抗治疗患者的肿瘤生存获益最大(平均无事件生存期:维得利珠单抗24.5个月,吗替麦考酚酯/硫唑嘌呤21.8个月,钙调磷酸酶抑制剂6.3个月)^[94]。因此,对于免疫治疗相关胃肠道不良事件,维得利珠单抗的综合疗效优于英夫利昔单抗。

关于何时重新启用免疫治疗,NCCN制定了相应的管理策略。通常来讲,严重irAEs,或一些具有高发病率/死亡率风险的中度irAEs,可能需要永久停用该类药物;约1/3患者重启治疗后可能再次出现相同的irAEs,若不良事件再次出现,需永久停用该类药物的免疫治疗。针对胃肠道、肝脏和胰腺不良事件的管理策略分别如下。胃肠道:2级不良事件需待症状缓解至≤1级后方可考虑重启免疫治疗;3级不良事件若先前为联合免疫治疗,可考虑改用抗PD-1或抗PD-L1单克隆抗体单药免疫治疗,复发风险取决于药物和/或方案,风险由高到低分别为抗CTLA-4单克隆抗体联合或不联合抗PD-1单克隆抗体>抗PD-1单克隆抗体联合抗LAG-3单克隆抗体>抗PD-1单克隆抗体;在极少数无法完全停用激素的情况下,若泼尼松等效剂

量≤10 mg/d,仍可考虑重启免疫治疗,可考虑同时联用维得利珠单抗。肝脏:在转氨酶升高不伴肝脏合成功能障碍的情况下,2级不良事件可考虑在ALT/AST恢复至基线水平,且激素已减量至泼尼松等效剂量≤10 mg/d时,重启免疫治疗;若4级不良事件出现肝脏合成功能障碍和/或需要经内镜逆行胰胆管造影处理的永久性胆道狭窄,则应永久停用免疫治疗。胰腺:≤3级胰腺炎,若无胰腺炎的临床/影像学证据,且淀粉酶/脂肪酶水平改善或正常,可考虑重启免疫治疗,重启前建议咨询胰腺专科医生;4级胰腺炎必须永久停用免疫治疗。

4 总结

免疫治疗革新了癌症治疗,但随着ICI获批的肿瘤适应证不断扩大,临床上irAEs的发生率也迅速升高。消化系统irAEs作为最常见的类型之一,其临床表现、生化指标与组织病理学特征均存在显著异质性。多数消化系统irAEs具有自限性,可通过皮质类固醇和/或霉酚酸酯有效控制,但广泛的免疫抑制可能削弱免疫治疗本身的疗效;而对一线免疫治疗无应答的患者常伴随较高的死亡率。目前,irAEs的基础与临床研究仍处于早期阶段,许多关键机制尚未明确。若能明确驱动irAEs发生的免疫效应通路,将为后续治疗提供更精准的靶向干预策略。

现有病理生理学模型提示,irAEs涉及多因素相互作用,包括T细胞介导的免疫损伤、共享抗原假说、自身抗体形成、多种炎症因子网络以及肠道微生态等。因此,靶向组织驻留记忆T细胞或自身抗原反应性T细胞、阻断irAEs局部微环境中的炎症因子,或清除自身抗体分泌性B细胞,均已成为探索irAEs靶向治疗的重要方向。此外,肠道微

生态也有望成为干预 irAEs 的潜在切入点。粪菌移植、益生菌补充及饮食调整等转化策略, 仍需在疗效稳定性、干预时机与疗程, 以及安全性方面加以优化。为此, 亟需开展大规模队列研究, 以鉴定能同时减轻 irAEs 并增强 ICI 疗效的微生物菌株及代谢物, 并阐明其作用机制。最终, 需通过干预性临床试验验证这些基于微生物菌株与代谢物的治疗策略的临床效果。

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