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·综 述·

免疫检查点抑制剂不良反应的研究进展

Research progresses on adverse events of immune checkpoint inhibitors

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[摘 要] 免疫检查点抑制剂(ICI)使用的增加导致了免疫相关不良反应(irAE)报告的增加。与传统癌症治疗的不同,这些irAE是独特的,通常呈现延迟起病的特点,并且持续时间较长。irAE可涉及任何器官或系统。irAE影响通常是低级别的,是可治疗和可逆的;然而,一些副作用可能是严重的,并导致永久性疾病,如免疫性心肌炎、重症肌无力、结肠炎等。治疗主要基于皮质类固醇和其他免疫调节剂,审慎的irAE管理对于改善患者生活质量和长期结局至关重要。

[关键词] 免疫检查点抑制剂;免疫相关不良事件;发病机制;干预策略
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目前,免疫检查点抑制剂(ICI)逐步被批准用于治疗各种类型的癌症。这些药物大都是针对CTLA-4信号或PD-1信号的单克隆抗体,对免疫应答具有普遍作用,而不依赖于单个癌症特异性抗原[1]。然而,随着ICI在临床实践中的逐步实施,出现了一个关键挑战,即ICI对免疫系统的不可控副作用,可能导致免疫相关不良反应(irAE)。ICI的毒性谱与标准化疗或其他生物制剂不同[2],大多数毒性是由对正常器官的过度免疫引起的。

1 流行病学

由于ICI在癌症治疗中的使用增加,irAE的累积年数量呈指数级增长[3]。超过1/2的癌症免疫治疗相关irAE报告病例与ICI有关[4]。irAE常涉及胃肠道、呼吸系统、内分泌腺体和肝脏等。少数情况下,心血管系统、肌肉骨骼系统和血液系统受累[5]。2006年至2019年irAE报告病例数排在前三位的分别是结肠炎、肺炎及甲状腺炎[6]。在对ICI总体安全性的36项Ⅱ/Ⅲ期试验的荟萃分析评估显示:所有不良事件的合并发生率为54%~76%[7]。irAE可发生在任何器官/系统中,中位发病时间通常在治疗开始后4~16周[6]。实际上,在ICI开始治疗后的几天内就已经有了irAE的发病描述,并且可发生于治疗结束1年以后[8-10]。

2 危险因素

根据使用的ICI和触发的特异性器官损伤,irAE的发生率差异很大,这表明有特定人群容易发生irAE,可能涉及潜在的遗传因素[11]。对irAE风险差异的一种解释可能是某些个体有自身免疫倾向。一些研究[12-14]报告称,约10%的风湿性irAE患者有自身免疫性疾病家族史,约25%的人有自身免疫性疾病家族史。此外,许多CTLA-4和PDCD1(编码PD-1)多态性与自身免疫性疾病有关[15-16]。一些研究报告了与irAE发生相关的个人危险因素,如自身免疫疾病史、肾功能不全[17]、体重指数增加[18]、年龄[19]。相比之下,女性和皮质类固醇使用被确定为irAE的保护性因素[20]。

3 病理学机制

CTLA-4和PD-1或PD-L1抑制剂可导致免疫信号的非特异性上调。尽管这些疗法的免疫毒性特征有共同之处,但在特定irAE和最常受累器官的频率和临床表现方面存在重要差异[21]。这些表型差异表明irAE发生的机制在ICI之间有所不同。一般而言,CTLA-4和PD-1抑制均增加T细胞活化和增殖,消除Treg细胞功能,并可能促进自身体液免疫[22]。但在特定条件下,上述现象可能在一种治疗类型比另一种治疗类型中更为突出,从而导致了irAE表型的差异。

3.1 T细胞激活

近年来的研究表明,成年期获得性CTLA-4缺乏的*Ctla4*$^{fl/fl}$小鼠也会发生多器官自身免疫性疾病[23],并导致广泛的多器官淋巴细胞浸润、Treg细胞缺陷和自身抗体产生[24]。抗CTLA-4抗体可增加肿瘤微环境中效应T细胞与Treg细胞的比率,并可能增强了抗肿瘤反应,从而使患者得到获益[23]。此外,Treg细胞和Th17细胞的失衡可能导致ICI相关的irAE[25]。增强的Th17细胞在许多自身免疫性疾病的发病机制中具有突出作用,包括类风湿性关节炎[26]、银屑病性关节炎[27]和炎症性肠病[28]。

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PD-1抑制也能增强T细胞活化，但导致irAE的表型与CTLA-4抑制有所不同。PD-1在T细胞上表达，而其配体PD-L1和PD-L2存在于抗原提呈细胞、肿瘤细胞和各种正常组织上，通常起到下调T细胞活性的作用[29]。PD-1和PD-L1均由Treg细胞表达，该通路似乎参与Th1细胞向Treg细胞的分化[30-31]。缺乏PD-1或PD-L1的小鼠根据其遗传背景可表现出各种各样的自身免疫性疾病的症状，在某些情况下，这些问题由自身抗体介导[32]。用单克隆抗体抑制PD-1和PD-L1可导致循环Treg细胞数量减少，而黑色素瘤患者高无进展生存率与此息息相关[33]。

3.2　肿瘤抗原的交叉反应

抗肿瘤T细胞和健康细胞上类似抗原之间的交叉反应可能是某些irAE发生的基础[34]，例如ICI治疗的黑色素瘤患者可出现白癜风[35]。ICIR-BIOGEAS注册中心的数据显示，在已报道的368例白癜风病例中，96%的病例是黑色素瘤患者，这表明T细胞与肿瘤抗原和黑色素细胞之间存在交叉反应性[36]。此外，由于肿瘤反应性T细胞群的低选择性，以及与正常组织的交叉反应性，有人提出了ICI相关心肌炎的交叉反应性[37-38]。

3.3　B细胞介导的自身抗体

由于ICI增加了T细胞的活化，增强的T细胞与B细胞的相互作用可导致自身抗体的产生。在抗CTLA-4抗体诱导的irAE小鼠模型中产生自身抗体是常见的[39]。事实上，在使用伊匹单抗的患者中能够观察到抗垂体抗体的产生，这一现象并未见于PD-1和PD-L1抑制剂的患者[39]。ICI治疗的患者在单剂量后出现B细胞变化，包括循环B细胞数量减少，$CD21^{low}$ B细胞和浆细胞数量增加进一步支持了B细胞在免疫毒性中潜在作用。

3.4　单克隆抗体的直接效应

由于ICI是针对免疫细胞和其他组织所表达分子的单克隆抗体，因此某些irAE可能是由这些疗法的补体介导的直接损伤引起的。例如，CTLA-4在垂体前叶强烈表达[39]，垂体炎主要见于伊匹单抗。此外，心肌PD-L1主要定位于内皮细胞，对免疫介导的心脏损伤至关重要[38]。

4　预测irAE的潜在标志物

有研究表明，治疗前血清自身抗体的存在与某些irAE的风险增加有关，如抗mAChR抗体患者的肌炎[40]、抗甲状腺抗体患者的甲状腺炎[41]、抗核抗体患者的结肠炎[42]等。黑色素瘤患者循环中B细胞数量降低30%及以上可以用于帮助识别高级别irAE发生的风险[43]。血清细胞因子水平也可能为患者对ICI诱导的irAE的易感性提供预测价值，例如，循环中的IL-17水平可能有助于预测哪些接受伊匹单抗治疗的黑色素瘤患者可能出现严重腹泻和结肠炎[44-45]。

5　干预策略

根据CTCAE（常见不良反应事件评价标准）分类，irAE的治疗取决于受影响的器官系统和毒性等级。CTCAE 1级irAE患者通常不需要干预治疗。2级不良反应的患者应停止ICI，直到不良反应减轻为止。3级或4级irAE的患者应首先服用类固醇。当然，对于某些器官特异性irAE，无论CTCAE的严重程度如何，都应考虑专科医生的评估与干预。

5.1　糖皮质激素

糖皮质激素是治疗irAE的主要手段，但内分泌irAE除外。强的松通常是首选的类固醇皮质激素，其剂量取决于CTCAE等级和临床严重程度[46]。一般来说，糖皮质激素应以控制活动性系统性疾病所需的最小剂量和使用时间为佳，如果预期长期使用，则需要引入类固醇保留策略或早期启动抗TNF和其他单克隆抗体。不建议预防性使用糖皮质激素来预防irAE[47]。

5.2　激素替代疗法

有症状的甲状腺功能不全、垂体功能减退、肾上腺功能减退或1型糖尿病患者通常会使用替代激素或胰岛素。患者很少能从这些irAE中完全康复，因此经常需要永久性治疗[48]。此外，内分泌疾病不需要暂停ICI，除非患者有症状或不稳定。

5.3　免疫抑制剂

如果irAE在类固醇治疗的48~72 h内没有明显改善，或者在没有症状发作的情况下不能逐渐减少，则应增加免疫抑制剂作为糖皮质激素的替代治疗，目前没有证据支持选择一种药物而不是另一种药物。例如，含霉酚酸酯的免疫抑制剂可用于治疗类固醇难治性irAE，特别是免疫相关肝炎、肾炎、胰腺炎和葡萄膜炎，而类固醇难治性肺炎患者可使用霉酚酸酯或环磷酰胺治疗[49]，关节炎患者可以服用羟氯喹或甲氨蝶呤[50]。

5.4　免疫球蛋白和血浆置换

静脉注射免疫球蛋白被用于神经和血液病irAE的二线治疗[51]。由自身抗体直接引起的irAE，如某些血液病或神经肌肉性疾病irAE，也可以通过血浆置换进行治疗[52]，血浆置换可以从循环中去除致病性自身抗体，对重症肌无力或格林-巴利综合征的严重病例特别有效。

5.5　单克隆抗体

目前，英夫利昔单抗已经在严重、难治性、免疫

相关结肠炎或炎性关节炎的治疗中取得疗效[53]。在大多数情况下，仅英夫利昔单抗单药即可改善这些irAE；在3级和4级结肠炎患者在糖皮质激素治疗前添加英夫利昔单抗可显著缩短症状缓解时间[54]。维多利珠单抗可代替英夫利昔单抗用于治疗免疫相关结肠炎[55-56]。维多利珠单抗的理论优势在于免疫抑制仅限于胃肠道，因此避免了系统性免疫抑制。此外，塔西单抗已被推荐用于治疗某些类固醇难治性irAE[57]。

尽管单克隆抗体在治疗类固醇难治性irAE方面具有优势，但它们与特定的不良反应相关。例如，TNF抗体存在加剧间质性肺病的风险[58]；而依那西普和塔西单抗分别与患者炎症性肠病风险增加和克罗恩病患者肠穿孔风险增加有关[59-60]。此外，也有神经性irAE的报道[61]，因此应谨慎使用单克隆抗体治疗。

6 预后评估

发生irAE的患者通常比未发生irAE的患者对癌症表现出更好的治疗反应，这表明自身免疫与ICI引发的抗肿瘤效应之间存在密切联系[62-63]。越来越多的证据表明，与未发生irAE的患者相比，患有irAE的患者在无进展生存率、总生存率和总有效率方面有显著改善，使用PD-1和PD-L1抑制剂治疗的患者的数据比使用CTLA-4抑制剂治疗的患者更为一致。

ICI治疗患者的整体irAE相关死亡率估计约为0.6%，接受PD-1抑制剂的患者个体死亡率为0.36%，接受PD-L1抑制剂的患者个体死亡率为0.38%，接受CTLA-4抑制剂的患者个体死亡率为1.08%，接受联合治疗的患者个体死亡率为1.23%[64-65]。不同治疗方案的死亡原因差异很大；例如，70%的CTLA-4相关死亡是由于结肠炎，而与PD-1和PD-L1抑制剂相关的死亡通常来自肺炎（35%）、肝炎（22%）和神经毒性（15%）[64]。在接受联合治疗（PD-1和CTLA-4抑制剂）并死亡的患者中，37%的死亡是由结肠炎引起的，25%是由心肌炎引起的。此外，死亡时间因使用的ICI而异；死亡发生在ICI开始联合治疗后的早期，从症状开始到死亡的中位时间为14.5 d，而单药治疗为32 d[64]。

7 结 语

2019年末，派姆单抗和阿维鲁单抗与TKI抑制剂阿昔替尼的组合疗法被批准用于晚期肾细胞癌的治疗，甲状腺功能减退（25%~35%）和关节痛（18%~20%）是最常见的irAE[66-67]，JAK抑制剂托法替布通过调节小鼠模型中的炎症细胞，增强了基于抗体疗法对肿瘤细胞的传递，并可作为进行短期托法替布与ICI合用的试验的理论基础[68-69]。此外，其他形式的免疫疗法，如针对B细胞的免疫疗法和针对天然免疫的免疫疗法，也正在引起人们的兴趣[70]。新的双特异性抗体和双免疫调节剂也将逐步运用于临床。随着嵌合抗原受体T细胞疗法越来越广泛地用于癌症治疗，这些疗法很可能将在未来与ICI联合的试验中进行验证。

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