免疫检查点抑制剂在实体瘤中的应用

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摘要 免疫系统在肿瘤的治疗中有重要作用. 以单克隆抗体为代表的免疫检查点抑制剂在抗肿瘤领域中取得了成功, 改变了肿瘤治疗的格局. 本文对细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen 4, CTLA-4)、程序性细胞死亡蛋白1(programmed cell death protein 1 pathway, PD-1/PD-L1)通路、新型免疫检查点分子及相关免疫检查点抑制剂进行综述, 总结了免疫检查点抑制剂的临床应用价值、免疫检查点抑制剂治疗带来的免疫相关不良反应. 寻找优势人群、处理免疫相关不良反应、克服药物耐药, 是目前该领域需要解决的问题.

关键词 免疫检查点抑制剂, CTLA-4, PD-1, PD-L1, 免疫相关不良反应

免疫系统在肿瘤的治疗中有重要作用. 在恶性肿瘤中, 多种因素会造成机体的免疫抑制, 继而导致免疫细胞抗肿瘤活性的消失. 目前, 以单克隆抗体为代表的一系列抑制负性免疫调节因子(免疫检查点)的药物在抗肿瘤的应用中取得了巨大的成功, 免疫检查点抑制剂已经成为恶性肿瘤治疗的一种新手段.

本文将对两个重要的免疫检查点——细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen 4, CTLA-4)、程序性细胞死亡蛋白1 (programmed cell death protein 1 pathway, PD-1/PD-L1)通路和一些最新的免疫检查点进行综述, 并总结这些免疫检查点抑制剂的临床应用价值.

1 免疫检查点及免疫检查点抑制剂

1.1 CTLA-4

CTLA-4是第一个应用于临床的免疫检查点受体. T细胞被激活后, CTLA-4在细胞膜的表达上升, 进而通过与T细胞共刺激蛋白CD28竞争性结合抗原呈递细胞上的B7家族的B7-1与B7-2, 抑制抗原呈递细胞对T细胞的激活, 进而下调T细胞的功能^[1~3](图1). 因此, CTLA-4对保持正常的免疫稳态具有重要作用. 在实验中, CTLA-4缺陷的小鼠出现了致死性的淋巴细胞增生^[4,5]. 根据体外实验中CTLA-4的免疫抑制作用, 研究者研发了抗CTLA-4的抗体, 这些抗体在临床前的实验中取得了一定成功^[6,7].

CTLA-4的抗体主要包括CTLA-4单抗ipilimumab

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(伊匹木单抗)和tremelimumab. Ipilimumab是一种人源的IgG1 κ 抗CTLA-4单抗, 2011年获得美国食品药品监督管理局(Food and Drug Administration, FDA)批准, 起初用于治疗转移性黑色素瘤. 两个III期的ipilimumab治疗晚期黑色素瘤的临床试验都取得了成功^[8,9]. 虽然两个试验的中位总生存期仅仅提高了几个月, 但是这两个临床试验的成功是标志性的——病人的2年生存率提高到了18%, 而这一数据在对照组(接受gp100疫苗)中仅为5%, 但其联合化疗治疗非小细胞肺癌^[10]、小细胞肺癌^[11]和前列腺癌^[12]的试验均失败.

另一种CTLA-4抗体是tremelimumab, 为一种人源IgG2同种型抗体, 目前尚未获得FDA批准. 在tremelimumab治疗晚期黑色素瘤的III期临床试验中, 虽然有一部分病人获得了持续缓解, 但传统的达卡巴嗪/替莫唑胺组合相比, 总体上并未获得总生存的获益^[13].

1.2 PD-1/PD-L1通路

PD-1/PD-L1通路是另一个受到关注的免疫检查

点通路. PD-1是T淋巴细胞的负调控因子, 当与其两个配体PD-L1或PD-L2结合后, 可以限制免疫反应中T细胞的活化^[14-16]. 在肿瘤组织中, 肿瘤细胞表面的PD-L1与T细胞上的PD-1分子结合, 传递抑制信号, 启动T细胞的程序性死亡, 使肿瘤细胞获得逃逸. 此外, PD-1在多种免疫细胞表面都存在表达, 包括B细胞和自然杀伤(natural killer, NK)细胞等. 阻断PD-1也会影响这些细胞的功能^[17,18](图1, 使用app.biorender.com制作).

2010年, 一项I期临床试验证明, 阻断PD-1/PD-L1通路在人体中的耐受性良好, 并有一定的抗肿瘤活性^[19]. 针对该通路的药物已成为近10年抗肿瘤药物的研发热点. 目前有多种针对PD-1/PD-L1通路的抗体已经进入临床应用阶段. 这些抗体的结构并不相同, 根据靶点可分为两大类: 抗PD-1的抗体和抗PD-L1的抗体. 目前被FDA批准的PD-1单抗包括: 帕博利珠单抗(pembrolizumab)、纳武利尤单抗(nivolumab)、西米普利单抗(cemiplimab), 以及抗PD-L1的抗体阿替利珠单抗(atenzolizumab)、度伐利尤单抗(durvalumab)、阿维

图1 常见免疫检查点的通路

Figure 1 Pathways of common immune checkpoint inhibitors

单抗(avelumab). 目前被中国国家药品监督管理局(National Medical Products Administration, NMPA)批准上市的除了PD-1单抗pembrolizumab、nivolumab, PD-L1单抗atezolizumab、durvalumab, 还有中国研发的PD-1单抗, 包括卡瑞利珠单抗(camrelizumab)、替雷利珠单抗(tislelizumab)、信迪利单抗(sintilimab)和特瑞普利单抗(toripalimab).

2014年, PD-1单抗pembrolizumab和nivolumab成为首批被FDA批准的用于难治性和不可切除性黑色素瘤的抗PD-1的治疗药物^[20-23]. 在一项头对头的比较中, PD-1单抗pembrolizumab的6个月无进展生存期(progression free survival, PFS)要优于CTLA-4单抗ipilimumab, 并使总生存期(overall survival, OS)延长^[24,25]. PD-1单抗nivolumab治疗晚期黑色素瘤的临床试验表明, 免疫治疗组1年的OS率为72.9%, 而接受化疗药物达卡巴嗪治疗的患者组的1年OS率为42.1%^[23]. 2015年, PD-1单抗pembrolizumab获批用于治疗PD-L1表达阳性的非小细胞肺癌, 因为其一线使用与含铂化疗相比, 可使PFS延长4.3个月, 且二线比紫杉类药物化疗更有效^[26,27]. 其他成功的临床试验将pembrolizumab的使用扩展至头颈部鳞状细胞癌^[28]、霍奇金淋巴瘤^[29]、尿路上皮癌^[30]、胃/胃食管交界部肿瘤^[31]和高度微卫星不稳定(microsatellite instability-high, MSI-H)/错配修复缺陷(deficient DNA mismatch repair, dMMR)的肠癌^[32]. 在MSI-H的不分瘤种的适应症获FDA批准后, pembrolizumab成为首个基于分子生物标志物而非癌症部位获批的药物. 然而, 不同组织的免疫微环境使得很难预测哪些患者将从抗PD-1治疗中获益^[33]. 与pembrolizumab相似, PD-1单抗nivolumab的使用范围也包括非小细胞肺癌^[34,35]、肾细胞癌^[36]、头颈部鳞癌^[37]、尿路上皮癌^[38]、肝细胞癌^[39]、霍奇金淋巴瘤^[40]和MSI-H的结直肠癌^[41]. Cemiplimab已被FDA获批治疗转移性或不能接受根治性手术或放疗的局部进展期皮肤鳞癌^[42]. Camrelizumab被NMPA批准用于霍奇金淋巴瘤^[43]、非鳞非小细胞肺癌^[44]、食管癌^[45]、肝癌^[46]以及鼻咽癌^[47], tislelizumab被批准用于霍奇金淋巴瘤^[48]、尿路上皮癌^[49]和鳞状非小细胞肺癌^[50], sintilimab获批用于霍奇金淋巴瘤^[51]、非鳞非小细胞肺癌^[52], toripalimab获批用于黑色素瘤^[53]、鼻咽癌^[54]. 此外, 还有更多的III期临床试验在探索抗PD-1单抗在更多肿瘤中的疗效. 与抗CTLA-4治疗的长期结局相仿, PD-1阻

断后可出现持久的免疫介导的生存获益^[55].

靶向PD-L1的药物也和PD-1单抗具有同样良好的应用前景. 两者的作用机制并不完全相同. 除了和PD-1结合之外, PD-L1还与B7互相作用, 促进免疫系统的负调控^[56]. PD-L1抗体可以阻断这一通路, 但并不会阻断PD-1/PD-L2通路. 2016年, 首个靶向PD-L1的人源化抗体atezolizumab获FDA批准用于治疗尿路上皮癌. 与历史对照相比, 总体缓解率为15%, 具有统计学显著性, 缓解率与肿瘤PD-L1表达相关^[57]. 此后, atezolizumab的适应症扩展至非小细胞肺癌^[58]、三阴性乳腺癌^[59]和小细胞肺癌^[60]. Durvalumab于2017年上市, 用于治疗尿路上皮癌^[61]和非小细胞肺癌^[62]. Avelumab用于治疗Merkel细胞癌^[63]、尿路上皮癌^[64]和晚期肾细胞癌^[65]. 目前已上市的免疫检查点抑制剂及获批适应症详见表1.

1.3 新型免疫检查点分子通路

淋巴细胞活化基因3(lymphocyte-activation gene 3, LAG-3)、含免疫球蛋白及ITIM结构域的T细胞免疫受体(T cell immunoreceptor with Ig and ITIM domains, TIGIT)、T细胞免疫球蛋白3(T-cell immunoglobulin mucin 3, TIM-3)、T细胞激活抑制物免疫球蛋白可变结构域(V-domain immunoglobulin suppressor of T-cell activation, VISTA), 近年来逐渐成为免疫检查点治疗领域的新靶点^[66,67](图1).

LAG-3是一种I型跨膜蛋白, 由胞外区、穿膜区和胞质区组成, 主要表达在活化的人NK细胞、T细胞、B细胞和树突细胞等细胞上, 传递负调节信号, 并可以维持T细胞的稳态^[68-70]. 在肿瘤微环境中, LAG-3的配体表达增加, 抑制CD8⁺ T细胞的抗肿瘤活性^[71]. 多种LAG-3融合蛋白和LAG-3单抗或抗LAG-3/PD-1双抗目前正处于I~III期临床试验阶段.

TIGIT也是一种I型跨膜蛋白, 主要在T细胞和NK细胞中表达, 可以平衡T细胞活化和保护机体免受自身免疫的攻击, 传递抑制信号^[72,73]. 目前, 抗TIGIT单抗tiragolumab联合PD-L1单抗atezolizumab在非小细胞肺癌的临床试验中, 对比atezolizumab单药, 初步分析取得了临床及统计学意义上的获益, 证明了TIGIT靶点的前景^[74].

TIM-3是T细胞应答的另一个负调控因子, 在CD8⁺ T细胞、Th1、Treg、树突细胞、NK细胞及肿瘤细胞

表 1 已上市的免疫检查点抑制剂及获批适应症

Table 1 Immune checkpoint inhibitors and their approved indications

靶点	药物名	公司	FDA 获批瘤种	NMPA 获批瘤种
PD-1	帕博利珠单抗 (pembrolizumab)	默沙东	肾细胞癌、原发性纵隔大B细胞淋巴瘤、尿路上皮癌、胃癌、宫颈癌、肝细胞癌、Merkel细胞癌、黑色素瘤、非小细胞肺癌、头颈部鳞癌、食管癌、子宫内膜癌、皮肤鳞癌、经典型霍奇金淋巴瘤、三阴性乳腺癌、高度微卫星不稳定肿瘤、高肿瘤突变负荷肿瘤	黑色素瘤、非小细胞肺癌、食管癌、头颈部鳞癌
	纳武利尤单抗(nivolumab)	百时美施贵宝	黑色素瘤、非小细胞肺癌、恶性胸膜间皮瘤、肾细胞癌、经典型霍奇金淋巴瘤、头颈部鳞癌、尿路上皮癌、肝细胞癌、食管癌、胃和胃食管交界部腺癌、高度微卫星不稳定的或错配修复缺陷的结直肠癌	非小细胞肺癌、头颈部鳞癌、胃腺癌和胃食管结合部腺癌、恶性胸膜间皮瘤
	卡瑞利珠单抗 (camrelizumab)	恒瑞医药	未获批	经典型霍奇金淋巴瘤、肝细胞癌、食管鳞癌、非小细胞肺癌、鼻咽癌
	替雷利珠单抗(tislelizumab)	百济神州	未获批	经典型霍奇金淋巴瘤、尿路上皮癌、非小细胞肺癌
	特瑞普利单抗(toripalimab)	君实生物	未获批	黑色素瘤、鼻咽癌
	信迪利单抗(sintilimab)	信达生物	未获批	经典型霍奇金淋巴瘤、非小细胞肺癌
PD-L1	西米普利单抗(cemiplimab)	赛诺菲/再生元	皮肤鳞癌、基底细胞癌、非小细胞肺癌	未获批
	度伐利尤单抗(durvalumab)	阿斯利康	非小细胞肺癌、小细胞肺癌	非小细胞肺癌、小细胞肺癌
	阿替利珠单抗(atezolizumab)	罗氏	非小细胞肺癌、三阴性乳腺癌、小细胞肺癌、肝细胞癌、黑色素瘤、尿路上皮癌	肝细胞癌、小细胞肺癌
CTLA-4	阿维单抗(avelumab)	默克雪兰诺	Merkel细胞癌、尿路上皮癌、肾细胞癌	未获批
	伊匹木单抗(ipilimumab)	百时美施贵宝	黑色素瘤、肾细胞癌、肝细胞癌、非小细胞肺癌、恶性胸膜间皮瘤、高度微卫星不稳定的或错配修复缺陷的转移性结直肠癌	恶性胸膜间皮瘤

中均有表达, 主要配体包括半乳凝素9等, 其主要参与调控肿瘤微环境中T细胞的凋亡^[75~77]。VISTA属于免疫球蛋白超家族, 为B7家族中的成员之一, 在肿瘤浸润淋巴细胞中高表达, 与TIM-3类似, 其主要作用也是抑制T细胞的功能^[78,79]。目前针对TIM-3和VISTA靶点的药物均在早期研发阶段, 尚无进入III期临床试验的药物。

2 免疫检查点抑制剂的临床应用

从后线治疗到一线治疗, 从晚期肿瘤到早中期肿瘤, 免疫检查点抑制剂在多种实体瘤, 如非小细胞肺癌、胃癌、食管癌、头颈部鳞癌等瘤种中表现出了良好的抗肿瘤疗效, 为许多患者带来了生存的获益, 甚至

是长期生存, 改写了多个瘤种的指南。

2.1 单药治疗

在晚期非小细胞肺癌中, PD-1抗体nivolumab最先获得成功。其I期扩展研究CA209-003的非小细胞肺癌队列中, 使用免疫治疗的疗效优于历史化疗的总数据^[80]。此后, nivolumab的两项大型III期临床试验CheckMate 017和CheckMate 057研究表明, 使用nivolumab二线或三线治疗晚期肺鳞癌和非鳞癌患者, 对比多西他赛化疗组, 均获得了总生存期的延长^[34,35]。这也使nivolumab获得了FDA治疗晚期非小细胞肺癌的适应症。而在PD-1抗体pembrolizumab的I期扩展试验KEYNOTE-001中, 非小细胞肺癌PD-L1高表达组在二线及以上治疗组的中位缓解时间超过12.5个月^[81], 这

一数据帮助pembrolizumab直接获得了FDA的批准。此后的KENOTE-010, KEYNOTE-024和KEYNOTE-042研究进一步探究了pembrolizumab在非小细胞肺癌二线及一线PD-L1高表达人群中的应用价值, 并均获得成功^[26,27,82]。相比前免疫治疗时代5年生存率仅约5%, 免疫治疗的使用, 将晚期非小细胞肺癌的5年生存率提高到23.2%, 即使是既往铂类治疗失败的患者, 5年生存率也达到了15.5%^[83]。而后IMpower110研究表明, 在PD-L1高表达的亚组中, 单药使用PD-L1单抗atezolizumab组有统计学及临床上的获益^[84], 因此, atezolizumab在2020年被FDA批准用于转移性非小细胞肺癌PD-L1高表达人群的一线单药治疗。在III期不可切的非小细胞肺癌中, PACIFIC研究主要探究了免疫治疗在维持治疗中的地位。在同步放化疗后, 接受PD-L1单抗durvalumab巩固治疗组的总生存期提高了18.4个月, 目前durvalumab也已成为III期不可切非小细胞肺癌同步放化疗后的标准治疗^[62]。

既往晚期肠癌一线标准治疗为靶向联合化疗。而在MSI-H/dMMR的病人中, 这一标准已经被改写。根据KEYNOTE-177的研究数据, 与传统标准治疗相比, PD-1单抗pembrolizumab单药治疗此类病人, PFS从8.2个月提高到了16.5个月, 有近1倍的延长^[32]。这一结果有着里程碑式的意义。由于MSI-H/dMMR这一分子特征对于抗PD-1治疗的显著获益^[85], 目前FDA已批准PD-1单抗pembrolizumab用于既往标准治疗后疾病进展、无满意替代治疗方案的MSI-H/dMMR晚期或转移性实体瘤患者的治疗。

在其他瘤种中, 免疫治疗单药的探索早期多集中于二线或三线的治疗, 如PD-1单抗nivolumab的CheckMate 040^[39], CheckMate 275^[38], ATTRACTION-2^[86]和ATTRACTION-3^[87]等临床试验, 而PD-1单抗pembrolizumab的KEYNOTE-224^[88], KEYNOTE-045^[30], KEYNOTE-059^[31]和KEYNOTE-181^[89], 分别证实了其在二线或二线以上肝癌、尿路上皮癌、胃与胃食管连接部腺癌、食管鳞癌中的应用价值。随着目前免疫治疗在各实体瘤中的临床试验结果不断被公布, 越来越多新的适应症逐渐获批, 而且适应症逐渐从后线推到一线, 并逐渐进入辅助治疗和新辅助治疗领域。例如, KEYNOTE-048研究证实了复发转移性头颈部鳞癌中PD-L1阳性的人群可以从pembrolizumab单药治疗中获益^[90], CheckMate 577研究表明了食管癌术后辅助治疗

使用nivolumab可比安慰剂降低31%的死亡风险^[91]。

2.2 联合治疗

为了提高疗效, 研究者考虑将作用机制不同的免疫检查点抑制剂进行联合使用, 如CTLA-4和PD-1单抗的双免疫联合疗法。CTLA-4单抗ipilimumab和PD-1单抗nivolumab的联合治疗为转移性黑色素瘤、晚期肾细胞癌、晚期非小细胞肺癌、晚期胸膜间皮瘤的患者提供了显著的生存获益, 因此FDA批准了双免疫疗法在这些疾病中的应用^[92-95]。CTLA-4和PD-1通路以互补的方式调节抗肿瘤免疫, 但双免疫联合治疗也会增加药物相关毒性的风险^[93]。

免疫治疗联合化疗在多个瘤种的临床试验中取得了成功, 如PD-1单抗pembrolizumab联合化疗一线治疗晚期非小细胞肺癌^[96,97]、PD-1单抗nivolumab联合化疗一线治疗晚期胃或胃食管交界处腺癌^[98]、PD-L1单抗atezolizumab联合化疗治疗广泛期小细胞肺癌^[60]。比起既往的标准治疗, 这些免疫治疗联合化疗的尝试延长了病人的生存期, 且总体毒性反应可控。此外, 免疫联合靶向治疗, 尤其是免疫联合抗血管生成药物的治疗模式, 如PD-1单抗pembrolizumab联合仑伐替尼一线治疗晚期肾癌^[99]、PD-L1单抗atezolizumab联合贝伐珠单抗一线治疗晚期非小细胞肺癌和晚期肝癌等^[100,101], 均在多个大型III期临床试验中获得了良好的结果。随着研究的进行, 此类治疗模式已逐渐被写入指南。

将放疗与免疫检查点抑制剂相结合是肿瘤治疗的另一种治疗选择。放疗的免疫调节作用是一把双刃剑。放疗通过暴露新生肿瘤抗原增加抗肿瘤T细胞应答的多样性, 同时通过诱导肿瘤细胞上PD-L1的表达削弱免疫应答^[102]。基于临床前数据, PD-1抑制剂和放疗可有一定的协同作用^[103]。转移性疾病患者也可能从这种模式中获益, 因为阻断许多肿瘤的免疫检查点增强了对放疗的远隔效应^[102,104]。

3 免疫相关不良反应

免疫检查点抑制治疗为肿瘤治疗带来了巨大的前景, 但与此同时, 也带来了一些不良反应。这些不良反应主要是由非特异性的免疫激活引起的, 也称为免疫相关不良反应(immune-related adverse events, irAEs)。

虽然这些免疫相关不良反应的特点有别于传统化疗方案和靶向治疗,但是严重的不良事件(3或4级)总体上低于传统治疗。约有15%~70%的患者在免疫治疗过程中发生免疫相关不良事件^[8,105]。在接受CTLA-4和PD-1/PD-L1抑制剂治疗的患者中,分别有20%和15%的患者观察到≥3级不良反应^[105]。

主要的免疫相关不良反应包括皮肤、胃肠道、肝脏、内分泌系统和其他一些少见的炎症。由于这些不良反应与免疫系统过度激活相关,因此常用的免疫抑制剂,如糖皮质激素、肿瘤坏死因子 α 抑制剂等均可以使用。目前,美国国家综合癌症网络(National Comprehensive Cancer Network, NCCN)有免疫治疗相关毒性的管理指南,中国临床肿瘤学会也在2019年出版了《免疫检查点抑制剂相关的毒性管理指南》。通常来说,轻度(1级)毒性通常无需治疗。如果发生2级或3级不良事件,应停用免疫检查点抑制剂,直至症状缓解和实验室异常值改善。我们通常使用糖皮质激素抑制免疫功能并治疗免疫相关不良反应。当糖皮质激素治疗失败时,可考虑使用英夫利西单抗或其他免疫抑制剂。危及生命(4级)的毒性需要完全停止治疗并可能需要采取挽救生命的措施,以防止因免疫检查点阻断导致的死亡(5级)。

最常见的免疫相关不良反应是皮肤毒性,占有毒性反应的1/3^[106]。皮疹、瘙痒、白癜风是最常被报告的皮肤毒性^[107]。皮肤毒性通常在治疗的早期出现^[108]。少见的不良反应包括一些严重的皮疹,如Stevens-Johnson综合征、中毒性表皮坏死松解等,这种情况下,应该及时住院并请皮肤专科会诊。

另外一种常见的免疫相关不良反应是结肠炎,通常在CTLA-4抗体治疗6周左右出现^[109]。使用CTLA-4单抗ipilimumab后发生3~4级腹泻的发生率可达10%,

甚至可能导致治疗相关死亡^[8,110]。内镜检查及病理活检有助于确诊。轻症腹泻的治疗包括口服糖皮质激素。如果口服治疗无效或治疗后复发,那么可能需要静脉使用糖皮质激素。英夫利昔单抗可能对糖皮质激素治疗后复发的病人有效^[111]。而在抗PD-1治疗的患者中,结肠炎发生率要低得多。

肺炎在接受抗PD-1治疗的病人中更为常见,约为1%~5%,而这一数据在抗CTLA-4治疗中仅不到1%^[112]。肺炎通常出现在接受PD-1单抗后的10~14周,但PD-1联合CTLA-4的治疗中,肺炎发生的时间可提前至开始治疗后6~8周^[105]。影像学可表现为间质性肺炎、过敏性肺炎、隐源性机化性肺炎等,可能与肺的一些基础疾病混淆。通常2~3级肺炎需要口服或静脉使用糖皮质激素治疗。

肝毒性在抗CTLA-4和PD-1的治疗过程中均会出现,表现为谷草转氨酶(aspartate aminotransferase, AST)和谷丙转氨酶(alanine aminotransferase, ALT)的升高,不过大多数病人仅仅出现实验室指标的异常,并无临床症状。抗CTLA-4治疗的病人中,3~4级转氨酶升高的发生率小于10%,而抗PD-1治疗中的这一不良反应的发生率更低。

免疫检查点抑制对于内分泌系统,包括垂体、肾上腺和甲状腺等器官都会有影响。临床表现各异,常见的包括乏力、头痛和恶心。实验室检查和影像学检查通常有助于确诊。受垂体功能的影响,这些药物可能对性腺的功能也造成影响。治疗手段通常包括糖皮质激素,有些患者可能需要使用长期激素替代治疗。其他的不良反应还包括心肌炎^[113]、葡萄膜炎^[114]、胰腺炎^[115]、肾炎^[116]以及神经系统^[117]和血液系统^[118]的不良反应。常见免疫相关不良反应总结见表2。

致命性毒性谱在抗CTLA-4和抗PD-1通路治疗中

表 2 常见免疫相关不良反应

Table 2 Common immune-related adverse events

不良反应	常见发生时间(周)	所有级别毒性发生率%(≥3级毒性发生率%)			
		CTLA-4单抗	PD-1单抗	PD-L1单抗	CTLA-4单抗联合PD-1单抗
皮疹	4~7	19.1~34.2(0.8~3.1)	4~19.9(0~3.5)	0.7~13(0~0.2)	16.7~30(1.6~3)
结肠炎	4~6	7.6~15.5(5.3~8.2)	1~7(0.3~3)	—	1~13(0.5~8)
内分泌毒性	8~12	7.6~37.8(3.8~7.8)	7.3~23.4(0~2)	7~11.6(0~0.5)	12.3~34(0.4~6)
肺炎	6~14	—	1.5~5.8(0~2.6)	1~4.9(0~2.4)	3~7(1~2)
肝毒性	5~18	3.8~24.4(0~10)	0.3~16(0~3)	0.7~6.8(0.3~2)	3.5~33(3~20)

也有很大差异。结肠炎是接受抗CTLA-4治疗的患者最常见的死亡原因, 约占70%, 而接受抗PD-1或抗PD-L1治疗的患者的死亡主要归因于肺炎(35%)、肝炎(22%)和神经毒性(15%)。在接受联合治疗的患者中, 免疫治疗相关的死亡主要归因于结肠炎(37%)或心肌炎(25%)。在所有治疗组中, 以病毒性心肌炎为表现的患者死亡率最高, 报告的131例事件中有52例(39.7%)^[119]。

4 总结与展望

近十年免疫检查点抑制剂在临床实践中的成功, 改写了肿瘤治疗的模式, 在肿瘤治疗中有划时代的意义。然而, 目前免疫治疗的实践中, 尚有许多未被解决的问题。

寻找真正有价值的生物标志物对免疫治疗筛选合适人群、实现个体化治疗都有重要意义。PD-L1表达水平在多项临床研究中证实和免疫检查点抑制剂疗效相关, 具有MSI-H/dMMR分子特征的肿瘤对免疫治疗的应答率更高; 而另一些研究表明, 肿瘤突变负荷也可作为免疫治疗疗效的预测标志物^[120], 但具有这三种特征的患者并非为同一人群, 三种标志物之间的分子联系也未被完全阐明。随着人们对肿瘤免疫微环境研究的深入, 相信会有更精准的生物标志物被应用于临床。

免疫治疗相关不良反应领域也是免疫治疗研究中被关注的热点。如果能在治疗前找到何种人群可能会发生irAE, 并进行严密的监测与早期处理, 将对免疫治疗的临床实践非常关键。一项来自真实世界回顾性分析表明, 基线类风湿因子阳性可能与皮肤毒性相关, 而基线甲状腺自身抗体阳性可能与甲状腺功能减退相关^[121]。然而, 对于更为严重的irAE, 目前还没有研究找到较好的预测标志物。随着免疫检查点抑制剂在各瘤种中的广泛应用, 大规模标本的分子研究及临床数据

分析将为这一领域带来更多启示。

肿瘤免疫治疗也不可避免地会面临耐药的问题, 但目前其耐药机制还不明确。低肿瘤突变负荷、微生物组不同、IFN- γ 和抗原呈递过程通路中的分子突变等均可能是原发耐药机制, 而继发性耐药机制可能为肿瘤新抗原的丢失^[122]。目前需要更多的基础研究来解释免疫治疗耐药的机制。新型免疫检查点药物的研发对于PD-1/PD-L1、CTLA-4等传统免疫检查点抑制剂耐药的情形非常重要。除了新靶点外, 一些针对双通路的免疫检查点抑制剂也在研发阶段, 如靶向TGF- β /PD-L1的双功能融合蛋白M7824, 同时阻断这两条信号通路可以解除免疫系统的抑制状态, 提高免疫系统对肿瘤细胞的杀伤作用。虽然目前其III期针对非小细胞肺癌对比PD-1单抗pembrolizumab的临床试验因预计无法达到主要终点而终止, 但双通路免疫检查点抑制剂仍然是未来免疫检查点抑制剂研发的方向之一。

免疫检查点抑制为恶性肿瘤的治疗带来了新的希望, 虽然目前关于免疫治疗的基础研究和临床应用面临着许多挑战, 但免疫治疗将进一步改变目前肿瘤治疗的格局, 前景广阔, 值得进一步研究探索。

北京协和医院是我国最早开展涉外医疗的机构之一, 1972年成立外宾医疗科, 2007年更名为国际医疗部。作为医院重点打造的国际化优质服务示范平台, 国际医疗部整合协和600余位顶尖专家教授资源和多学科综合实力, 以“大综合、小专科”的模式, 为国内外患者提供国际一流、高品质、全生命周期的医疗服务。同时国际医疗部提供一站式健康管理服务, 以病人为中心, 将体检与多科诊疗紧密结合。

依托国际医疗部综合平台优势开展的多学科诊疗模式能够为患者制定最优质的个性化诊疗方案, 尤其在恶性肿瘤的筛查、手术、放疗及免疫治疗的综合治疗方面, 通过为患者提供精准治疗方案, 使其更好地从治疗中获益。

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Immune checkpoint inhibitors in solid tumors

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The immune system plays an important role in the treatment of tumors. Immune checkpoint inhibitors represented by monoclonal antibodies have achieved success in the field of anti-tumor and changed the pattern of tumor treatment. In this paper, we review immune checkpoint inhibitors of cytotoxic T lymphocyte associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD1/PD-L1) pathway, and new immune checkpoint targets. We also summarize the clinical applications and immune-related adverse events (irAEs) of immune checkpoint inhibitors. Key problems remain to be solved, such as how to identify the benefit population, how to manage irAEs better, and how to overcome drug resistance.

immune checkpoint inhibitor, CTLA-4, PD-1, PD-L1, immune-related adverse event

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