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·专家论坛·

肺癌免疫治疗耐药的挑战与对策

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[摘 要] 尽管以PD-1/PD-L1抑制剂为基础的免疫治疗显著提升了肺癌患者的生存期,但耐药问题依然严峻。本文阐述了免疫治疗耐药的定义、发生机制及预测模型,介绍了针对耐药的治疗策略,包括免疫治疗继续应用、再挑战、寡转移背景下的局部治疗联合全身免疫治疗、广泛进展后的联合治疗等。此外,还探讨了新型治疗手段如过继性细胞疗法、抗体偶联药物、双特异性抗体和肿瘤疫苗等在克服耐药中的应用前景。同时,总结了肺癌免疫治疗的挑战与发展方向,强调了持续研究、创新治疗策略以及跨学科合作的重要性。为未来肺癌治疗的个体化、精准化和高效化提供新思路与研究方向。

[关键词] 肺癌;免疫治疗;耐药;免疫检查点抑制剂
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Challenges and therapeutic strategies for immunotherapy resistance in lung cancer

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[Abstract] Despite significant improvements in survival among lung cancer patients treated with PD-1/PD-L1 inhibitor-based immunotherapy, the issue of drug resistance remains a major challenge. This article delineates the definition, mechanisms, and predictive models of immunotherapy resistance, and introduces therapeutic strategies to address resistance, including continued use of immunotherapy, rechallenge, local treatment combined with systemic immunotherapy in the context of oligometastasis, and combination therapy after extensive progression. Furthermore, it explores the application prospects of novel therapeutic approaches such as adoptive cell therapy, antibody-drug conjugates, bispecific antibodies, and tumor vaccines in overcoming drug resistance. Additionally, the article summarizes the challenges and development directions of immunotherapy for lung cancer, emphasizing the importance of ongoing research, innovative treatment strategies, and interdisciplinary collaboration. These efforts aim to provide new ideas and research directions for achieving personalized, precise, and efficient lung cancer treatment in the future.

[Key words] lung cancer; immunotherapy; drug resistance; immune checkpoint inhibitors
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以免疫检查点抑制剂(immune checkpoint inhibitor, ICI)(如PD-1/PD-L1抑制剂)为基础的免疫治疗,已成为癌症驱动基因阴性非小细胞肺癌(non-small cell lung cancer,NSCLC)患者的标准治疗选择,显著提升了患者的生存期[1]。然而,在临床实践中耐药成了一个亟待攻克的难题。据统计,对于接受一线免疫单药治疗或联合其他免疫治疗的NSCLC患者,约有21%~27%会发生原发性耐药。使用免疫治疗联合化疗的患者约有10%发生原发性耐药;更为严峻的是,52%~57%的NSCLC患者在初次接受免疫治疗后会发生继发性耐药[2]。纪念斯隆-凯特琳癌症中心的一项研究[3]揭示,在1 201例

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接受PD-1/PD-L1抑制剂治疗的NSCLC患者中，高达78%对PD-1/PD-L1抑制剂初期有应答的患者最终出现了继发性耐药，进一步凸显了耐药问题的普遍性与严峻性。因此，为肺癌免疫治疗耐药患者开发有效的治疗策略尤为重要且紧迫。本文综述肺癌免疫治疗耐药机制的研究进展，分析针对耐药性问题的应对策略及其面临的挑战，旨在为攻克这一难题提供新的思路和研究方向。

1　免疫治疗耐药的定义及发生机制

肿瘤ICI治疗耐药领域面临的挑战之一是缺乏统一的临床定义。基于耐药机制，免疫治疗耐药通常被划分为原发性耐药、适应性耐药和获得性耐药三大类型[4]。2020年，美国癌症免疫治疗学会(Society for Immunotherapy of Cancer, SITC)制定了针对PD-1/PD-L1抑制剂治疗的耐药定义，依据患者情况分为晚期患者连续治疗耐药、晚期患者中断治疗后耐药，以及辅助或新辅助治疗后耐药[5]。2021年欧洲肿瘤内科学会(European Society for Medical Oncology, ESMO)对晚期NSCLC患者PD-1/PD-L1/CTLA-4抑制剂获得性耐药的标准进行了更为细致的划分，主要包括治疗类型、缓解深度、缓解持续时间，以及治疗的连续性[6]。随后，为克服免疫耐药，基于免疫治疗的联合治疗策略应运而生。因此，2023年SITC进一步发布了免疫治疗联合化疗、靶向药物及其他免疫药物的耐药定义[7]。明确这些定义对于实现患者的精准分层对指导患者后续治疗具有重要意义。

肺癌的免疫耐药机制错综复杂，涵盖肿瘤细胞、肿瘤微环境(tumor microenvironment, TME)及机体多重因素[8]。这些因素相互作用，通过伪装(camouflage)、胁迫(coercion)和细胞保护(cytoprotection)的“3C”理论[9]，帮助肿瘤细胞躲避免疫监测和清除，影响免疫治疗的疗效(图1)。

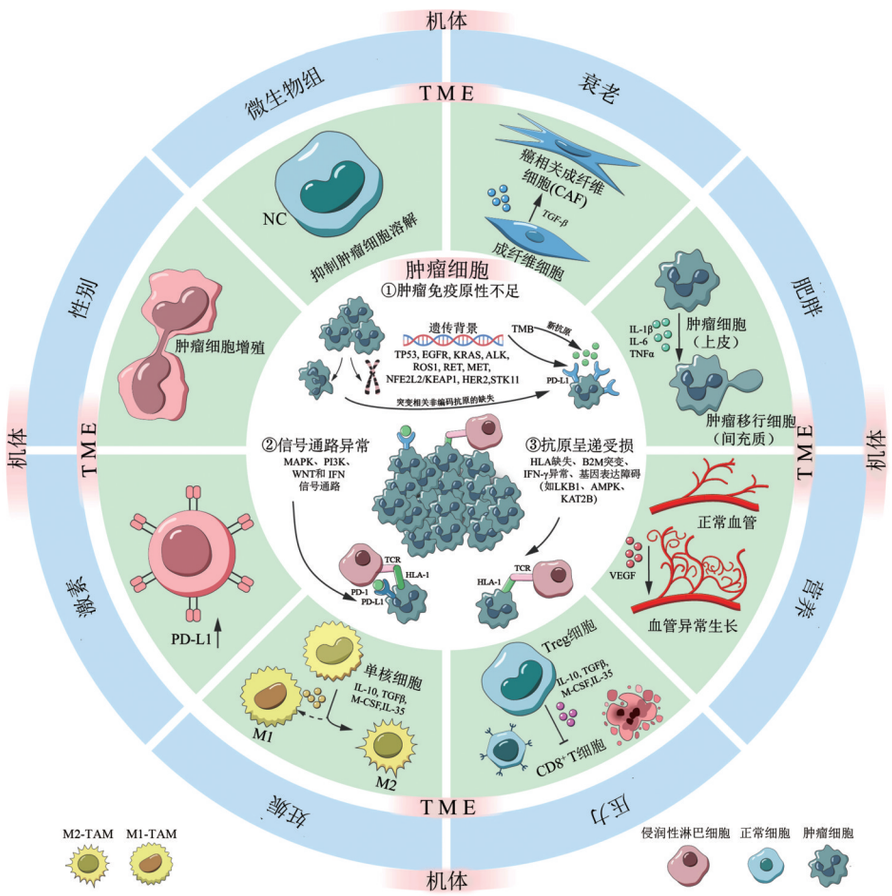

图1　肺癌免疫治疗的耐药机制

在肿瘤细胞层面，关键免疫调节基因的突变通过降低肿瘤细胞的免疫原性、破坏抗原提呈机制及激活的异常信号通路，为肿瘤细胞的生存与增殖提供了有利条件[10-12]。在此过程中，肿瘤细胞的代谢重编程还可以通过产生一系列代谢产物抑制TME中的免疫细胞[13]。同时，肿瘤细胞的表观遗传调节异常

也会导致免疫治疗耐药[14-16]。

肿瘤细胞外源性耐药机制则主要聚焦于抑制性TME。TME中的免疫抑制性细胞通过分泌抑制性细胞因子或直接抑制效应T细胞的功能,抑制抗肿瘤免疫反应[17-23]。此外,机体相关多种因素也可以直接或间接地作用于免疫系统,从而影响免疫治疗的疗效[8,24]。

2 免疫治疗耐药的预测模型

免疫治疗效果在不同肿瘤患者间存在显著差异,部分患者出现免疫治疗无效[25-26]及免疫相关不良反应(immune-related adverse event, irAE)[27]。这凸显了精准人群识别和构建耐药预测模型的重要性。

生物标志物的识别在精准人群识别的过程中至关重要。肿瘤细胞PD-L1表达、微卫星不稳定性或错配修复缺陷及高肿瘤突变负荷被美国食品药品监督管理局(Food and Drug Administration, FDA)批准为PD-1/PD-L1抑制剂的预测生物标志物[28]。

随着多种研究手段的发展,与免疫相关基因的突变[29-30]、肿瘤抗原提呈缺陷[31-32],以及多细胞免疫结构的形成(如三级淋巴结构)[33]等与免疫治疗疗效相关的生物标志物逐渐被发掘。但因数据量有限,全面评估ICI疗效仍需进一步验证和优化。

鉴于肿瘤及免疫微环境的高度异质性、影响免疫治疗疗效因素的多维性,计算机建模与机器学习技术在筛选免疫治疗受益群体和预测预后方面展现出巨大潜力[34-37]。例如,仅需使用6个患者基线和临床特征的LORIS模型[38],可在多种实体瘤中准确预测治疗应答和患者生存。TIDE模型通过整合已发表的ICI试验、非免疫治疗肿瘤特征、大规模组学数据和生物标志物,实现了对ICI临床反应的预测[39]。此外,PERCEPTION预测模型也被证明,可以通过批量转录组数据和单细胞转录组数据来预测肿瘤患者对于美国FDA批准药物的敏感性及耐药性[40],其预测效力优于目前已发表的基于基因转录组信息构建的模型。这些算法的出现将极大地推动以大数据为驱动的精准治疗在肿瘤治疗领域的应用。

3 针对免疫治疗耐药的治疗策略

接受免疫治疗的肿瘤患者可能会表现出不同反应,包括典型的应答和非典型的应答模式[41]。因此,需要根据不同类型的应答反应采取针对性的治疗策略。

当前,肺癌免疫治疗耐药的应对策略主要集中于以靶向PD-1/PD-L1为基础的联合治疗,旨在通过多元化的组合方式增强治疗效果[17]。另外,一些新型治疗手段也正崭露头角,如肿瘤疫苗[42]、溶瘤病毒(oncolytic virus, OV)[43]、抗体偶联药物(antibody-drug conjugate, ADC)[44],以及粪便微生物群移植(fecal microbiota transplantation, FMT)[45]等。这些创新策略共同构成了肺癌免疫治疗耐药挑战下的多维度解决方案。

3.1 免疫治疗的持续应用及再挑战

研究[46]发现,对于出现假性进展、分离应答的患者,免疫治疗持续应用具有一定益处。一项回顾性分析结果[47]显示,既往免疫治疗后接受PD-1/PD-L1抑制剂治疗的Ⅳ期NSCLC患者的客观缓解率(objective response rate, ORR)有限,但疾病控制率却相对较高。TOPP等[48]汇总分析发现,87.8%的NSCLC患者接受免疫治疗进展后继续治疗靶病灶缩小或稳定,并带来持久的临床获益。美国FDA指出,在ECOG评分良好、前线免疫治疗获益、仅靶病灶进展或仅非重要器官系统出现新病灶时,更适合免疫治疗继续应用[25]。

免疫治疗再挑战是指既往使用免疫治疗并因各种原因终止治疗后重新接受免疫治疗的用药模式[49],主要包括免疫治疗耐药、irAE和免疫治疗完成既定疗程后肿瘤复发三种情境[50]。对不同原因导致治疗终止的患者进行免疫治疗再挑战的疗效各不相同。初始ICI治疗耐药的NSCLC患者,可能对免疫治疗再挑战反应不佳[51-53]。然而,对于成功完成首次ICI治疗疗程且在足够长的无治疗间隔期后进展的患者,在考虑其既往ICI治疗中的体能状态和irAE后,可考虑重新进行ICI治疗[54-55]。另外,KEYNOTE-010[56]、KEYNOTE-024[57]均表明晚期NSCLC患者接受免疫治疗周期满后,因复发再次选择ICI治疗可获得一定的临床益处。因此,在决定是否进行免疫治疗再挑战或免疫治疗持续应用时,需要综合考虑患者的具体情况、ICI药物的疗效,以及安全性等因素。

3.2 寡转移背景下的治疗策略

尽管寡转移的定义尚未明确,但其已被广泛定义为PET-CT或CT扫描显示存在≤ 5个病灶进展[58]。针对寡进展应尽可能采用局部治疗,同时维持现有的全身免疫治疗[58-60]。一项Ⅱ期临床试验结果[61]显示,立体定向放疗联合标准治疗相比仅接受标准治疗,NSCLC寡进展患者无进展生存期(progression-free survival, PFS)延长了4倍以上。另一项Ⅱ期临床试验结果[62]也表明,局部消融治疗后加用帕博利珠单抗治疗寡转移性NSCLC似乎延长了PFS,同时不降低其生活质量。然而,2024年美国临床肿瘤学会(American Society of Clinical Oncology, ASCO)报道的随机对照研究NRG-LU002[63]却得出了不

同的结论。该研究显示,对于野生型NSCLC寡转移患者,在一线免疫治疗有效后进行巩固性的局部治疗,相比继续维持治疗,并未带来生存获益,反而明显增加了肺毒性。由于目前仍缺乏有效的Ⅲ期临床试验数据,这一领域的研究仍需进一步探索,以优化治疗策略,提高患者的生存率和生活质量。

3.3　广泛进展后以PD-1/PD-L1抑制剂为基础的联合治疗

3.3.1　与化疗联合

化疗可以增强抗原提呈和效应细胞的功能,消除免疫抑制细胞,增加免疫治疗疗效[64-65]。KEYNOTE-189[66]、KEYNOTE-407[67]、KEYNOTE-042[68]等临床试验均证实,与单纯化疗相比,化疗联合免疫治疗可显著延长NSCLC患者的生存时间。因此,免疫治疗联合化疗成为晚期NSCLC患者的一线标准治疗策略。然而,一项Ⅱ期试验结果[69]显示,二或三线单药免疫治疗耐药后接受帕博利珠单抗联合化疗并不能提高疗效,只有PD-L1强阳性(≥50%)且先前免疫治疗获益的患者可能有长期的生存获益。

为提高疗效,目前正在探索几个有前途的方向包括:优化联合化疗方案;优化化疗和免疫治疗的给药顺序;确定治疗的最佳持续时间;筛选免疫治疗最佳受益群体[65]。

3.3.2　与放疗联合

放疗不仅能清除肿瘤细胞,还可以因其独特的远隔效应作为一种“佐剂”增强癌症患者对免疫治疗的反应性[70-71]。虽然远隔效应罕见,但与免疫疗法联合可以增强该效应[72]。

放疗联合免疫治疗对不同阶段的肺癌患者均展现出一定疗效。一项Ⅱ期试验显示,免疫联合放疗在未经治疗的早期或肺实质复发的无淋巴结转移NSCLC患者中,显著提高了4年无事件生存期且毒性反应可控[73]。对于局部晚期NSCLC患者,放疗联合免疫治疗也显著提高了生存率。Ⅲ期试验PACIFIC[74]及其5年生存结果[75]表明,放疗联合ICI治疗具有持续的总生存期(overall survival,OS)和PFS益处。另一项Ⅲ期试验GEMSTONE-301[76]也表明,确定性同步或序贯放化疗后使用舒格利单抗对于NSCLC患者是一种有效的巩固治疗手段。在2024年ASCO大会上,有报告指出阿得贝利单抗联合化疗序贯胸部放疗同样展现出了良好的疗效与安全性。

然而,放疗联合免疫治疗的应用仍面临治疗模式的优化及放疗剂量的确定等挑战。对此,美国威斯康星大学的研究团队[77]提出了一种全新的策略——“瘤内放疗剂量异质性”激活免疫应答。该策略通过不同剂量的放疗照射肿瘤的不同部位,增强放疗激活免疫应答的效应,从而更好地配合ICI疗法。未来的研究可以此为基础,进一步优化放疗的剂量和分布,并将此策略推广至更多的肿瘤模型选择中。未来还可探索放疗与其他免疫疗法的联合应用,以期为肺癌患者提供更加有效的治疗方案。

3.3.3　与抗血管治疗联合

临床前研究[78-79]表明,抗血管治疗联合免疫治疗可以协同刺激抗肿瘤免疫。在NSCLC中,目前主要有两种抗血管治疗策略:一是靶向血管内皮生长因子(vascular endothelial growth factor,VEGF)或血管内皮细胞生长因子受体(vascular endothelial growth factor receptor,VEGFR)的单克隆抗体;二是抑制多种血管生成和增殖途径的小分子酪氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI)[80]。关于二者之间的优劣争议,目前尚无定论。

IMpower150研究[81]表明,在转移性NSCLC患者中,阿替利珠单抗联合贝伐珠单抗及化疗均可显著延长PFS和OS。ONO-4538-52/TASUKI-52研究[82]也印证了这一包含化疗的四药方案的有效性。

虽然免疫与抗血管治疗的疗效显著,但是该治疗策略伴随的毒性问题却不容忽视。因此,仅依赖抗血管生成药物与ICI药物的“无化疗”方案成为一个重要研究方向。多项研究证明,帕博利珠单抗联合雷莫芦单抗[83]、信迪利单抗联合安罗替尼[84]、纳武利尤单抗联合重组内皮抑素[85]等治疗策略在NSCLC患者中均表现出良好的疗效和安全性。

尽管部分试验取得了较好的疗效,但CONTACT-01[86]、SAPPHIRE[87]、SAFFRON-301[88]等多项大型Ⅲ期试验却均显示阴性结果。这表明,仍需深入研究,以进一步提高疗效。由于VEGF阻断也可抑制抗肿瘤免疫反应,因此,该联合治疗策略的净临床获益将由VEGF信号转导通路的相对效应及其对抗肿瘤免疫反应的抑制之间的平衡来确定[79]。另外,用药的顺序[89]及每种药物的剂量[90]也会对疗效产生不同的影响。未来需要开展更多大样本的研究,探索最佳联合方案并筛选获益人群,为NSCLC患者提供更加有效和安全的治疗策略。

3.3.4　与其他ICI联合

双重ICI治疗策略可减少耐药的发生。CTLA-4与PD-1/PD-L1抑制剂的联合与其协同效应,可显著激活抗癌免疫反应[91]。众多研究[92-95]已证实,该联合疗法能提升临床疗效,已成为晚期NSCLC患者的一线治疗选项之一。

目前,双重ICI治疗主要包括纳武利尤单抗联合伊匹木单抗以及度伐利尤单抗联合曲美木单抗两种策略[96]。基于Ⅲ期CheckMate-9LA的研究成果,纳武

利尤单抗联合伊匹木单抗的治疗方案已被批准用于一线治疗NSCLC[97]。III期POSEIDON研究[98]表明,在度伐利尤单抗和化疗的基础上短期加用曲美木单抗,能够显著改善NSCLC患者的OS和PFS。然而,在特定人群中,双重ICI治疗并未改善疗效[99],反而可能增加irAE[100]。因此,制定个体化治疗方案,在最小化毒性的同时实现益处最大化,仍然是当前临床挑战之一。

为探索更有效的治疗策略,目前多项研究正聚焦于其他检查点(如TIM3、TIGIT、LAG3)的抑制剂与PD-1/PD-L1或CTLA-4的抑制剂联合使用[64]。在II期CITYSCAPE的研究中,替瑞利尤单抗联合阿替利珠单抗在复发或转移性NSCLC患者中的ORR和PFS显示出具有临床意义的改善,且安全性良好[101]。但III期SKYSCRAPER-02研究显示,替瑞利尤单抗联合阿替利珠单抗和化疗并未延长广泛期小细胞肺癌(extensive-stage small cell lung cancer,ES-SCLC)患者的PFS和OS[102],表明抗TIGIT联合抗PD-1/PD-L1在不同癌症中的疗效可能存在异质性。在2024年ESMO大会上发布的一项概念验证研究中,纳武利尤单抗联合瑞拉利单抗与含铂双药化疗的联用方案在NSCLC患者中显示出良好的临床获益[103]。这些研究结果为未来的肺癌治疗提供了新的思路和方向。

3.3.5 以靶向PD-1/PD-L1为基础的双特性异性抗体(bispecific antibody,bsAb)

尽管双重ICI联合治疗能增强治疗效果,但会导致irAE风险增加[104]。为此,bsAb作为一种新型治疗手段应运而生,它旨在提高免疫治疗疗效的同时降低irAE[96]。

针对两个免疫检查点的bsAb在临床试验中初见成效。一项II期临床试验表明,KN046联合化疗作为一线治疗在转移性NSCLC患者中表现出良好疗效和耐受性,为进一步的III期试验提供了有利依据[105]。另一项II期临床研究表明,卡度尼利单抗联合化疗一线治疗驱动基因阴性、PD-L1阴性的晚期NSCLC患者的疗效优越且安全性良好,未来或可成为这类患者的更优治疗选择[106]。

此外,针对PD-1和VEGF的bsAb正逐渐展现出其显著的临床潜力。III期试验HARMONi-A结果[107]显示,依沃西单抗联合化疗可显著改善接受过TKI治疗的NSCLC患者的PFS,且安全性良好,患者耐受性高。随后,“头对头”III期试验HARMONi-2表明,在PD-L1表达阳性的局部晚期或转移性NSCLC患者中,依沃西单抗成功达到了PFS的主要终点,不仅显著延长了患者的PFS,而且疗效优于帕博利珠单抗[108]。

3.3.6 与其他治疗手段联合

在探索肿瘤免疫治疗的新途径中,OV因其将“冷肿瘤”(免疫原性较低)转化为“热肿瘤”(免疫原性较高)的特性而备受瞩目[109]。而且,许多OV也被证明可以诱导PD-1/PD-L1的表达[110]。因此,将OV与ICI治疗联合或许可以为免疫耐药提供新的治疗方向[111]。然而,这一联合策略仅在黑色素瘤的Ⅰ/Ⅱ期临床试验中展现出积极前景,在更大规模的III期临床试验中却未达到预期效果[112]。这表明,OV与ICI治疗联合可能受到多种因素的影响,对于OV与ICI治疗联合的机制需要进行更深入的研究。

此外,肠道微生物组已被证实为导致免疫治疗耐药的关键因素之一[8,18]。精准调控肠道微生物组可增强机体对ICI治疗的反应[45]。鉴于此,FMT与ICI联合为免疫治疗提供了新的视角和可能性。在抗PD-1/PD-L1治疗难治性晚期实体癌患者中,PD-1/PD-L1抑制剂联合FMT为患者带来了显著的临床获益[113]。

ICI联合表观遗传学调控药物也颇具成效。一项在晚期NSCLC患者中进行的Ⅰ/Ⅰb期研究[114]显示,帕博利珠单抗联合伏立诺他显示出初步的抗肿瘤活性且耐受性良好。

3.4 新型治疗

3.4.1 过继性细胞疗法

过继性T细胞疗法也是肺癌治疗领域的一个新方向,包括肿瘤浸润淋巴细胞(tumor-infiltrating lymphocyte, TIL)疗法、T细胞受体嵌合型T细胞(T cell receptor-gene engineered T cell,TCR-T细胞)疗法和嵌合抗原受体基因修饰T细胞(chimeric antigen receptor T cell,CAR-T细胞)疗法[115]。

自体TIL的过继性细胞疗法目前在肺癌治疗中发挥重要作用。在一项II期研究[116]中,对ICI治疗耐药的转移性NSCLC患者给予自体TIL疗法lifileucel可观察到缓解。ICI治疗联合TIL输注在一项Ⅰ期试验中也被证明是可行的,且不良反应可控[117]。

CAR-T细胞疗法[118]和TCR-T细胞疗法[119]也在NSCLC的治疗中极具潜力。细胞疗法与ICI相结合,可能会进一步增强肿瘤特异性免疫细胞的治疗效果[120-121]。此外,细胞因子诱导的杀伤细胞治疗作为一种维持疗法,也被证明对晚期肺癌患者安全有效[122]。

3.4.2 ADC

ADC药物治疗在肺癌治疗领域也颇具前景。在目前的临床试验中,ADC的主要靶点包括HER2、TROP2、HER3、MET、B7-H3等[123]。其中,靶向HER2的ADC药物尤为引人注目。2022年,德曲妥珠单抗(T-DXd)用于治疗HER2突变、经治的NSCLC患者,成

为首个被美国FDA批准上市的肺癌ADC药物[124]。临床研究DESTINY-Lung02[125]表明，T-DXd对于转移性NSCLC患者疗效显著且安全性可控。

除了靶向HER2的ADC药物外，其他ADC药物也在肺癌领域进行了积极探索。Ⅲ期试验TROPION-Lung01[126]表明，靶向TROP2的达托匹坦布德曲妥珠单抗在经治、晚期或转移性NSCLC患者中显著改善了PFS。靶向B7-H3的DS7300a和HS-20093[127]也显示出初步治疗前景，目前正在小细胞肺癌(small cell lung cancer, SCLC)患者中进行临床试验。临床试验IDeate-Lung01[128]表明，DS-7300在接受过至少一线含铂化疗联合或不联合抗PD-1/PD-L1治疗的ES-SCLC患者中显示出具有临床意义的ORR。另外，ADC药物与PD-1/PD-L1抑制剂联合治疗NSCLC的治疗策略，在TROPION-Lung02[129]、TROPION-04[130]等临床试验中均展现出显著的治疗潜力，为NSCLC患者带来新的治疗希望。随着更多研究的深入和技术的不断进步，ADC药物有望成为肺癌治疗的重要选择之一。

3.4.3　肿瘤疫苗

在肺癌治疗领域，治疗性肿瘤疫苗也在临床试验中展现出显著疗效。CIMAvax-EGF疫苗已在多个国家获批用于临床，显著提高了患者的生存率[131]，成为肺癌治疗领域的一大亮点。此外，Tedopi疫苗也展现出了广阔的应用前景。ATALANTE-1研究[132]表明，对于HLA-A2阳性、晚期NSCLC且对免疫治疗出现继发性耐药的患者，Tedopi疫苗相比化疗能够显著提高生存期，且安全性更佳。PD1-Vaxx(IMU-201)疫苗通过诱导体内产生阻断PD-1/PD-L1信号转导的多克隆抗体，实现了类似ICI的抗肿瘤作用。同时，它还能诱导记忆T细胞和记忆B细胞反应，进一步克服免疫治疗耐药[133]。Ⅰ/Ⅱ期试验SLU01[134]表明，DC疫苗DCVAC/LuCa联合卡铂和紫杉醇可延长Ⅳ期NSCLC患者的OS且耐受性良好。

最近，肿瘤疫苗的研发又取得了新进展。2024年，BNT116肺癌疫苗在英国成功进行了首次人体临床试验，标志着肺癌疫苗的研发又迈出了重要的一步[135]。此外，PDC*lung01肺癌疫苗的临床数据也备受瞩目。初步结果显示，PDC*lung01联合帕博利珠单抗治疗PD-L1≥50%、HLA-A*02阳性、驱动基因阴性且未经全身治疗的晚期NSCLC，患者ORR高达63.2%，中位PFS达到10.9个月。肺癌治疗性疫苗的研发正不断取得突破，为患者提供了新的治疗选择和希望。

4　结　语

免疫治疗改变了肺癌治疗格局，使其从单一疗法迈向联合疗法、从晚期干预提前至早期治疗，以及从广泛无差别治疗转向个体化精准治疗，预示着肺癌治疗新时代的到来。然而，耐药性依然是免疫治疗领域中的一大挑战。随着对耐药机制的逐步深入，其复杂性也日益凸显，这要求研究者不断深化探索，研发出更佳的联合治疗策略，最终克服免疫治疗耐药这一难题。

在肺癌免疫治疗的探索之路上，亟待攻克的难关在于如何将“冷肿瘤”转化为“热肿瘤”，进一步提升治疗效果。目前，以PD-1/PD-L1抑制剂为基础的联合治疗策略已成为主流，并取得了一定成效，但仍有广阔的提升空间。因此，寻找并验证一个既能有效激活“冷肿瘤”又能最大化疗效的最佳治疗组合，是当前研究的重中之重。此外，一系列新型治疗手段如过继性细胞疗法、ADC、bsAb、肿瘤疫苗以及OV等，正逐步进入人们的视野，为克服免疫治疗耐药性和提高疗效提供了更多可能性。然而，这些新兴疗法同样面临着上述挑战。

最后，联合治疗带来的不良反应的预测与管理，以及免疫治疗优势人群的精准筛选，也是当前亟待解决的问题。这些挑战要求研究者不仅要深入探索免疫治疗的机制，还要加强跨学科合作，综合运用生物信息学、人工智能等先进技术，以实现肺癌治疗的个体化、精准化和高效化。

利益冲突声明：在撰写本综述文章的过程中，作者严格遵守学术诚信和科研道德的原则，无任何实际的或潜在的利益冲突。

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