·综　述·

胃癌领域抗肿瘤药物相关间质性肺病/肺炎的研究进展及展望

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［摘要］胃癌发病率高，疾病负担沉重，且治疗困难。近年来，免疫检查点抑制剂（immune checkpoint inhibitor，ICI）、人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）和紧密连接蛋白18.2（Claudin 18.2，CLDN18.2）抑制剂等多种新型抗肿瘤药物为胃癌患者带来获益，单药治疗和不同联合治疗方案均在胃癌临床治疗中展现出巨大潜力。然而，由抗肿瘤药物诱发的间质性肺病/肺炎（interstitial lung disease/pneumonia，ILD/p），尤其是免疫抑制剂类药物和抗体药物偶联物（antibody-drug conjugate，ADC）药物相关ILD的发生风险，已然成为影响患者获益的关键安全性问题。由于不同抗肿瘤药物诱发ILD的风险和机制各不相同，且ILD多数起病隐匿，较难察觉。因此，深入理解不同抗肿瘤药物相关ILD的发生风险及其独特机制、合理且个体化的用药监测及患者管理至关重要。有鉴于此，本文系统性回顾分析近年来胃癌领域抗肿瘤药物相关临床研究中ILD/p的发生率、临床特征及ILD/p相关危险因素，旨在阐明不同抗肿瘤药物之间的风险分层、机制差异，以提升临床认知，从而使更多胃癌患者临床获益。

［关键词］胃癌；抗肿瘤药物；间质性肺病；肺炎；进展

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Research progress and future perspectives of anticancer drug-induced interstitial lung disease/pneumonia in gastric cancer

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［**Abstract**］Gastric cancer presents a high incidence rate and substantial disease burden, posing significant therapeutic challenges. Recent advances have yielded significant benefits for gastric cancer patients through novel anti-tumor agents, including immune checkpoint inhibitor (ICI), human epidermal growth factor receptor 2 (HER2)-targeted therapies, and claudin 18.2 (CLDN18.2)-directed agents. Both monotherapy and various combination regimens demonstrate considerable promise in gastric cancer treatment. However, a critical safety concern potentially limiting patient benefit is drug-induced interstitial lung disease (ILD)/pneumonitis, particularly associated with ICI and antibody-drug conjugate (ADC). The risk and underlying mechanisms of ILD vary considerably across different anti-tumor drug classes, and its often insidious onset makes early detection difficult. Therefore, a deep understanding of the distinct ILD risks and mechanisms associated with different agents, coupled with rational, individualized drug monitoring and patient management, is paramount. This review systematically analyzes the incidence rates, clinical characteristics, and risk factors associated with ILD/pneumonitis reported in recent clinical trials of anti-tumor therapies for gastric cancer. It aimed to elucidate the risk stratification and mechanistic differences between drug classes, thereby enhancing clinical awareness and ultimately helping to maximize clinical outcomes for gastric cancer patients.

［**Key words**］Gastric cancer; Anticancer drug; Interstitial lung disease; Pneumonitis; Progress

全球癌症统计报告[1]数据显示，2022年全球胃癌（包括食管胃结合部腺癌）的新发病例约96.9万例，死亡病例约66.0万例，在所有癌症中均位居第5位。而2022年中国恶性肿瘤流行情况分析（纳入700个肿瘤登记处的2018年数据和106个登记处的2010—2018年数据）显示，中国胃癌的新发病例达35.87万例，死亡病例为26.04万例，胃癌发病率和死亡率在所有癌症中分别位居第5位和第3位[2]。胃癌的疾病负担沉重，防控形势严峻。近年来，免疫检查点抑制剂（immune checkpoint inhibitor，ICI）、人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）靶向药物和紧密连接蛋白18.2（Claudin 18.2，CLDN18.2）靶向药物等多种新型抗肿瘤药物在胃癌治疗中取得重大进展。这些药物的单药治疗和不同联合治疗方案为胃癌患者带来了更多的治疗选择和生存获益。但与此同时，药物相关间质性肺病/肺炎（interstitial lung disease/pneumonia，ILD/p）等安全性问题也逐渐凸显，若处理不当可能导致治疗暂停或中断，甚至危及生命，从而影响患者的临床获益[3-4]。

ILD/p的发病机制复杂且尚未完全阐明。有研究[5]表明，抗肿瘤药物或其代谢物可与肺组织蛋白结合形成新抗原，通过抗原-抗体复合物沉积触发免疫反应导致ILD/p，或通过诱导中性粒细胞增多直接损伤肺内皮/上皮细胞。此外，肺泡巨噬细胞可非特异性地摄取抗体药物偶联物（antibody-drug conjugate，ADC），释放骨桥蛋白导致局部免疫微环境紊乱，进而诱发ILD/p。其余机制涉及氧化应激、磷脂代谢障碍及炎症介质级联释放等。这些机制常交互作用，具体过程因药物种类及个体差异而异，需结合药物特性和患者背景实施个体化监管[5]。为提高临床医师对胃癌患者抗肿瘤治疗中ILD/p的认识，确保患者治疗安全和获益，本文系统性回顾胃癌领域抗肿瘤药物相关的临床研究，筛选出报道ILD/p发生的研究，并对胃癌领域抗肿瘤药物相关ILD/p的发生情况、发生机制、临床特征及相关危险因素进行系统综述。

1 数据库检索

以Gastric cancer, stomach cancer、upper gastrointestinal cancer、interstitial lung disease、lung injury、lung toxicity、pneumonitis、drug-induced为英文检索词，以胃癌、胃恶性肿瘤、上消化道恶性肿瘤、间质性肺病、肺损伤、肺毒性、肺炎、药物相关肺损伤为中文检索词，检索PubMed、Embase、Web of Science、万方数据库、维普网、中国生物医学文献数据库、中国知网及各大会议摘要。检索时间为建库至2025年3月。从中筛选出报道ILD/p发生的相关临床研究以进行系统分析。

2 ICI诱导ILD/p的重要临床研究进展

ICI可逆转肿瘤介导的免疫细胞功能抑制状态，已经应用于胃癌治疗[6]。以程序性死亡蛋白-1（programmed death-1，PD-1）、程序性死亡蛋白配体-1（programmed death ligand-1，PD-L1）和细胞毒性T淋巴细胞相关抗原4（cytotoxic T lymphocyte associated antigen-4，CTLA-4）为靶点的ICI已开展了单药、联合化疗和双ICI联合治疗的临床研究和应用（表1）。

表1 胃癌领域免疫治疗相关临床试验及ILD/p发生率

Tab. 1 ICI-related clinical trials in gastric cancer and incidence of ILD/p

Target	Clinical trial	Clinical phase	Intervention	Treatment setting	Incidence of ILD/pneumonia all grade	Incidence of ILD/pneumonia grade 3+
PD-1	KEYNOTE-062[8]	Ⅲ	Pembrolizumab+Cis+Fu/Cap	1L	0.78%	NA
	KEYNOTE-063[9]	Ⅲ	Pembrolizumab	2L	2.10%	NA
	NCT02742935[10]	Ⅰ	Camrelizumab	2L+	3.30%	3.30%
	ATTRACTION-4[11]	Ⅱ/Ⅲ	Nivolumab+SOX/CAPOX	1L	4.20%	1.90%
	CheckMate-649[12]	Ⅲ	Nivolumab+FOLFOX/CAPOX	1L	＜1.00%	＜1.00%
	PERSIST[13]	Ⅱ	Sintilimab+SOX	perioperative	1.00%	1.00%
	NCT04061928[14]	Ⅱ	Toripalimab+chemoradiotherapy	neoadjuvant	35.00%	NA
PD-L1	JAVELIN Gastric 100[16]	Ⅲ	Avelumab	1L	2.50%	0.80%
PD-L1+CTLA-4	INFINITY[20]	Ⅱ	Tremelimumab+durvalumab	neoadjuvant	5.60%	5.60%

FLOFOX: Oxaliplatin+5-fluorouracil/leucovorin; CAPOX: Oxaliplatin+capecitabine; SOX: Oxaliplatin+S-1; NA: Not available.

2.1 PD-1抑制剂

PD-1是表达于免疫细胞表面的蛋白质，通过与肿瘤细胞表面的PD-L1或PD-L2相结合来发挥其免疫抑制作用。然而，当PD-1抑制剂特异性结合PD-1后，PD-L1和PD-L2的表位暴露，这可能导致PD-L1和PD-L2与其他免疫细胞上的受体相结合，从而引发免疫相关不良反应，包括ILD/p。虽然目前有关PD-1抑制剂诱导ILD/p的机制尚未完全阐明，但是Kim等[7]研究发现，在经免疫治疗后出现ILD/p患者的支气管肺泡灌洗液中γ干扰素（interferon-γ，IFN-γ）和白细胞介素-17（interleukin-17，IL-17）等促炎因子水平升高，且存在IFN-γ^+ IL-17^- $CD8^+$ T细胞及CXC趋化因子受体3（CXC chemokine receptor 3，CXCR3）$^+$ CC趋化因子受体6（CXC chemokine receptor 6，CCR6）$^+$ 辅助性T细胞17/辅助性T细胞1（T helper 17/T helper 1，Th17/Th1）细胞富集。提示免疫治疗可诱导Th17/Th1细胞和细胞毒性$CD8^+$ T细胞在肺组织中的克隆性扩增及活化，驱动IFN-γ/IL-17介导的炎症瀑布反应，进而导致ILD/p。

临床研究[8]显示，帕博利珠单抗一线治疗胃癌的Ⅲ期研究中ILD/p的发生率为0.78%，而在PD-1抑制剂后线治疗胃癌的临床研究中ILD/p的发生率升高至2.1%~3.3%（含1例5级死亡事件）[9-10]，提示PD-1抑制剂治疗胃癌的ILD/p发生率与治疗线数及患者状态有关。化疗可以通过激活免疫原性来增强免疫治疗效果，因此化疗联合免疫治疗在胃癌治疗中显示出更好的效果。然而，这种联合治疗会增加不良反应的风险。例如，在ATTRACTION-4研究[11]中，纳武利尤单抗联合化疗的ILD/p总发生率为4.2%。而在CheckMate-649研究[12]中，尽管ILD/p总发生率＜1.0%，但是出现5例5级事件。此外，在体能状态更佳的围手术期患者中，ILD/p发生率可降至1.0%，说明患者基线状态可以影响ILD/p发生率[13]。然而，当免疫治疗与放化疗联用时，ILD/p发生率显著升高至35%，说明ILD/p的发生与不同联合治疗策略有关[14]。

2.2 PD-L1抑制剂

PD-L1抑制剂通过阻断PD-1/PD-L1通路，恢复免疫系统的抗肿瘤活性。然而，肿瘤细胞表面的PD-L2仍可以与PD-1相结合，从而避免PD-L2通过排斥导向分子B（repulsive guidance molecules B，RGMB）过度激活T细胞及避免ILD/p的发生[15]。因此，PD-L1抑制剂在安全性方面可能优于PD-1抑制剂。尽管在一线化疗后使用阿维鲁单抗（avelumab）维持治疗胃癌的Ⅲ期临床研究[16]中，ILD/p总发生率为2.5%，但是在针对度伐利尤单抗（durvalumab）、阿替利珠单抗（atezolizumab）等多种PD-L1抑制剂联合化疗治疗胃癌的临床试验[17-18]中，均未报告ILD/p相关事件。

2.3 双ICI联合治疗

从作用机制上看，PD-1/PD-L1信号通路与CTLA-4存在互补作用，联合治疗可增加T细胞增殖，促进IFN-γ等细胞因子和颗粒酶B（granzyme B，Gra B）释放，抑制调节性T细胞的功能，从而增强抗肿瘤免疫反应[19]。然而，这种联合治疗也会增加治疗相关不良反应的发生风险。例如，在Ⅱ期INFINITY研究[20]中，队列1探索了曲美木单抗（tremelimumab）联合durvalumab新辅助治疗高度微卫星不稳定性可切除胃癌患者的安全性，结果显示，ILD/p总发生率为5.6%（1例≥3级）。然而在其他研究[12]中，双ICI联合治疗用于胃癌治疗尚未报道ILD的发生情况。未来，有关双ICI联合治疗胃癌时ILD/p的发生情况仍需进一步研究，以确保治疗的安全性。

3 HER2靶向治疗药物诱导ILD/p的重要临床研究进展

HER2过表达或基因扩增与胃癌的发生、发展密切相关。全球范围内，胃癌患者的HER2阳性率为7.3%~21.4%[21-22]，而中国胃癌患者的HER2阳性率为9.7%~13.0%[23-24]，因此HER2是胃癌治疗中具有重要临床价值的靶点。随着HER2靶向治疗药物的不断涌现，其在胃癌的治疗中取得了显著进展，然而HER2不仅在肿瘤细胞中表达，也同样在肺支气管上皮细胞中表达[25]。因此，HER2靶向治疗药物可能会由于脱靶效应，进而引发ILD/p等不良反应（表2）。

3.1 HER2靶向单克隆抗体

HER2靶向单克隆抗体已成为胃癌治疗的重要药物，目前已广泛开展与化疗、免疫治疗等其他药物联合治疗的临床研究。在两项Ⅲ期研究[26-27]中，HER2单抗联合免疫治疗（含或不含化疗）用于HER2阳性晚期胃癌的ILD/p总发生率分别为5.1%和4.7%。在围手术期治疗领域，曲妥珠单抗联合化疗新辅助治疗HER2阳性可切除胃癌的ILD/p总发生率为6.0%[28]。然而另一项强化联合方案（曲妥珠单抗±帕妥珠单抗联合化疗）新辅助治疗HER2阳性且可切除胃癌的临床试验[29]未报告ILD/p相关事件。

表2 胃癌领域抗HER2相关临床试验及ILD/p发生率

Tab. 2 HER2-targeted clinical trials in gastric cancer and incidence of ILD/p

Target	Clinical trial	Clinical phase	Intervention	Treatment setting	Incidence of ILD/pneumonia all grade	Incidence of ILD/pneumonia grade 3+
HER2 monoclonal antibody	KEYNOTE-811[26]	Ⅲ	Trastuzumab+pembrolizumab+FP/CAPOX	1L	5.10%	1.40%
	MAHOGANY[27]	Ⅱ/Ⅲ	Margetuximab+retifanlimab	1L	4.70%	0.00%
	NEOHX[28]	Ⅱ	Trastuzumab+capecitabine/oxaliplatin	Perioperative	6.00%	6.00%
HER2 ADC	DESTINY-Gastric01[38]	Ⅱ	T-DXd	3L	9.60%	2.40%
	DESTINY-Gastric02[39]	Ⅱ	T-DXd	2L	10.10%	3.50%
	DESTINY-Gastric03[40]	Ⅱ	T-DXd (6.4 mg/kg)+5-fluorouracil/Cap+pembrolizumab	1L	19.00%	7.00%
	DESTINY-Gastric06[46]	Ⅱ	T-DXd	3L	3.20%	0.00%
	GATSBY[49]	Ⅱ/Ⅲ	T-DM1	2L	7.10%	4.00%
	CTR20190639[50]	Ⅰ	ARX788	2L	20.00%	3.30%
HER2 TKI	TyTAN[53]	Ⅲ	Lapatinib+paclitaxel	2L	2.29%	0.76%

TKI: Tyrosine kinase inhibitor; FP: Fluoropyrimidine+cisplatin.

3.2 双特异性抗体

针对HER2的新型双特异性抗体类药物可同时结合HER2的胞外结构域ECD4（曲妥珠单抗结合位点）和ECD2（帕妥珠单抗结合位点），从而导致细胞表面的HER2下调，表现出比曲妥珠单抗更强的抗肿瘤活性[30-31]。然而现有研究结果[31-32]表明，HER2双特异性抗体类药物似乎并未因双重靶向而增加不良反应的发生风险。有关双特异性抗体治疗胃癌时ILD/p的发生情况仍需进一步探索，以确定药物的安全性。

3.3 ADC药物

ADC药物是一类新型靶向抗肿瘤药物，由抗体、连接子和细胞毒性载荷构成。ADC药物可通过抗体部分靶向肿瘤细胞表面抗原并递送细胞毒性载荷发挥抗肿瘤作用。此外，搭载可裂解连接子和小分子载荷的ADC药物还可通过载荷的跨膜扩散产生“旁观者效应”，杀伤邻近抗原阴性肿瘤细胞，进一步增强抗肿瘤疗效[33]。然而ADC药物可能因脱靶效应或游离有效载荷损伤肺泡细胞而诱发ILD/p[34-35]。

德曲妥珠单抗（trastuzumab deruxtecan，T-DXd）是一种ADC药物，由曲妥珠单抗通过可裂解连接子与DNA拓扑异构酶Ⅰ抑制剂DXd偶联而成。临床前研究[36-37]证实，T-DXd可通过其抗体Fc片段与肺毛细血管周围小窝内高表达Fcγ受体的肺泡巨噬细胞结合，进而被非特异性吞噬；这一过程会诱导巨噬细胞异常分泌大量分泌型磷蛋白1（secreted phosphoprotein 1，SPP1），导致局部免疫微环境紊乱，引发肺间质炎症和组织损伤，这可能是T-DXd诱导ILD/p的机制之一。此外，T-DXd相关ILD/p的发生呈现明显的剂量依赖性特征。这一特征在多项临床研究中得到充分验证：在DESTINY-Gastric01和02研究[38-39]中，使用6.4 mg/kg T-DXd单药分别三线和二线治疗HER2阳性胃癌时，尽管中位总生存期（median overall survival，mOS）超过1年，ILD/p的总发生率却分别高达9.6%和10.1%（≥3级分别占2.4%和3.5%）。DESTINY-Gastric03研究[40]进一步显示，当采用6.4 mg/kg T-DXd联合化疗和帕博利珠单抗一线治疗进展期胃癌时，ILD/p发生率为19%（其中≥3级占7%），而在5.4 mg/kg T-DXd剂量组中则未观察到ILD发生。然而，这种剂量依赖性风险似乎与有效载荷DXd本身的剂量无关。动物实验[37]表明，食蟹猴在接受递增剂量的T-DXd后出现剂量依赖性ILD/p，而单独注射DXd的动物即使在高剂量下也未出现肺毒性。此外，其他靶向不同受体的基于DXd的ADC药物（如HER3-DXd、Dato-DXd等）也同样观察到ILD/p发生[34, 41]。综上，T-DXd诱导的ILD/p可能是一种非靶点依赖性的肺毒性反应。

维迪西妥单抗作为另一款抗HER2的ADC药物，其结构设计与T-DXd存在显著差异：该

药物采用迪西妥单抗作为抗体部分，通过可裂解连接子搭载微管抑制剂单甲基奥瑞他汀E（monomethyl auristatin E，MMAE）作为有效载荷。其抗体部分迪西妥单抗相比于曲妥珠单抗，靶向HER2的不同表位且具有更高的HER2亲和力[42-43]。在C008临床研究[44]中，使用维迪西妥单抗三线治疗HER2高表达/中表达胃癌时，尽管mOS不足1年，但是却未观察到ILD/p的发生，提示ADC药物诱导ILD/p的风险可能受到抗体对靶点的亲和力特性、有效载荷的类型等多重因素影响。未来需进一步探索其作用机制，并在临床实践中平衡疗效与安全性，从而使更多患者获益。

ADC药物相关ILD/p的发生率似乎也与患者基线状况及临床诊疗实践中的不良反应管理密切相关。一项日本真实世界研究[45]显示，接受T-DXd治疗的胃癌患者中，高龄（≥75岁）、有ILD/p病史、既往或现患有放射性肺炎、合并慢性阻塞性肺疾病或肺气肿的患者更容易出现ILD/p。在DESTINY-Gastric06研究[46]（DESTINY-Gastric01的中国桥接注册研究）中，T-DXd三线治疗HER2阳性胃癌的ILD/p总发生率仅3.2%（3例，均为1~2级），显著低于DESTINY-Gastric01研究（9.6%），这一差异可能归因于临床医师对ILD认知的深化、管理体系的完善，以及随着临床医师用药经验积累，早期识别和干预ILD/p的能力提升。2024年《德曲妥珠单抗临床管理路径及不良反应处理中国专家共识（2024版）》发布[47]，通过建立标准化监测体系与分级干预策略，从而有效地降低T-DXd相关不良反应的发生率及严重程度，显著提升用药安全性，为临床实践提供重要指导。

然而，ILD/p的发生似乎并与旁观者效应无关。例如，恩美曲妥珠单抗[48]由曲妥珠单抗搭载不可裂解连接子与美坦辛衍生物［药物抗体比（drug-to-antibody ratio，DAR）=4］，不具备旁观者效应。在国际Ⅱ/Ⅲ期GATSBY研究[49]中，通过恩美曲妥珠单抗治疗HER2阳性局部晚期或转移性胃癌，结果显示，ILD/p总发生率为7.1%。另一不可裂解连接子ADC药物ARX788（DAR=1.9）的Ⅰ期胃癌研究[50]显示，ILD/p发生率高达20.0%。然而ILD/p的高发生率可能源于临床研究背景的差异：ARX788研究中的高危人群特征（如体能状态较差等）及早期研究阶段对ILD/p认知不足（如GATSBY研究开展时期缺乏系统管理方案），而非药物作用机制本身导致。

双抗ADC药物可同时靶向HER2蛋白上的ECD2和ECD4，双抗ADC药物似乎并未因双重靶向而增加不良反应的发生风险。例如，ZW49是一种双抗ADC药物，在其治疗局部晚期（不可切除）或转移性HER2阳性癌症患者的Ⅰ期研究[51]中，未报告ILD/p相关事件。

3.4 酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI）类药物

TKI类药物诱导ILD/p的具体机制尚未完全阐明，可能与免疫异常及遗传因素相关[52]。在Ⅲ期TyTAN研究[53]中，同时靶向HER2及表皮生长因子受体（epidermal growth factor receptor，EGFR）的TKI类药物拉帕替尼联合紫杉醇二线治疗晚期胃癌的ILD/p发生率为0.8%（1例3级）。而在另一项拉帕替尼联合CAPOX一线治疗晚期胃癌的Ⅲ期研究[54]中，未报道ILD/p相关事件。此外，针对吡咯替尼（HER2靶点）开展的单药或联合治疗HER2阳性胃癌的研究[55-56]中，均未报告ILD/p相关事件。上述结果提示不同TKI药物或联合治疗方案对肺部不良反应的影响存在差异，在临床实践中需结合具体用药策略对ILD/p等的发生加强监测。

4 CLDN18.2靶向治疗药物诱导ILD/p的重要临床研究进展

CLDN18.2在肿瘤细胞膜表面的异常暴露及其高度组织特异性的表达模式使其成为理想的治疗靶点[57]。靶向CLDN18.2胞外结构域ECL1段的单克隆抗体佐妥昔单抗（zolbetuximab），在Ⅲ期SPOTLIGHT研究[58]和GLOW研究[59]中，使用zolbetuximab联合化疗在CLDN18.2高表达［免疫组织化学（immunohistochemistry，IHC）2+/3+且≥75%肿瘤细胞阳性］、HER2阴性胃癌患者一线治疗中展现出治疗潜力。然而值得注意的是，在上述两项研究中，ILD/p发生率分别为2.15%（6/279）和2.36%（6/254），且均为严重不良反应。此外，现有研究并未发现ILD/p等的发生率与入组标准中CLDN18.2表达的阈值存在相关性。在Ⅱ期FAST研究[60]中，使用zolbetuximab联合化疗治疗更宽松的CLDN18.2阳性标准（IHC2+/3+且≥40%肿瘤细胞阳性）、HER2阴性胃癌的结果显示，ILD/p发生率为2.6%

（2例严重不良反应），与上述Ⅲ期研究结果类似，提示此类不良反应的发生可能存在独立于靶点表达水平外的特殊机制（表3）。

除zolbetuximab外，针对CLDN18.2阳性胃癌的多种治疗策略正在探索中，包括CAR-T细胞疗法（CT041）、新型单抗（TST001）及ADC药物（CMG901/AZD0901）等[61]。然而，目前尚未见ILD相关不良反应报道，靶向CLDN18.2所诱发ILD/p的相关机制仍需进一步探索。

5 其他靶点药物和化疗诱导ILD/p的重要临床研究进展

胃癌治疗领域正经历从传统化疗向精准靶向治疗的模式转变。随着对胃癌分子机制研究的深入，哺乳动物雷帕霉素靶蛋白（mechanistic target of rapamycin，mTOR）、Dickkopf相关蛋白1（Dickkopf-related protein 1，DKK1）、血管内皮生长因子（vascular endothelial growth factor，VEGF）等关键信号通路的作用逐渐明确，推动了相关靶向药物的临床开发（表3）。

5.1 抗血管生成药物

抗血管生成药物可通过抑制血管形成和重塑肿瘤微环境发挥抗肿瘤效应，在胃癌治疗中展现出重要价值，但不同治疗方案间ILD/p发生率存在显著差异，其发生风险受药物种类、剂量强度和联合策略等多重因素调控。以血管内皮生长因子受体2（vascular endothelial growth factor receptor 2，VEGFR2）抑制剂阿帕替尼为例，其单药治疗及仑伐替尼、雷莫西尤单抗的Ⅲ期联合治疗方案均未报告ILD/p事件[62-63]，而在阿帕替尼联合卡瑞利珠单抗及化疗的新辅助治疗Ⅱ期研究[64]中，ILD/p发生率却为4.0%，表明免疫治疗的加入显著增加了ILD/p的发生风险。此外，多激酶抑制剂瑞格非尼联合免疫治疗在Ⅰb期REGONIVO研究[65]中显示出剂量依赖性风险，160 mg组ILD/p发生率高达33.0%，而80、120 mg组未见相关事件，提示ILD/p的发生与药物暴露剂量密切相关。而正在进行的呋喹替尼联合紫杉醇二线治疗研究（FRUTIGA）[66]尚未报告肺毒性事件，进一步印证了不同抗血管生成药物间存在显著的毒性异质性。上述研究数据说明，在临床实践中需要建立基于药物特性、剂量强度和联合方案的个体化风险评估体系，未来需通过精准剂量探索和生物标志物分析，平衡肿瘤微环境调控与肺毒性风险，以优化治疗策略。

表3 胃癌领域其他靶点相关临床试验及ILD/p发生率

Tab. 3 Other targets-related to clinical trials in gastric cancer and incidence of ILD/p

Target	Clinical trial	Clinical phase	Intervention	Treatment setting	Incidence of ILD/pneumonia all grade	Incidence of ILD/pneumonia grade 3+
CLDN18.2	SPOTLIGHT[58]	Ⅲ	Zolbetuximab+mFOLFOX6	1L	2.15%	NA
	GLOW[59]	Ⅲ	Zolbetuximab+CAPOX	1L	2.36%	NA
	FAST[60]	Ⅱ	Zolbetuximab+EOX	2L	2.60%	NA
Antiangiogenic drugs	NCT03878472[64]	Ⅱ	Apatinib+camrelizumab+S-1±oxaliplatin	neoadjuvant	4.00%	NA
	REGONIVO[65]	Ⅰb	Regorafenib (160 mg)+nivolumab	3L+	33.00%	33.00%
FGFR2	FIGHT[67]	Ⅱ	Bemarituzumab+mFOLFOX6	1L	1.30%	1.30%
mTOR	GRANITE-1[70]	Ⅲ	Everolimus	2L+	3.00%	0.70%
DKK1	WAKING[68]	Ⅱa/b	DKN01+atezolizumab	2/3L	8.30%	0.00%

FGFR2: fibroblast growth factor receptor 2; mTOR: mechanistic target of rapamycin; DKK1: dickkopf-1; mFOLFOX6: 5-Fluorouracil+oxaliplatin+calcium folinate; EOX: Epirubicin+oxaliplatin+capecitabine; NA: Not available.

5.2 成纤维细胞生长因子受体2（fibroblast growth factor receptor 2，FGFR2）

FGFR2是胃癌治疗的潜在靶点。贝玛妥珠单抗（bemarituzumab）是一种人源化免疫球蛋白G1（immunoglobulin G1，IgG1）单克隆抗体，可特异性结合FGFR2b的细胞外结构域，抑制FGFR2b活化，并对表达FGFR2b的肿瘤细胞发挥更强的杀伤作用。在国际Ⅱ期FIGHT研究[67]中，bemarituzumab联合mFOLFOX6一线治疗FGFR2b过表达和（或）*FGFR2b*基因扩增

胃癌患者的有效性和安全性得到了初步评估，结果显示，ILD/p发生率为1.3%（1例5级）。目前两项Ⅲ期临床研究（FORTITUDE-101和FORTITUDE-102）[68-69]正在进一步验证其联合化疗或免疫化疗方案在晚期胃癌中的临床价值。

5.3 其他靶点或治疗方式

除上述药物外，其他新型胃癌治疗药物也需要关注肺部相关不良反应。例如mTOR抑制剂依维莫司（everolimus）在Ⅲ期METGastric研究[70]中后线治疗晚期胃癌患者的ILD/p总发生率为3.0%（≥3级为0.7%）；DKK1抑制剂DKN-01联合atezolizumab的ILD/p发生率达8.3%[68]。而间充质-上皮转化（mesenchymal-epithelial transition，MET）抑制剂（如奥纳妥珠单抗）及部分化疗方案的相关临床研究[71-74]中的ILD/p发生率尚未明确。在临床实践中仍需建立系统化的监测机制，这对早期识别药物相关性肺损伤及改善预后具有重要临床意义。

6 总结及展望

全球胃癌疾病负担重，预计2040年时全球胃癌疾病负担将较2020年增长70%，每年新发病例将达到180万例，死亡例数将高达130万例[75]。靶向药物、ICI类药物等作为常用胃癌领域抗肿瘤药物，均可能导致不同程度的ILD/p。不同药物导致的肺损伤机制各有特点，主要是直接或间接作用导致的肺泡上皮细胞、气道上皮细胞或血管内皮细胞等的损伤。尽管最终结局相似，但是对其发生机制的深入了解将有助于临床医师精准施策，从而有效地抑制和逆转肺损伤。

为了实现更好的临床管理并提升患者治疗获益，临床专家需深入了解药物相关ILD/p的发生机制和危险因素。未来可通过开展全国范围内大型真实世界研究，通过整合真实世界数据与生物样本库资源，建立临床实用的早期预警生物标志物检测体系，并基于循证医学证据，制定包含风险分层评估、剂量调整及重启治疗标准的分级管理指南或专家共识。这有望在保障疗效的同时，显著降低ILD/p的发生风险。随着精准医学理念的深入、实践经验的积累及治疗方案的不断优化，中国胃癌患者的临床获益必将持续提升。

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