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胃癌抗HER2靶向治疗进展与展望

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摘要 HER2(human epidermal growth factor receptor 2)是胃癌关键治疗靶点, 利用免疫组化技术(IHC)和荧光原位杂交技术(FISH)可以将HER2表达水平划分为阳性(IHC: 3+/2+, FISH+)和阴性. 曲妥珠单抗联合化疗是标准一线方案,当前研究聚焦于优化联合治疗方案及新型一线策略探索. 随着该药向新辅助治疗推进, 后续一线及后线治疗选择也面临新挑战. 除HER2高表达水平患者可因抗HER2治疗受益外, 随着抗体药物偶联物(antibody-drug conjugates, ADC)技术的出现, 国产HER2-ADC维迪西妥单抗(RC48)联合特瑞普利单抗(Toripalimab)在HER2中/低表达人群中也展现出高客观缓解率(ORR=43%). 上述研究共同推动2025年中国临床肿瘤学会四分类标准的制定, 扩大了抗HER2治疗获益患者群体. 此外, 抗HER2小分子靶向药包括吡咯替尼等研发仍持续进行. 本文旨在系统总结HER2分类标准及靶向治疗最新进展, 以期为胃癌精准诊疗策略的优化与未来研究方向提供参考.

关键词 胃癌, HER2, 抗体偶联药物, 免疫联合治疗, 精准治疗

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胃癌是中国第二大致死性恶性肿瘤, 其发病率和死亡率长期居高不下, 对公共卫生构成重大挑战. 尽管近年来外科手术、化疗和免疫治疗不断进步, 但大多数患者在确诊时已处于晚期阶段, 中位总生存期仍不足一年[1]. 如何通过分子分型实现精准治疗, 成为提高疗效和延长生存的关键.

ToGA研究首次证实, 曲妥珠单抗(Trastuzumab)联合铂类、氟尿嘧啶类化疗能够显著延长HER2(human epidermal growth factor receptor 2) 阳性晚期胃癌患者的生存期, 开启了HER2分子靶向治疗新时代[1~3], 使HER2成为胃癌首个精准治疗靶点. 虽然曲妥珠单抗在胃癌晚期一线治疗中占据重要地位, 但在新辅助、辅助治疗中证据近10年来都十分匮乏; 同时患者中位进展时间8.1月, 如何寻找合适的治疗优化模式是临床重

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要问题; 一线治疗后, 后续抗HER2治疗, 如拉帕替尼(Lapatinib)、吡咯替尼(Pyrotinib)等虽然多有探索, 但是多项研究均以失败告终, 研发道路艰辛. 究其原因考虑与胃癌HER2表达异质性强、抗HER2治疗导致HER2表达缺失、下游MET(mesenchymal-epithelial transition factor)通路激活等因素有关. 如何突破HER2阳性胃癌高度异质性, 探索抗HER2耐药机制和耐药策略是胃癌新药研发需要解决的重要问题.

随着抗体偶联药物(antibody-drug conjugates, ADC)技术的面世, 第三代ADC药物具备较好的靶点亲和力、组织穿透性和旁观者效应(对目标靶抗原肿瘤细胞邻近的其他肿瘤细胞也具有杀伤活性)[4], 对于应对胃癌高度异质性具有优势. 随着更多分子机制的解析和新型药物的问世, 传统"HER2阳性"利用免疫组化技术(immunohistochemistry, IHC)来进行定义的阴性、阳性难以覆盖全部潜在获益人群, 尤其对于ADC等新一代治疗手段, 其疗效实际上已延伸至HER2中低表达人群.

中国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)、中国抗癌协会及相关学术组织在综合国内外研究证据的基础上, 于2025年联合发布了《胃癌及胃食管结合部腺癌HER2靶向治疗中国指南(2025年版)》[4]. 该指南系统提出了基于IHC与荧光原位杂交(fluorescence *in situ* hybridization, FISH)的HER2四级分层体系, 明确了检测标准、分层诊断路径及相应地治疗策略, 为HER2检测与临床决策的标准化奠定了坚实基础[5~7].

本文将系统回顾抗HER2治疗在胃癌中的研究进展, 重点探讨HER2分层体系的演变、预后价值及其在靶向治疗中的应用前景. 总结最新临床证据, 阐明HER2胃癌精准诊疗.

1 胃癌HER2 临床意义及其分层体系

HER2作为胃癌最早被确立的治疗靶点, 在疾病的分型、诊断及治疗决策中具有核心地位. HER2表达不仅反映了肿瘤的分子生物学差异, 也与组织学类型、肿瘤免疫微环境、患者预后密切相关. 2025年中国指南对HER2分层体系进行了系统修订, 为精准治疗提供了科学依据[8].

1.1 HER2 分层定义的更新

近年来, 随着分子诊断技术及抗HER2治疗策略的快速发展, HER2在胃癌中的临床分层定义发生了重要演进. 2025年《中国胃癌临床诊疗指南》基于国内外循证医学证据, 首次提出以IHC和FISH为核心的四级分层体系, 将胃癌HER2状态细分为HER2高表达(IHC 3+或IHC 2+且FISH阳性)、HER2中等表达(IHC 2+且FISH阴性)、HER2低表达(IHC 1+)以及HER2缺失表达(IHC 0)[9]. 该分层体系突破了既往"HER2阳性/阴性"的二分模式, 为不同HER2表达水平患者的精准治疗提供了更为精细的生物学依据. 表1展现了最新临床指南对HER2 IHC分型的标准. 图1展示了HER2 IHC方法各分层的病理切片情况, 以及HER2 2+FISH检测的结果.

在该分层框架下, HER2高表达(既往HER2阳性)患者仍然是曲妥珠单抗及其他抗HER2单克隆抗体治疗的核心获益人群, 其分子基础在于*HER2*基因扩增导致的蛋白高表达及下游信号通路持续激活. 而*HER2*中等及低表达患者虽未满足传统*HER2*阳性定义, 但多项近期临床研究已显示其可从ADC药物治疗中获得明确临床获益[2,11,12]. 例如, 维迪西妥单抗(disitamab vedotin, RC48)等HER2-ADC药物可通过旁观者效应实现对中低HER2表达肿瘤细胞的杀伤, 从而显著拓展了HER2靶向治疗的适用人群.

HER2状态的准确判定是胃癌分层治疗的前提. 由于胃癌存在显著的组织学异质性及空间分布差异, 不同检测技术间的一致性、可重复性及结果解读的规范化一直是临床实践的挑战. 近年来, 检测技术从传统组织学方法逐步延伸至分子与液体活检层面, 检测体系的标准化与质控水平不断提高. 2025年指南强调, 在IHC和FISH等组织学检测基础上, 应结合循环肿瘤DNA(circulating tumor DNA, ctDNA)等新兴分子技术, 建立多维度、多时间点的HER2状态评估体系, 以更好地指导临床决策. 图2展现了《胃癌抗HER2治疗中国专家共识(2024年版)》和《中国临床肿瘤协会胃癌诊疗指南(2024年版)》关于HER2检测的分层标准和推荐治疗策略[13].

传统的HER2检测以IHC为基础, 评分范围为0~3+, 其中IHC 2+需进一步通过FISH明确*HER2*基因扩增状态. 为确保结果准确, 相关检测应在具备完善质量管理体系的实验室中完成, 并采用经NMPA批准的抗体和探针[3,9,14,15]. 在特殊情况下, 如强阳性染色细胞比例不足10%, 未达到IHC 3+标准, 但FISH证实存在HER2扩增, 由胃癌多学科团队进行综合评估与判读[16]. 规范的病理报告需明确标注HER2分级, 并记录HER2/CEP17比

表 1 HER2 IHC分型

Table 1 HER2 immunohistochemistry classification

评分	染色模式	判读标准	阴性/阳性认定
0	阴性	肿瘤细胞完全无着色, 或<10%的肿瘤细胞呈现微弱、不完整的膜着色	阴性
1+	微弱阳性	≥10%的肿瘤细胞呈现微弱、不完整的膜着色	阴性
2+	中度阳性	≥10%的肿瘤细胞呈现弱至中度的完整基底侧膜、侧膜或顶端膜着色	需经FISH或ISH进行基因扩增检测确认
3+	强阳性	≥10%的肿瘤细胞呈现强而完整的基底侧膜、侧膜或顶端膜着色	阳性

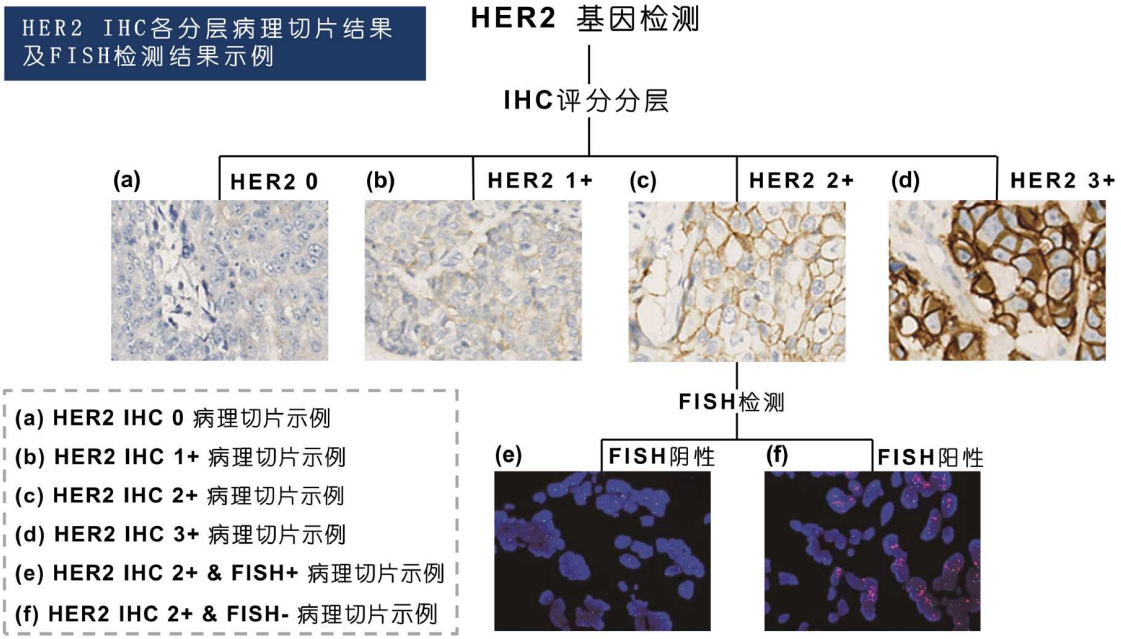

图 1 HER2 IHC各分层病理切片结果及FISH检测结果. (a) HER2 IHC 0分病理切片示例; (b) HER2 IHC 1+病理切片示例; (c) HER2 IHC 2+病理切片示例; (d) HER2 IHC 3+病理切片示例; (e) HER2 IHC 2+/FISH+病理切片示例; (f) HER2 IHC 2+ & FISH+ 病理切片示例. 病理切片图像源自文献[10]

Figure 1 Histopathological assessment results of HER2 IHC across all score strata and corresponding FISH test results. (a) Example of HER2 IHC 0 pathological section; (b) example of HER2 IHC 1+ pathological section; (c) example of HER2 IHC 2+ pathological section; (d) example of HER2 IHC 3+ pathological section; (e) example of HER2 IHC 2+ & FISH+ pathological section; (f) example of HER2 IHC 2+ & FISH+ pathological section. Images of pathological sections were sourced from Ref. [10]

值, 以为后续治疗决策提供可靠依据.

需要注意的是, 胃癌中HER2表达具有显著的肿瘤内及肿瘤间异质性[17~21]. 在HER2阳性或潜在阳性患者中, HER2异质性发生比例可高达30%~70%[22]. 研究表明, HER2异质性既可存在于单个肿瘤内部不同区域之间(瘤内异质性), 也可表现为不同肿瘤病灶或不同蜡块之间(瘤间异质性). 一项纳入618例胃癌患者的研究显示, 约50%的病例在单张切片内即可观察到瘤内异质性, 而30.1%的病例在不同蜡块间存在显著差异[23]. 这种高度不均一的表达模式使单点或单蜡块活检极易产生假阴性, 从而限制基于单次检测结果制定治疗决策的准确性[22]. 除空间异质性外, HER2状态还具有时间异质性. 多项研究表明, 在疾病进展(progressive disease, PD)或抗HER2治疗后, HER2表达状态可能发生改变[24~30]. 部分患者在曲妥珠单抗治疗后由HER2高表达转为HER2缺失, 直接影响后续治疗线次的选择[28~30]. 因此, 在确认PD之后或再次治疗前进行HER2状态复检, 对于优化治疗决策具有重要临床意义.

为克服HER2异质性带来的诊断偏倚, 多蜡块或多区域检测策略已被推荐作为标准化实践. 其基本原则是对同一病例的多个肿瘤区域(通常2~4个蜡块)进行检测, 并以评分最高的结果作为最终HER2判定. 多项大

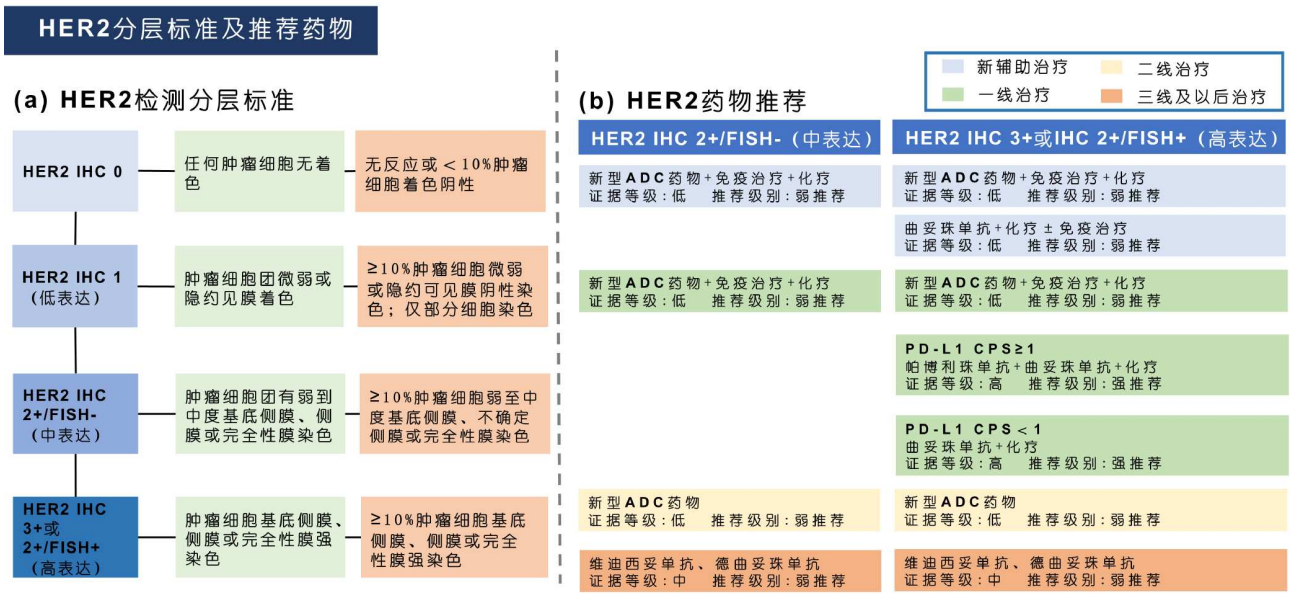

图 2 HER2检测分层标准和推荐治疗策略
Figure 2 HER2 testing scoring criteria and corresponding recommended treatment strategies

样本研究证实, 该策略可显著提高HER2强阳性(IHC 3+)及HER2过表达(IHC 2+/3+)的检出率, 降低假阴性风险. 现阶段, 随着德曲妥珠单抗(trastuzumab deruxtecan, T-DXd)等新型ADC药物的临床应用, 以及2025版CSCO胃癌诊疗指南对HER2高、中、低及阴性四级分层的明确提出, 对病理检测全面性和精确性的要求进一步提高, 使能够充分覆盖肿瘤异质性的多区域检测策略在当前临床实践中愈发关键[31].

除了肿瘤异质性以外, 肿瘤组织取样困难有时也是影响HER2检测的一大因素. 液体活检的临床应用为解决这些难题提供了思路. 液体活检主要是对循环肿瘤细胞(circulating tumor cell, CTC)、细胞游离DNA (circulating free DNA or cell free DNA, cfDNA)、ctDNA及外泌体进行定性或定量分析[32~34]. 在胃癌中, 液体活检的临床应用目前主要集中于晚期患者HER2基因扩增的检测, 其在解决肿瘤异质性及取材受限问题中具有独特优势. 多项研究证实ctDNA中HER2拷贝数改变与组织FISH高度一致[32,33,35~42], 已有数据敏感性达到90%, 特异性达到94%, 一致性较好(Kappa=0.778, P<0.01)[39,43]. 在HERALD/EPOC1806试验中, cfDNA检测到HER2扩增的实体瘤患者经T-DXd治疗的客观缓解率(objective response rate, ORR)达56.5%, 无进展生存期(progression-free survival, PFS)7.0个月[44]. 这些数据表明, 液体活检方法在HER2检测方面已经展现出超越传统方法的准确性和快速性优势, 具有很大的临床应用价值. 在肿瘤组织难以及时取得的临床场景中, 液体活检可作为判断胃癌HER2状态的替代或补充方法[42]. 此外, CTC计数动态变化可预测化疗反应及预后[45]. 液体活检正成为实时监测和个体化决策的重要手段, 该方法有助于进行精确患者分层及动态监测HER2靶向治疗的反应[39~41].

1.2 临床病理学特征

在正常胃黏膜腺细胞中, HER2蛋白表达极少. 而在恶性胃上皮细胞中, HER2表达水平存在不同程度升高[3,14,15]. 多中心流行病学研究(HER-EAGLE研究)显示, 中国人群中HER2高表达比例约12%, 与ToGA研究的全球数据基本一致[9,46~48]. 该结果说明HER2检测在中国患者中具有良好可比性和代表性, 也为本土指南制定提供了流行病学依据. HER2表达水平与胃癌的病理类型、发生部位及转移模式密切相关. HER2高表达胃癌约占全部病例的12.8%~23.2%, 多见于肠型腺癌及近端胃体或胃食管结合部腺癌, 此类肿瘤常伴*HER2*基因扩增、细胞分化良好及腺管形成明显, 临床上更易发生肝转移, 而腹膜播散相对较少[9,49~52]. HER2中等及低表达型胃癌约占21%~24%, 其病理类型以混合型

或弥漫型为主. 研究表明, 这两类亚型的免疫微环境较HER2高表达组更具免疫原性, 肿瘤中可见较高水平的肿瘤浸润淋巴细胞(tumor infiltrating lymphocytes, TILs)[49~52]. 在转移模式上, 中低表达型患者的腹膜播散率较高, 而肝转移发生率介于HER2高表达与HER2缺失组之间. HER2缺失组(IHC 0)占全部胃癌的56%~61.6%, 以弥漫型或印戒细胞癌为主, 生物学侵袭性强, 腹膜转移常见, 而肝转移相对较少[49~52]. 该人群通常伴有更高比例的E-cadherin基因突变及上皮-间质转化(epithelial-mesenchymal transition, EMT)特征.

总体来看, 不同HER2表达亚型不仅在病理形态上呈现显著差异, 其转移倾向、免疫微环境及分子特征亦不同, 为个体化治疗奠定了基础.

1.3 HER2 阳性胃癌肿瘤微环境特征

相关研究表明, HER2阳性胃癌固有的肿瘤微环境呈现出明显的免疫抑制性. 这会导致原发耐药, 而治疗压力下, 以M2型肿瘤相关巨噬细胞(tumor-associated macrophagesm, TAMs)、肌成纤维细胞(myofibroblast, myCAFs)、髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)和调节性T细胞(regulatory T cells, Tregs)为主导的免疫抑制网络进一步扩增和活化, 又会驱动继发性耐药. 微环境中的这些免疫相关细胞通过构建物理屏障、分泌抑制性因子及代谢干扰等多重途径, 共同营造了一个保护肿瘤细胞、抵消HER2靶向治疗效果的微环境.

TAMs-M2亚群细胞在微环境中的富集已被证实与HER2阳性胃癌的不良预后和耐药性相关[53]. 其可以通过MIF-CD74轴与肿瘤细胞相互作用, 增强肿瘤组织的免疫抑制功能[54]; 还可以通过谷氨酰胺代谢关键酶GLS驱动M2型极化, 从而介导肿瘤细胞对曲妥珠单抗等靶向药物的抵抗[55]. 一项以泽尼达妥单抗(zanidatamab, ZW25)获得性耐药患者为队列的研究发现, 患者肿瘤微环境中M2型TAMs比例显著升高, 并可以通过分泌白细胞介素-10(interleukin-10, IL-10)和转化生长因子-β(transforming growth factor-β, TGF-β)、上调精氨酸酶1(arginase-1, ARG1)消耗L-精氨酸, 进而直接抑制$CD8^+$ T细胞的免疫功能[56]. 此外, 一项研究发现在PD-L1联合阳性评分(combined positive score, CPS)<1的患者中存在着独特的$CXCR4^+$M2亚型巨噬细胞, 其功能依赖于CXCR4-CXCL12信号轴, 可能通过招募调节性T细胞、促进上皮-间质转化等方式驱动免疫抑制. 该亚型细胞的出现已被证实与不良预后相关[57].

癌相关成纤维细胞(cancer-associated fibroblasts, CAFs)中的myCAFs亚群也在塑造免疫抑制性微环境过程中发挥了重要作用. 研究表明, HER2信号可以通过EGR1上调促进CAFs向富含RSPO3的myCAFs转化[58]. 这些myCAFs通过分泌致密的纤维连接蛋白和胶原形成物理屏障, 限制T细胞浸润; 同时通过分泌CXCL12 (C-X-C motif chemokine ligand 12)建立化学排斥场, 阻碍效应T细胞向肿瘤核心迁移[59].

MDSCs和Tregs在这一过程中的角色同样不可忽略. 在治疗前的肿瘤组织中, M2巨噬细胞$CD163^+$亚型和$Foxp3^+$亚型Tregs细胞的密度显著高于癌旁组织[60]. 研究发现, HER2阳性胃癌可以通过激活PI3K/AKT通路(phosphatidylinositol 3-kinase/protein kinase B signal pathway)和MAPK通路(mitogen-activated protein kinase signal pathway)上调趋化因子CXCL12和CCL2, 增强MDSCs的招募[61]. 进入微环境中的MDSCs可以进一步通过分泌IL-10、TGF-β和ARG1抑制$CD8^+$ T细胞和自然杀伤细胞(natural killer cell, NK)活性, 导致免疫逃逸加剧[61]. 此外, 受到HER2信号的刺激, 依赖于NF-κB通路的CCL22分泌增加. 这一信号会促进Tregs的扩增[62]. 在HER2阳性胃癌中, Tregs浸润增加与$CD8^+$ T细胞浸润减少两个因素共同促成免疫抑制环境的形成[60,63].

NK细胞同样值得关注. 除了上述几种细胞对NK细胞产生的影响之外, 相关研究还表明, NK细胞通过分泌趋化因子CCL3和CCL4, 与$CD8^+$ T细胞表面的受体CCR5结合, 招募并促进$CD8^+$ T细胞向肿瘤微环境进一步浸润[60].

PD-L1 CPS评分也是HER2阳性胃癌免疫微环境的一个重要指标. 一项相关研究表明. CPS≥1的患者其肿瘤微环境更多地呈现相对活跃的免疫状态, 主要表现为NK细胞、$CD4^+$及$CD8^+$ T细胞等效应免疫细胞不仅浸润密度更高, 而且与肿瘤细胞的空间分布更为紧密(即更高的“空间有效评分”)[64,65]. 单细胞测序进一步证实, 该组患者的基因表达特征以T细胞共刺激和CXCR3趋化因子信号等免疫激活通路为主[66]. 与之形成鲜明对比的是, CPS<1的患者则呈现出偏向免疫抑制的微环境, 其细胞间通讯网络倾向于促进肿瘤进展的胶原形成、VEGF信号及IL-1介导的炎症通路[57,67~70].

抗HER2治疗对于肿瘤微环境的影响同样值得关注. 一方面, 治疗本身可带来积极的免疫微环境改变. 相关研究表明, 曲妥珠单抗可通过FcγRIII介导的抗体

依赖性细胞毒性效应(antibody dependent cell-mediated cytotoxicity, ADCC)招募NK细胞至肿瘤部位, 促进NK细胞在肿瘤组织中的浸润[71], 尤其在获得疾病稳定(stable disease, SD)或部分缓解(partial response, PR)的获益患者中更为明显[60]. 除了NK细胞以外, B淋巴细胞($CD20^+$)的浸润密度在治疗获得PR的患者中显著高于被确认PD的患者, 提示良好治疗反应相关, 并且B淋巴细胞针对Tregs和M2巨噬细胞的抑制作用加强, 一定程度上有助于克服免疫抑制[60]. 同时, 联合使用HER2×CD3双特异性抗体(如Runimotamab)能激活T细胞分泌IL-2, 从而进一步增强NK细胞介导的ADCC效应. 同样可以减弱微环境的免疫抑制影响[72]. 另一方面, 化疗也可能导致免疫抑制细胞的浸润增加, 加剧免疫逃逸. 目前已有相关研究指出, 新辅助化疗后, HER2阳性胃癌中的$FoxP3^+$ Tregs浸润进一步增加, 这可能进一步强化肿瘤微环境的免疫抑制特性[73].

要而言之, HER2阳性胃癌的肿瘤微环境呈现出明显的免疫抑制特性, 这一特性的形成受到多种免疫细胞和信号通路的作用. 抗HER2治疗对微环境的影响是两重性的, 而具体的影响尚待进一步探索.

1.4 胃癌中HER2 状态的预后价值

HER2状态在胃癌预后中的价值长期存在争议. 多数早期研究及一项涵盖42项研究、12749例患者的Meta分析指出, HER2阳性与生存期缩短及浆膜侵犯、淋巴结转移、晚期分期等不良特征相关, 提示其可能推动肿瘤进展[74~77]. 然而, 也有研究未发现HER2与生存显著关联, 如多项研究均显示HER2过表达组与阴性组的总体生存差异不明显, 多因素分析亦表明HER2并非独立预后因子[46,78]. 这些不一致可能归因于胃癌的生物学异质性, 以及IHC/FISH检测方法、取材部位、抗体和评分标准差异; 同时HER2在不同疾病阶段可能具有不同意义. 随着靶向治疗的发展, HER2的角色正由传统预后指标转向预测指标, 其高表达是曲妥珠单抗及多种ADC治疗的关键条件, 而HER2中低表达人群的获益进一步拓展了其临床价值. 总体来看, HER2既是部分胃癌的生物学标志, 也是指导治疗和预测疗效的重要分子指标, 其动态监测有助于实现更精准的个体化治疗.

2 HER2 靶向治疗的循证进展

在靶向治疗和免疫治疗快速发展的时代背景下, HER2靶点已成为胃癌系统治疗中最活跃的研究方向之一. 自ToGA试验确立曲妥珠单抗联合化疗作为HER2阳性晚期胃癌一线标准治疗方案以来[12,79], 为了克服耐药并扩大受益人群, 研究不断向纵深推进. 一方面, ADC药物如T-DXd的出现, 标志着将抗HER2治疗的获益拓展至HER2低表达人群成为可能, 未来抗HER2治疗或将突破传统“阳性/阴性”二分类的局限[80~82]. 另一方面, 免疫联合策略带来了新的突破, KEYNOTE-811试验开创的“靶向+免疫+化疗”新模式, 将ORR提升至74.4%, 为HER2阳性患者提供了更强劲的一线治疗选择[83].

随着多项国际与国内的II、III期研究证据积累, HER2靶向治疗的应用场景持续延伸, 已经形成从后线到一线、并积极探索新辅助治疗的全程化管理格局. 抗HER2治疗策略也呈现联合用药趋势, 从单抗到ADC, 再到与免疫治疗的联合, 多样化的治疗策略构成了丰富的治疗体系. 这些进展驱动诊断从简单的阴性阳性二分法细化为连续的表达谱系分析, 并引领治疗策略从传统化疗迈向基于HER2状态及肿瘤微环境特征的个体化、联合化治疗新时代. 本节将围绕不同治疗阶段的关键研究进展, 系统解析HER2靶向治疗在胃癌中的临床证据与未来趋势.

2.1 抗HER2 ADC的研究进展

由于独特的作用机制, ADC药物可部分克服传统抗HER2药物的耐药机制, 如旁路激活等问题. 此外, 由于“旁观者效应”[4], ADC也为部分HER2低表达胃癌患者带来了治疗突破, 扩大了治疗获益人群.

本团队临床前研究系统评估了新型ADC药物RC48的抗肿瘤活性及其作用机制, 并在体外细胞系与多种患者来源异种移植(patient-derived xenograft, PDX)模型中均显示出高度一致的生物学效应[11,84~86]. 针对HER2表达水平不同的四株胃癌细胞系(NCI-N87、SNU-216、NUGC-4、HGC-27)开展了药效评估. 结果显示RC48在所有细胞系中均表现出显著的剂量依赖性细胞毒作用. 进一步比较发现, 在HER2高表达细胞中, RC48的抑制肿瘤作用显著高于曲妥珠单抗; 而在HER2中、低表达细胞中, RC48仍能杀伤肿瘤细胞. 在体内实验中, 团队构建了包含HER2高表达(IHC3+/FISH+)、中表达(IHC2+/FISH−)及低表达(IHC1+)等9个胃癌PDX模型, 系统评估RC48在不同HER2表达背景下的疗效. 结果显示, RC48在所有模型中均表现出显著

抑瘤作用, 目标群体指数(target group index, TGI)值范围达82%~134%, 且在多数模型中明显优于曲妥珠单抗. 尤其值得强调的是, 在既往HER2不被归类为阳性的IHC2^{+}/FISH^{-}与IHC1^{+}模型中, RC48依然展现出强劲的抗肿瘤活性(TGI达到或超过100%), 而曲妥珠单抗在同类模型中的抑瘤作用相对有限. 这一现象与RC48可释放可膜穿透型介导毒素并产生旁观者效应的机制高度吻合, 即其释放的细胞毒素可扩散至邻近HER2低表达或异质性肿瘤细胞, 从而突破传统HER2抗体治疗对靶标高表达的依赖. 剂量梯度实验亦表明RC48在5 mg kg^{-1}即可达到接近最大药效, 为临床剂量设计提供了重要依据[87].

总体而言, 这些临床前证据奠定了RC48在晚期胃癌中广泛、HER2中低表达使用的实验依据, 并推动其进入多项后续临床研究与真实世界验证[88]. 在临床应用层面, HER2靶向治疗在不断演进, 应用场景进一步扩大, 靶向HER2的ADC药物正逐步突破传统基于IHC/FISH分型的“HER2阳性”限定. 上述提到过的RC48的后续研究进一步拓展了这一获益边界. 在三线及后线治疗阶段, HER2高表达胃癌的可选方案仍相对匮乏[84,89], 而RC48-C008研究在经≥2线治疗的IHC 2+或3+患者中取得了24.8%的ORR与7.9个月的中位总生存期[11], 验证了RC48在此治疗线的临床价值.

国内的多项真实世界队列及临床试验一致指出, RC48在HER2中等及低表达(IHC 2+/FISH^{-}或IHC 1+)的晚期胃癌患者中仍展现出显著抗肿瘤活性, 其疗效呈“连续谱”而非截然二分的表达依赖关系[90,91]. 这一生物学特征主要归因于RC48所具备的旁观者效应. 这一效应使其释放的细胞毒素能够作用于邻近HER2低表达或异质性肿瘤细胞, 从而克服传统单抗疗法受限于表达阈值的固有限制[4,90].

近年来, 多药联合策略进一步提升了RC48的应用前景. 2025年ASCO公布的RC48-C027试验显示, 在HER2高表达或HER2阳性患者中采用RC48联合PD-1抑制剂及曲妥珠单抗, 可实现82.4%的ORR; 而在HER2中/低表达人群中, RC48联合特瑞普利单抗(Toripalimab)亦展现出更高的ORR和更长的PFS[85,92]. 鉴于RC48联合PD-1抑制剂及曲妥珠单抗在二线治疗中展现出显著协同效应, 且疗效突出, 现推荐将其探索性应用于一线治疗, 尤其针对HER2低表达人群. 其他研究亦表明, RC48-C013试验中RC48联合特瑞普利单抗的ORR达43%, 韩国HER-RAM研究中曲妥珠单抗、雷莫芦单抗(Ramucirumab)及紫杉醇(Paclitaxel, PTX)的三联方案则实现了7.1个月的PFS与13.6个月的OS[86].

此外, 在既往治疗失败的HER2高表达晚期胃癌中, T-DXd也已在多项关键研究中展现出显著的生存获益. DESTINY-Gastric01研究纳入经≥2线治疗失败的HER2高表达患者, 结果显示T-DXd较化疗显著延长中位OS (12.5 *vs*. 8.4个月)及PFS(5.6 *vs*. 3.5个月), 确立了其在三线及以后治疗中的优势[12]. 随后开展的DESTINY-Gastric06中国桥接研究进一步验证了该疗效在中国人群中的一致性[93], 并直接促成T-DXd于2024年在中国获批, 用于经至少两线系统治疗后的局部晚期或转移性HER2高表达胃癌及胃食管结合部腺癌.

T-DXd已在多项III期研究中展示稳健的生存获益并推动其在更早治疗线的前移: DESTINY-Gastric01在≥2线失败的HER2高表达晚期胃癌中显著改善中位OS(12.5 *vs*. 8.4个月)与PFS(5.6 *vs*. 3.5个月), 并在后续DESTINY-Gastric02/04等试验中进一步确立其二线地位(DESTINY-Gastric04显示与雷莫芦单抗+PTX相比, OS与PFS显著改善, ORR被提高至44.3%). 相对而言, RC48目前在临床上主要以三线适应证开展并获批(RC48-C008在经≥2线治疗后IHC 2+/3+患者中报道ORR 24.8%, 中位OS 7.9个月), 但RC48在真实世界及多项后续试验中对HER2中/低表达(IHC 2+/FISH−或IHC 1+)患者展现出持续且具有生物学相关性的抗肿瘤活性, 且在多项联合策略(如RC48与PD-1抑制剂±曲妥珠单抗)中观察到极高的ORR(RC48-C027报道组内ORR达82.4%), 表明RC48在低表达或表达异质性的患者群体中具有独特的临床价值.

在二线治疗领域, T-DXd同样展现出强有力的竞争优势. DESTINY-Gastric02研究显示, T-DXd治疗的HER2高表达患者中位OS达12.1个月, ORR为42%, 支持其在二线使用的可行性[94]. 此外, 2025年ASCO公布的DESTINY-Gastric04全球Ⅲ期研究进一步巩固其标准化地位: 与雷莫芦单抗联合PTX相比, T-DXd显著延长中位OS(14.7 *vs*. 11.4个月, HR 0.70)和PFS(6.7 *vs*. 5.6个月), 并将ORR提升至44.3%[95]. 这一证据链清晰表明, T-DXd正逐步由三线治疗向二线治疗前移, 并有望重塑HER2靶向治疗的整体策略. 值得关注的是, T-DXd的治疗潜力也正逐步延伸至HER2低表达甚至传统意义上的HER2阴性亚群[96]. 这一发现为拓展T-DXd治疗适应证提供了理论与临床依据. 表2展示了最新的T-DXd和RC48相关实验及数据.

此外，小分子药物与T-DXd联合方案的探索在HER2阳性胃癌中的应用也值得关注，包括增强子蛋白锌指同源物2(enhancer of zeste homolog 2, EZH2)抑制剂和聚腺苷二磷酸-核糖聚合酶(poly ADP-ribose polymerase, PARP)抑制剂. EZH2通过催化组蛋白H3K27三甲基化(H3K27me3)调控基因沉默，该基因的异常表达已被证实与多种实体肿瘤的发生和进展相关[100~102]. 一项旨在评价Valemetostat Tosylate联合DXd ADC治疗实体瘤受试者的Ib期、多中心、开放性研究指出，将EZH2抑制剂(如Valemetostat)与T-DXd和Dato-DXd联合用药可以有效降低肿瘤细胞的化疗抗性，进一步产生协同作用[103]. PARP是一种DNA修复酶，在DNA损伤修复和细胞凋亡中发挥重要作用[104~106]. 一项在晚期实体瘤评估AZD5305剂量递增单药治疗和与抗肿瘤联合治疗的I/IIa期研究则指出，PARP抑制剂与T-DXd联合用药可能表现出协同效应，进一步显著提升ADC的抗肿瘤作用[107,108].

深入来看，尽管T-DXd与RC48均属于靶向HER2的ADC范畴，但二者在构成学、药理学特性及临床定位上存在若干关键差异，这些差异决定了二者在不同HER2表达谱和治疗时点上的相对优势. 二者在构成学上的主要差异在于, T-DXd使用曲妥珠单抗作为抗体部分，将载药DXd接在抗体部分上[109~111]. DXd是一种TOP1抑制剂药物[112]，可以特异性抑制核内的拓扑异

表 2 **T-DXd和RC48系列研究及实验数据**

Table 2 Clinical trial data from the T-DXd and RC48 clinical research programs

研究名称	分期	研究设计	入组人群	主要终点	疗效数据	3级以上不良反应	文献
DESTINY-Gastric01	II	试验组: DS-8201 (6.4 mg kg^{-1}, q3w) 对照组: Irinotecan方案 (150 mg m^{-2} q2w)或Paclitaxel方案 (80 mg m^{-2} q4w)	HER2 IHC 3+或2+且ISH阳性 试验组: ITALICSTART*n*ITALI-CEND=187 对照组: *n*=62	ORR OS	ORR(43%)、OS(12.5个月)、PFS(5.6个月)、DOR(duration of response, 反应持续时间)(11.3个月)	中性粒细胞减少(51%)、贫血(38%)、白细胞减少(21%)、食欲下降(17%); 治疗相关死亡(肺炎)1例	[12]
DESTINY-Gastric02	II	T-DXd (6.4 mg kg^{-1} q3w)	一线含曲妥珠单抗方案治疗后进展且HER2 IHC3+或2+且ISH+ *n*=79	ORR	ORR(41.8%)、DCR (disease control rate, 疾病控制率)(81.0%)、DOR(8.1个月)、PFS(5.6个月)、OS(12.1个月)	总体(30.4%), 贫血(13.9%), 恶心(7.6%), 中性粒细胞计数减少(7.6%), 白细胞计数减少(6.3%); 药物相关死亡2例	[94]
DESTINY-Gastric04	III	A组: 曲妥珠单抗 (6.4 mg kg^{-1} q3w) B组: 雷莫芦单抗 (8 mg kg^{-1} q4w)+PTX (80 mg m^{-2} q4w)	一线含曲妥珠单抗方案治疗后进展且HER2 IHC3+或2+且ISH+ *n*=494	OS、PFS、ORR、DOR、DCR	A组: OS(14.7个月), PFS(6.7个月), ORR (44.3%) B组: OS(11.4个月), PFS(5.6个月), ORR (29.1%)	A组: 总体(50.0%), 中性粒细胞减少(28.7%), 贫血(13.9%) B组: 总体(54.1%), 中性粒细胞减少(35.6%), 贫血(13.7%)	[97]
DESTINY-Gastric06	II	T-DXd (6.4 mg kg^{-1} q3w)	在晚期/转移性疾病阶段接受过至少两种前期治疗方案后出现进展且HER2 IHC3+或2+且ISH+ *n*=126	ORR、PFS、OS、DOR、DCR	ORR(28.8%), PFS(5.7个月), OS(11.1个月), DOR(6.7个月), DCR (79.5%)	总体(74.7%) 中性粒细胞计数减少(22.1%) 贫血(28.4%) 治疗相关死亡2例	[98]
RC48-C005& RC48-C009	II/III	RC48 (2 mg kg^{-1} q2w)	至少一线进展, 均为转移性疾病且IHC 2+; ITALICSTART*n*ITALI-CEND=107	ORR、PFS、OS、DCR、DOR	ORR(50.5%), DOR (7.3个月), PFS(5.9个月), OS(14.2个月), DCR(82.2%)	总体(54.2%) 周围感觉神经病变(18.7%) 中性粒细胞减少(12.1%)	[99]
RC48-C008	II	RC48 (2.5 mg kg^{-1} q2w)	接受过至少二线治疗且至少IHC 2+, *n*=125	ORR、PFS、OS、DOR、DCR、TTP(Time to Progress, 疾病进展时间)	ORR(24.8%), DCR (42.4%), PFS(4.1个月), OS(7.9个月), DOR(4.7个月), TTP (4.2个月)	与RC48相关总体(32.0%), 中性粒细胞技术下降(14.4%), 白细胞计数下降(14.4%), 严重不良事件(36.0%)	[11]
RC48-C013	I	水平1: RC48(2.0 mg kg^{-1})+特瑞普利单抗 (3 mg kg^{-1} q2w) 水平2: RC48(2.5 mg kg^{-1})+特瑞普利单抗 (3 mg kg^{-1} q2w)	至少一线进展且IHC≥1或ISH阳性; G/GEJ队列, *n*=28	安全性,确定RP2D、ORR、DOR、DCR、PFS、OS	G/GEJ队列、ORR (43%)、PFS(6.2个月)、OS(16.8个月)、DOR(5.1个月)	总体(59%), 中性粒细胞计数下降(23%), 白细胞计数下降(13%)	[85]

构酶I, 干扰肿瘤细胞的DNA复制以进一步抑制肿瘤细胞增殖[12,113]. RC48则将细胞毒药物单甲基澳瑞他汀E (monomethyl Auristatin E, MMAE)连接在抗体部分上[110], 有效载药部分MMAE可以特异性作用于细胞内的微管蛋白, 破坏细胞骨架, 阻碍肿瘤细胞的分裂和迁移[114,115]. 除了结构和作用机理上的区别以外, 二者在临床定位上的主要区别为: T-DXd凭借累积的随机对照数据与生存获益证据, 已逐步从三线上移至二线并成为标准选项之一; 而RC48以其对HER2低表达/异质性肿瘤的活性及在联合方案中的高反应率, 为那些HER2表达不足以满足传统"阳性"阈值但仍可能从ADC获益的患者提供了重要补充. 因此, 若两药在同一可选治疗时点可用, 临床决策应综合考虑患者的HER2表达强度与分布、既往治疗史与可用循证证据及各ADC的安全性谱与患者可耐受性等.

2.2 抗HER2 ADC的安全性研究

虽然ADC药物在胃癌治疗中展现出显著疗效, 但其临床应用仍面临多重挑战与局限性. 尤其是ADC药物的长期耐受性与安全性管理. 长期用药的耐受性是关键考量. 尽管多数不良反应(如血液学毒性、消化道反应)可通过剂量调整和支持治疗管理, 但T-DXd特有的间质性肺病(interstitial lung disease, ILD)风险仍需全程严密监测与干预, 增加了治疗复杂性. 药物设计的固有局限: ADC的疗效与毒性谱高度依赖于其抗体、连接子和载荷的设计. 不稳定的连接子可能导致载荷过早释放, 增加全身毒性; 而高效力载荷(如拓扑异构酶I抑制剂)在杀伤肿瘤的同时, 也可能对表达低水平靶抗原的正常组织(如肺)造成损伤, 这限制了其治疗窗口.

联合治疗的困境也亟需重视. 尽管ADC与免疫治疗等联合是克服耐药的方向, 但毒性叠加风险(如ILD与免疫性肺炎)可能限制其应用. 同时, ADC高昂的成本也影响了其在更广泛患者中的可及性. 未来需通过开发更稳定的连接子、探索新靶点与载荷, 以及优化联合策略, 在提升疗效的同时改善安全性. 表3整理了抗HER2 ADC药物相关的实验安全性数据.

2.3 HER2 双抗和小分子抑制剂

基于HER2阳性胃癌活跃的肿瘤微环境, 本研究团队提出的KN026联合KN046方案在国际上首次实现了同时靶向HER2与免疫检查点的无化疗治疗模式. 该方案通过双重阻断HER2胞外结构域(extracellular domain, ECD)2与4, 并联合抑制PD-1/PD-L1与CTLA-4通路, 从而增强抗肿瘤免疫应答. 在一项针对晚期HER2阳性非乳腺癌(包括胃癌)的Ib/II期联合分析中, ORR高达78.9%, 中位缓解持续时间(median duration of response, mDOR)13.4个月, 中位无进展生存期(median progression-free survival, mPFS)11.0个月, 显示出优异的疗效和可控的安全性[121].

与此同时, ZW25作为新一代基于Azymetric™平台的双特异性抗体, 也在HER2阳性实体瘤中展现出卓越活性. 该药物可同时结合HER2的两个非重叠表

表 3 抗HER2 ADC药物相关的实验安全性数据

Table 3 Experimental safety data related to anti-HER2 ADC drugs

用药方案	研究名称	人群	ILD/肺炎(任何级别)	≥G3 ILD	≥G3中性粒细胞减少	≥G3贫血	≥G3血小板减少	周围神经病变(任何级别)	备注要点	文献
T-DXd	DESTINY-Gastric01	HER 2+晚期G/GEJ	10.0%	2.4%	51%	38%	12%	<1%	ILD为决定性毒性; 血液学毒性最重	[116,117]
	DESTINY-Gastric02	HER 2+GC	≈ 12%~13%	≈ 2%	27%	13.9%	NA	NA	安全谱与DG01一致	[117]
	DESTINY-Gastric04	HER 2+GC, 二线	13.9%	0.8~1.0%	30%~32%	18%~20%	6%~8%	≈ 1%	降剂量→≥G3 ILD下降, 但ILD总发生率不变	[97]
RC48	回顾性研究	HER2+/HER2-low GC	<1%	≈ 0	12%~18%	7%~10%	<10%	60%~70%	PN为核心毒性	[118]
RC48+PD-1	NCT04280341&回顾性研究	GC联合治疗	<2%	NA	15%~20%	<10%	NA	≈ 50%	未见不可预期叠加毒性	[85,118]
ARX788	ACE-Gastric01	GC/实体瘤	NA	NA	<10%	<10%	NA	低频	以角膜毒性为特征	[119,120]

位，通过“双互补位结合”机制实现更强的HER2信号双重阻断，并促进受体的内吞和降解，从而增强抗HER2驱动的肿瘤抑制效应. ZW25-201研究结果显示，在确证HER2阳性的患者中，ORR高达84%，进一步验证了双特异性抗体在HER2靶向治疗中的潜在优势[122].

除了双抗以外，靶向HER2的小分子药物研发同样受到瞩目. 目前靶向HER2小分子抑制剂的相关研究众多, 而吡咯替尼是其中最为值得关注的药物之一. 吡咯替尼是一种第二代、不可逆的泛HER受体酪氨酸激酶抑制剂, 靶向表皮生长因子受体(epidermal growth factor receptor, EGFR)、HER2和HER4. 体外和动物实验显示，吡咯替尼可有效抑制HER2高表达肿瘤细胞的增殖和存活，其机制包括阻断HER2及下游PI3K/AKT和MAPK信号通路、增强内质网应激和自噬流，以及通过miR-16-5p/ZBTB16/G6PD轴促进蛋白质泛素化降解, 调控肿瘤代谢稳态并诱导细胞凋亡等[123~125]. 目前已有多项研究表明，在HER2阳性胃癌模型中，吡咯替尼呈现出良好的抗肿瘤作用. 此外, 吡咯替尼联合细胞周期蛋白依赖性激酶4/6抑制剂(cyclin dependent kinase 4/6, CDK4/6)用药可能带来额外抑瘤收益. 现有的一项队列研究表明，在胃癌患者中同时使用CDK4/6抑制剂联合吡咯替尼，总体ORR达到50%，总生存期(overall survival, OS)达到12.48个月，mPFS也提升至3.88个月，疗效较单一用药更为突出[126]. 但仅有少量临床证据并不足以直接认定吡咯替尼联合CDK4/6抑制剂具有更高的治疗收益, 尚需随机对照研究进一步验证.

针对吡咯替尼的临床早期探索性研究提示，吡咯替尼联合化疗方案在HER2阳性晚期胃癌中具有显著抗肿瘤活性[127]. 一项多中心Ib/II期研究表明, 吡咯替尼联合卡瑞利珠单抗及CapeOX方案一线治疗HER2阳性晚期胃/胃食管结合部腺癌, ORR达到77.8%, 且安全性可控[128]. 此外，在EGFR高拷贝数胃癌中，吡咯替尼可通过促进EGFR与内质网伴侣蛋白GRP78的结合，诱导内质网应激介导的细胞凋亡，这揭示了其在特定亚群中的深层作用机制[129]. 然而，耐药仍是治疗中的关键挑战. 相关基础研究显示, 获得性吡咯替尼耐药与SCF/c-kit信号通路及其下游PI3K/AKT和MAPK通路的激活相关. 抗血管生成TKI类药物阿帕替尼(Apatinib)可通过抑制该通路, 在临床前模型中有效逆转耐药, 并与吡咯替尼产生协同抗肿瘤作用[81]，为临床耐药逆转提供了潜在联合策略. 进一步的机制研究阐明了吡咯替尼区别于可逆抑制剂的独特分子行为：它能促使HSP90分子伴侣从HER2上解离，进而诱导HER2泛素化并通过蛋白酶体途径降解. 更重要的是, 吡咯替尼可显著促进HER2受体内吞[130~132]. 这一特性为其与ADC的联合奠定了理论基础. 研究表明，吡咯替尼诱导的HER2内吞可大幅增强T-Dxd等ADC的细胞内化, 从而在体外及体内模型中显著提升其抗肿瘤活性，表现出明确的协同效应[130].

2.4 围手术期及转化治疗中HER2 靶向的前移探索

外科切除仍是局部进展期胃癌实现根治的重要手段. 然而，术后局部复发及远处转移风险较高，单纯手术难以满足长期控制需要，因此围手术期综合治疗已成为标准模式.

多项Ⅱ期研究显示，曲妥珠单抗或其联合方案作为新辅助治疗可显著提高病理完全缓解率(pathological complete response, pCR 9.6%~50%)及R0切除率(85.9%~100%)[133~141]. 例如, ML42058研究中曲妥珠单抗联合阿替利珠单抗及化疗的pCR率达38.1%，明显优于对照组[133]. 然而, 长期生存数据仍不足, 关于术后辅助阶段的HER2靶向治疗现有证据也相对有限. 2025版指南鼓励患者优先参与临床试验[138,142].

在转化治疗领域，HER2靶向联合化疗亦显示出可观潜力. Mitsui等人[143]报道曲妥珠单抗联合DCS方案在不可切除HER2高表达胃癌中ORR高达93.8%，超过半数患者成功完成R0切除. Arigami等人[144]研究同样发现，接受转化手术的患者五年生存率显著高于单纯化疗组(68.6% *vs*. 5.6%). 尽管这些结果令人鼓舞, 转化治疗在HER2高表达胃癌中的应用仍处于探索阶段，仍需通过多中心前瞻性研究加以确认.

2.5 靶向HER2 治疗未来发展前瞻

近年来，靶向HER2治疗取得飞速发展，相关作用机制不断被探明, 临床治疗手段也在不断拓新. 但仍面临着诸如耐药性、肿瘤异质性等诸多问题. 未来靶向HER2的治疗亟需更多研究.

HER2靶向治疗的耐药性已经成为胃癌治疗中的一个难点. 具体的耐药机制不仅涉及广泛的信号通路逃逸与肿瘤微环境改变，也包括由特定基因突变(如HER2 exon20插入突变)驱动的结构性耐药[145]. 相关研究指出，肿瘤细胞针对HER2的耐药性主要源于以下几方面相互作用：HER2受体自身的基因突变(如S310F、

V777L)可导致构象改变，直接妨碍曲妥珠单抗等药物结合；下游PI3K/AKT/mTOR通路因PTEN缺失或PIK3CA突变等因素持续活化，同时EGFR、MET、HER3等其他受体酪氨酸激酶可代偿性激活，通过异源二聚体维持生存信号[145,146]；肿瘤微环境中免疫抑制性细胞浸润及相关细胞因子分泌，也会削弱ADCC效应等细胞毒性作用，导致治疗反应下降. 其中，HER2 exon20插入突变作为一种特殊的结构性耐药机制，与常见的基因扩增有本质区别. 该突变在激酶结构域内插入氨基酸序列，重塑ATP结合口袋，导致HER2处于组成性激活状态，且使拉帕替尼等传统酪氨酸激酶抑制剂难以结合，曲妥珠单抗亦难以有效阻断其持续激活的下游信号[147~149].

面对上述耐药性挑战，当前临床治疗策略正向更精准更强效的方向发展. ADC药物如T-DXd通过靶向递送细胞毒药物并发挥"旁观者效应"[4]，能克服信号通路依赖并可杀伤异质性肿瘤细胞，其在后线治疗中已显示出显著疗效，并在向新辅助和HER2低表达患者治疗探索[94~96]. 此外，ADC与不可逆TKI类药物(如吡咯替尼)的联合在临床前研究中也已有报道展现出协同效应[81,130]，而针对exon20插入突变设计的新型高选择性TKI类药物(如波齐替尼、莫博赛替尼等)[150~152]等药物也正在探索中.

标准的靶向HER2一线治疗基于ToGA试验，曲妥珠单抗联合化疗是HER2阳性晚期胃癌的一线标准方案，能将OS从11.1个月延长至13.8个月，但超过90%的患者在1年内会出现PD[3]. 为进一步提高疗效，临床上常将HER2靶向药物与其他药物联合使用.

联合免疫治疗KEYNOTE-811试验已经证明，在标准靶向化疗基础上加入帕博利珠单抗可显著提升ORR至74.4%[62]，此外，该研究队列的PFS在PD-L1 CPS≥1患者中达10.9个月，这证实了免疫联合对特定人群的增效作用[153]. 新型双抗如KN026(靶向HER2两个表位)在经治患者中显示出前景；而"双抗联合"策略，如KN026(HER2双抗)联合KN046(PD-L1/CTLA-4双抗)，在早期试验中ORR达56%，代表了靶向与免疫协同的新模式[121]. 除了上面提到的联合方案以外，为克服由肿瘤微环境介导的耐药，包括联合抗血管生成药(如贝伐珠单抗[Bevacizumab])以改善微环境、联合下游通路抑制剂(如PI3K或MEK抑制剂)以阻断代偿信号，以及联合靶向微环境中特定抑制细胞(如TAMs、CAFs)的调节剂等多种用药策略也已见诸临床试验[154~156].

人工智能(artificial intelligence，AI)对于检测结果分析、辅助患者诊疗和预后预测也已有诸多进展. 在疾病诊断方面，传统HER2 IHC检测虽然在识别HER2高表达病例方面表现可靠，但在区分HER2低表达与阴性病例时存在显著且不可接受的一致性缺陷. 一项研究发现，病理学家对HER2 IHC 0分病例的整体一致率仅25%，对1+病例的一致率则更低至不足1%[157]. AI技术通过客观、定量地分析病理图像，正成为解决这一难题的有效工具. 其主要从以下路径改善HER2检测的一致性与临床效用：首先，AI能对IHC图像进行精准量化，将主观评分转化为客观数据，展现出更高的汇总敏感度(0.97)和汇总特异度(0.82)[158]. 其次，为了突破IHC检测本身的流程与成本限制，已有研究开发出仅需常规苏木精-伊红(hematoxylin-eosin staining，HE)染色切片即可预测HER2状态的深度学习模型(如HER2-Net)[159]，这些模型在多中心外部验证中取得了高准确率(AUROC 0.9769)的结果，为HER2阳性的标准化初筛提供了新方案. 而针对IHC 2+(不确定)病例，这一AI模型还能进一步预测其FISH结果(阳性/阴性)[159]，但其敏感性仍有待提升.

在AI疗效预测方面，一支国内团队构建了一种多模态对齐与预测模型(multimodal alignment and prediction，MAP)，对4个中心共6991例乳腺癌患者的乳腺钼靶、超声及MRI等术前影像信息进行分析发现，与传统穿刺活检相比，MAP模型预测的HER2状态与术后标本结果具有更高一致性，并在新辅助治疗人群中表现出更优的疗效预测能力[160]. 表明多模态影像驱动的AI模型有潜力突破活检取样局限，为HER2精准分型及个体化治疗决策提供新的技术路径. 而本团队构建的跨模态MuMo(multimodal molecular)模型，精准预测HER2阳性胃癌患者对抗HER2治疗的疗效反应[161]. 该模型整合HER2基因扩增/表达、分子病理特征、影像学特征等多模态信息，从而突破了传统HER2单指标检测(IHC/FISH)在疗效预测方面的局限. 研究表明，MuMo在预测曲妥珠单抗等抗HER2治疗的临床获益方面明显优于现有指标[161].

3 总结

总体而言，HER2靶向治疗的迅速发展为胃癌精准治疗开辟了新的路径. 从最初的曲妥珠单抗联合化疗，到免疫联合，HER2-ADC的广泛应用，再到双特异性抗体、小分子抑制剂等联合策略的探索，HER2相关研究正推动胃癌治疗模式向分层精准治疗转变. 2025年中

国指南的发布标志着HER2检测与治疗体系的进一步规范化，也反映出中国在该领域的临床实践与循证研究已逐步与国际接轨. 未来, 随着分子分型、液体活检及实时监测技术的不断完善，HER2靶向治疗将更加精准地覆盖从高表达到低表达人群. 通过多学科协作与临床研究的持续深入，有望进一步提高晚期胃癌患者的长期生存率，并推动胃癌治疗全面进入分子精准与个体化的新阶段.

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Summary for “胃癌抗HER2靶向治疗进展与展望”

Progress and prospects in anti-HER2 targeted therapy for gastric cancer

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Human epidermal growth factor receptor 2 (HER2) was among the earliest molecular targets to be identified and clinically validated in gastric cancer, and it has remained one of the most influential biomarkers guiding therapeutic decision-making in this disease. HER2 status was defined using a binary classification system, categorizing tumors as either HER2-positive (immunohistochemistry [IHC] 3+ or IHC 2+ with confirmed fluorescence *in situ* hybridization [FISH] amplification) or HER2-negative. The pivotal introduction of trastuzumab in combination with cytotoxic chemotherapy as first-line treatment marked a transformative milestone in the management of advanced HER2-positive gastric cancer, establishing the foundation of HER2-directed therapy and significantly improving clinical outcomes. More recently, advances in the understanding of the gastric cancer immune microenvironment have catalyzed the development of rational combination strategies, while the exploration of novel first-line modalities—including next-generation HER2-directed bispecific antibodies—has become an area of intense clinical investigation.

As trastuzumab is increasingly incorporated into neoadjuvant and perioperative treatment paradigms, new challenges have emerged regarding the optimal sequencing of therapies in the first-line and subsequent treatment settings for HER2-positive disease. In this evolving landscape, it has become clear that the therapeutic relevance of HER2 extends beyond tumors with high-level overexpression or amplification. The advent of antibody–drug conjugate (ADC) technology has fundamentally expanded the spectrum of patients who may benefit from HER2-targeted approaches. In particular, the domestically developed HER2-ADC disitamab vedotin (RC48) has demonstrated clinically meaningful antitumor activity in tumors with low to intermediate HER2 expression, a population historically considered ineligible for HER2-directed therapy. For example, RC48 in combination with the PD-1 inhibitor toripalimab achieved an objective response rate (ORR) of 43% in this subgroup, highlighting the capacity of ADCs to overcome limitations associated with heterogeneous or low-level target expression. In parallel, combination regimens integrating HER2 blockade with anti-angiogenic therapy have shown encouraging results; notably, a triplet regimen comprising trastuzumab, ramucirumab, and paclitaxel reported improvements in both progression-free survival (median PFS 7.1 months) and overall survival (median OS 13.6 months). Collectively, these data provided a critical evidentiary basis for the adoption of a refined four-tier HER2 classification system in the 2025 Chinese Society of Clinical Oncology (CSCO) guidelines, thereby broadening eligibility for HER2-directed interventions and facilitating more precise therapeutic stratification.

Although HER2-targeted ADCs are currently approved primarily for use in the second-and third-line settings, their integration into first-line therapy is actively being explored through combinations with immune checkpoint inhibitors, anti-angiogenic agents, and conventional chemotherapy. At the same time, the development of small-molecule HER2-targeted agents, such as pyrotinib, continues to progress, offering alternative mechanisms of HER2 inhibition and additional flexibility in treatment sequencing. As the therapeutic armamentarium rapidly expands, careful attention to safety and tolerability is increasingly important, particularly in light of the distinct toxicity profiles associated with ADCs and multidrug combination regimens.

In conclusion, the treatment paradigm for HER2-positive gastric cancer is undergoing a profound transformation. The transition from a binary HER2 classification framework to a more nuanced stratification system, together with the rapid evolution of HER2-targeted therapies—including ADCs, bispecific antibodies, and innovative combination strategies—is reshaping the practice of precision oncology in gastric cancer. This review systematically summarizes the updated HER2 classification criteria and recent advances in HER2-directed treatment, with the aim of informing optimal clinical decision-making and guiding future research toward improved outcomes across a broader patient population.

gastric cancer, HER2, antibody–drug conjugates, immunotherapy combinations, precision therapy

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