·综　述·

抗体偶联药物用于乳腺癌治疗的耐药机制研究进展

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［摘　要］ 抗体偶联药物（antibody-drug conjugate，ADC）作为一类创新疗法，在乳腺癌治疗中展现出显著效果。ADC由单克隆抗体、连接子、细胞毒性有效载荷偶联而成，综合了抗体的高特异性靶向能力和细胞毒性药物的高效杀伤力。然而，随着ADC在临床的广泛应用，乳腺癌患者中ADC的耐药性问题逐渐显露。文章概述ADC在乳腺癌领域的应用现状，并将ADC耐药机制归类为：靶抗原-抗体结合不足、ADC药物内化和转运途径受损、溶酶体功能受损、载荷释放异常、肿瘤对载荷缺乏敏感性以及细胞周期蛋白缺陷等。并且进一步汇总目前为克服ADC耐药性而研发的应对策略，包括ADC与其他药物（如化疗药物、靶向药物和免疫检查点抑制剂等药物）联合应用方案以及新型药物研发的进展，以求为ADC耐药的乳腺癌患者的治疗提供参考选择。

［关键词］ 乳腺癌；抗体偶联药物；耐药机制

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Advances in the drug resistance mechanism of antibody-drug conjugates in breast cancer

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［**Abstract**］ Antibody-drug conjugates（ADC），as a class of innovative therapies，have shown significant activity in breast cancer. ADCs are conjugated from monoclonal antibodies，linkers and cytotoxic payloads，which harnesses the highly specific targeting capabilities of antibodies along with the potent cancer killing effects of the cytotoxic drugs，demonstrating significant efficacy in the treatment of breast cancer. Nonetheless，as ADCs have been widely used in clinical practice，resistance to ADCs has been observed in breast cancer patients. In this review，we summarized ADCs' current applications in the treatment of breast cancer and classified the mechanisms underlying ADC resistance into several distinct categories as follows：inadequate antigen-antibody binding，impaired internalization and trafficking pathways of ADCs，defective lysosomal function，aberrant payload release，tumor insensitivity to the payloads，and cyclin deficiency. Furthermore，we summarized the contemporary strategies designed to address ADC resistance，such as the combined use of ADCs with other therapeutic agents，including chemotherapeutic agents，targeted therapies，and immune checkpoint inhibitors，as well as the development of new drugs. This review aims to offer reference options for the treatment of patients with ADC-resistant breast cancer.

［**Key words**］ breast cancer；antibody-drug conjugate；resistance mechanism

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乳腺癌是女性最常见的癌症之一，国际癌症研究中心发布的2022年全球癌症统计报告显示，其发病率和病死率均居全球女性肿瘤第1位[1]。化疗和内分泌治疗是乳腺癌治疗的基石，但是随着新技术和新药物的不断研发，靶向治疗、免疫治疗和抗体偶联药物（antibody-drug conjugate，ADC）在乳腺癌领域也得到广泛应用[2-4]。ADC通过化学连接子实现单克隆抗体与细胞毒性药物之间的偶联，其兼顾高特异性靶向能力和强效杀伤作用，成为当下乳腺癌治疗领域的热点。ADC中的抗体成分识别肿瘤

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细胞表面抗原，并与其特异性结合。形成的抗原抗体复合物经内吞和胞饮作用进入肿瘤细胞内，被胞内溶酶体吞噬。溶酶体蛋白酶裂解ADC，将载荷以活性形式释放进入胞质，从而诱导肿瘤细胞死亡[5]。具有可裂解连接子的ADC裂解后的载荷不包含连接子，透膜性高，可以同时在邻近肿瘤细胞发挥抗肿瘤活性，即“旁观者效应”，从而进一步提升药物疗效[6]。大量临床研究证明ADC显著改善乳腺癌患者生存获益及生活质量，但随着ADC应用的普及，其原发或继发性耐药问题逐渐显露。文章主要结合国内外最新研究进展，探讨ADC的耐药机制以及逆转耐药方案。

1 ADC在乳腺癌中的应用现状

靶向人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）的ADC主要包括：恩美曲妥珠单抗（trastuzumab emtansine，T-DM1）、德曲妥珠单抗（trastuzumab deruxtecan，T-DXd）、维迪西妥单抗（disitamab vedotin，RC48）、曲妥珠单抗-多卡马嗪（trastuzumab duocarmazine，SYD985）、MRG002、ARX788、A166、FS-1502、DP303c[7]。2013年T-DM1基于EMILIA试验结果，获得美国食品药品监督管理局（Food and Drug Administration，FDA）批准用于既往接受过曲妥珠单抗和紫杉烷治疗的HER2阳性晚期乳腺癌（advanced breast cancer，ABC）患者[8]。2019年KATHERINE试验阳性结果进一步拓展T-DM1适应证，FDA批准其用于新辅助紫杉类和曲妥珠单抗治疗后残留侵袭性疾病的HER2阳性早期乳腺癌患者的辅助治疗[9]。基于DESTINY-Breast01的结果，2019年T-DXd获FDA批准用于HER2阳性转移性乳腺癌（metastatic breast cancer，mBC）的后线治疗[10]。DESTINY-Breast03研究首次将T-DXd与T-DM1进行头对头比较，在初次分析中，相比T-DM1，T-DXd降低患者疾病进展或死亡风险达72%，风险比（hazards ratio，HR）为0.28，95%置信区间（confidence interval，CI）为0.22~0.37[11]，在2022年获FDA批准用于HER2阳性mBC患者的二线治疗。同年，DESTINY-Breast04提出HER2低表达概念，T-DXd进一步拓展适应证，获批用于HER2低表达ABC患者的治疗[12]。

目前主要靶向滋养层细胞表面抗原2（trophoblast cell surface antigen 2，Trop-2）的ADC主要包括戈沙妥珠单抗（sacituzumab govitecan，SG）、德达博妥单抗（datopotamab deruxtecan，Dato-DXd）、芦康沙妥珠单抗（sacituzumab tirumotecan，SKB264）、ESG-401、JS-108、FDA018[7]。在Ⅲ期ASCENT研究中，SG相对于标准化疗，患者中位总生存期（median overall survival，mOS）分别为12.1个月 *vs* 6.7个月（HR=0.48，95%CI：0.38~0.59，$P<0.001$）[13]，体现出更好的疗效。基于此，2021年SG获FDA批准用于既往接受过至少2种系统治疗（晚期阶段至少接受过1次化疗）的不可切除的局部晚期乳腺癌（locally advanced breast cancer，LABC）/转移性三阴乳腺癌（metastatic triple-negative breast cancer，mTNBC）患者。TROPiCS-02研究中，100%的患者既往接受过细胞周期蛋白依赖性激酶（cyclin dependent kinase，CDK）4/6抑制剂，SG组相比化疗组，无进展生存期（progression-free survial，PFS）显著延长（5.5个月 *vs*. 4.0个月，HR=0.66，P=0.000 3），两组mOS分别为14.4个月和11.2个月（HR=0.79，95%CI：0.65~0.96，P=0.020）[14]。基于该研究，2023年FDA批准SG用于既往接受过内分泌治疗且至少接受过2线系统治疗的激素受体（hormone receptor，HR）阳性、HER2阴性mBC患者的二线治疗。TROPION-Breast01目前公布的主要研究结果显示，在既往接受过1~2线化疗的mBC患者中，Dato-DXd组中位PFS（mPFS）较化疗组延长（6.9个月 *vs*. 4.9个月，HR=0.63，95%CI：0.52~0.76）[15]，Dato-DXd有望成为HR阳性/HER2阴性ABC的后线治疗选择。单臂Ⅰ/Ⅱ期篮式研究KL264-01，纳入41例多线经治的HR阳性/HER2阴性mBC患者，纳入的乳腺癌患者总客观缓解率（objective response rate，ORR）为36.8%，mPFS为11.1个月（95%CI：5.4~13.1）[16]，显示出SKB264在多线治疗的HR阳性/HER2阴性mBC患者中的巨大潜力。除上述靶点外，针对HER3、B7-H4、Claudin-18.2、LIV-1等靶点的新型ADC也在不断创新[7]。在乳腺癌领域获FDA批准的ADC见表1。

2 ADC耐药机制

2.1 靶抗原-抗体结合的不足

在临床前模型中，Loganzo等[17]在T-DM1耐药的肿瘤细胞表面发现HER2表达水平降低，恢复HER2的表达可逆转该细胞系对T-DM1的耐药性，这表明，HER2表达缺失是靶向HER2 ADC产生耐药性的原因之一。DAISY研究评估T-DXd在不同HER2表达的mBC患者二线及后线治疗的疗效，20例耐药患者中有13例（65%）出现HER2水平表达下降[18]。Coates等[19]对3例SG耐药的mTNBC患者肿

表1 乳腺癌领域获FDA批准的ADC

Table 1 The FDA-approved ADC in breast cancer

ADC	Target	Indication	Efficacy
T-DM1	HER2	2013：T-DM1 received FDA approval for the second-line treatment in patients with HER2-positive advanced breast cancer who have previously received trastuzumab and a taxane，separately or in combination	EMILIA trial（*n*=991）：mPFS in T-DM1 group versus lapatinib plus capecitabine group were 9.6 months *vs.* 6.4 months，respectively（HR=0.65，95% CI：0.55-0.77，*P* < 0.001）At the second interim analysis，mOS for both groups was 30.9 months *vs.* 25.1 months（HR=0.68，95%CI：0.55-0.85，*P* < 0.001）
		2019：the FDA approved T-DM1 for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane- and trastuzumab- based treatment	KATHERINE trial（*n*=1 486）：a median follow-up of 41 months，the 3-year iDFS was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group（HR=0.5，*P* < 0.000 1）
T-DXd	HER2	2019：the FDA granted accelerated approval to T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting	DESTINY-Breast01 trial（*n*=184）：ORR reached 60.9%；DCR and CBR were 97.3% and 76.1%，respectively；mDOR and mPFS were 14.8 months and 16.4 months，respectively
		2022：the FDA approved T-DXd for adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting，or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy	DESTINY-Breast03 trial（*n*=524）：the mPFS was 28.8 months with T-DXd and 6.8 months with T-DM1（HR=0.33，95%CI：0.26-0.43，*P* < 0.000 1）. T-DXd significantly prolonged OS and reduced the risk of death by 36%
		2022：the FDA approved T-DXd for the treatment of patients with unresectable/metastatic HER2-low expression breast cancer（patients who have received chemotherapy at the metastatic stage or relapse during adjuvant chemotherapy/within 6 months of completion of treatment）	DESTINY-Breast04 trial（*n*=557）：among all patients，the mPFS was 9.9 months in the T-DXd group and 5.1 months in the physician's choice group（HR=0.5，95% CI：0.40-0.63，*P* < 0.001）；mOS was 23.4 months and 16.8 months，respectively（HR=0.64，95%CI：0.49-0.84，*P*=0.001）
SG	Trop-2	2021：the FDA granted regular approval to sacituzumab govitecan for patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies，at least one of them for metastatic disease	ASCENT trial（*n*=529）：the mPFS was 5.6 months with sacituzumab govitecan and 1.7 months with chemotherapy（HR=0.41，95%CI：0.32-0.52，*P* < 0.001）. The mOS was 12.1 months with sacituzumab govitecan and 6.7 months with chemotherapy（HR=0.48，95%CI：0.38-0.59，*P* < 0.001）
		2023：the FDA approved sacituzumab govitecan for patients with unresectable locally advanced or metastatic hormone receptor-positive，HER2-negative（IHC 0，IHC 1+or IHC 2+/ISH-）breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting	TROPiCS-02 trial（*n*=543）：treatment with sacituzumab govitecan had significantly longer mPFS than chemotherapy（5.5 months *vs.* 4.0 months，HR=0.66，*P*=0.000 3）；mOS：14.4 months *vs.* 11.2 months（HR=0.79，95%CI：0.65-0.96，*P*=0.020）

CBR：clinical benefit rate；CI：confidence interval；DCR：disease control rate；HER2：human epidermal growth factor receptor-2；HR：hazards ratio；iDFS：invasive disease free survival；mDOR：median duration of response；mOS：mean overall survival；mPFS：median progression-free survival；ORR：objective response rate；IHC：immunohistochemistry；ISH：*in situ* hybrization.

瘤组织进行检测，发现原发耐药患者组织中基本检测不到TROP2表达。而继发耐药患者中存在TROP2 T256R突变，相比野生型，突变型肿瘤细胞的TROP2蛋白在细胞膜的表达减少，大量定位于细胞质中，与SG结合能力减弱，降幅超过80%。

2.2 ADC内化和转运至溶酶体途径受损

抗体与靶抗原结合后被内吞到细胞中，内吞作用可以通过不同的内化途径发生，根据是否需要网格蛋白的参与分为网格蛋白介导的内吞和网格蛋白非依赖性内吞，后者包括小窝蛋白介导的内吞作用、网格蛋白独立载体/糖基磷脂酰肌醇锚定蛋白富集的早期内吞区室的内吞途径和巨胞饮作用[20]。内皮素A2（endophilin A2，Endo Ⅱ）是一种支架蛋白（由SH3GL1编码），介导一种独特的、不依赖网格蛋白的胞吞途径，称为快速内啡肽介导的内吞作用。当Endo Ⅱ过表达时，配体诱导的内吞作用增加。而研究者敲低肿瘤细胞中SH3GL1表达后，同样发现T-DM1对肿瘤细胞的治疗效果受抑制[21]。抗原抗体复合物被内吞进入肿瘤细胞后，内吞再循环过快会导致转运至溶酶体中的ADC数量减少。在T-DM1获得性耐药临床前模型中，研究者观察到与囊泡鸟苷三磷酸酶活性和肌动蛋白动力学相关的蛋白质表达上调，导致T-DM1的载荷在肿瘤细胞中释放减少，这可能导致耐药性的产生[17]。

2.3 溶酶体功能障碍

含可裂解连接子ADC可以在酸性条件如肿瘤微环境中裂解而释放载荷，但含有不可裂解连接子的ADC需要在溶酶体蛋白水解酶作用下裂解。液泡型质子转移ATP酶（vacuolar H^+-adenosine 5'-triphosphatease，V-ATPase）是一种存在于溶酶体膜上的质子泵，可调节溶酶体内pH值，V-ATP酶抑制剂可导致溶酶体pH值升高，使蛋白水解酶活性受损，从而阻碍T-DM1在溶酶体中的裂解[22]。溶质载体（solute carrier，SLC）属于膜转运蛋白超家族，参与多种分子跨膜转运。SLC46A3是一种溶酶体膜蛋白，可将T-DM1的代谢产物Lys-SMCC-DM1从溶酶体中转运到细胞质。研究者在临床前模型中观察到SLC46A3抑制剂可以减弱T-DM1的细胞毒性作用[23]。SLC46A3表达缺失是对携带DM1的ADC产生原发和获得性耐药的机制之一，恢复SLC46A3表达后，耐药细胞系对药物治疗的敏感性得以恢复[24]。

2.4 载荷释放异常以及肿瘤对载荷缺乏敏感性

2.4.1 药物外排泵

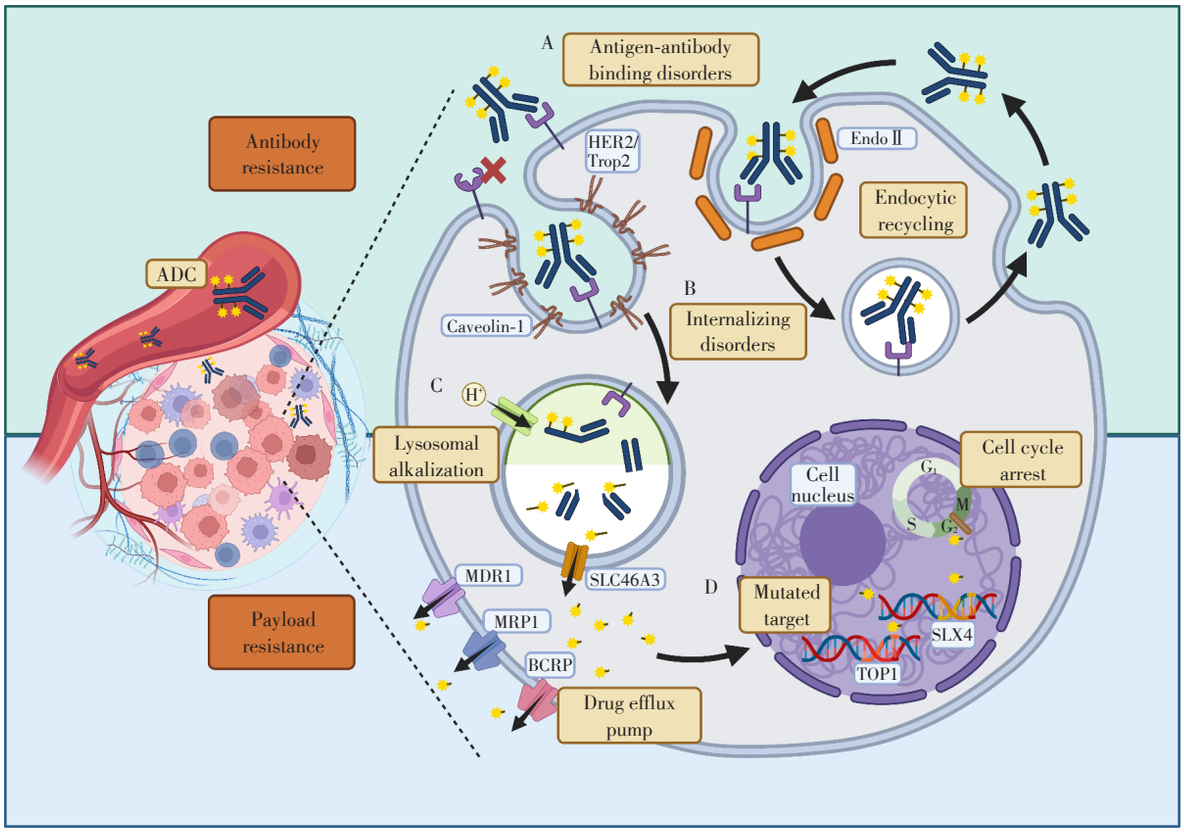
细胞毒性载荷是ADC药物发挥抗肿瘤活性的主要成分，而ATP结合盒转运蛋白，包括P-糖蛋白或称多重耐药蛋白-1（multidrug resistance protein 1，MDR1）、多药耐药相关蛋白1（multidrug-resistance-associated protein 1，MRP1）和乳腺癌耐药蛋白（breast cancer resistance protein，BCRP），可以利用ATP水解产生能量将细胞质中的载荷泵出肿瘤细胞，导致肿瘤对化疗药物的多重耐药性[25]。在不同T-DM1耐药细胞系中观察到MDR1、MRP1的过表达，且使用MDR1、MRP1抑制剂可恢复细胞对ADC的敏感性[17,26-27]。SG的载荷是拓扑异构酶1（topoisomerase 1，TOP1）抑制剂伊立替康的活性代谢产物SN38，是BCRP的转运底物之一。在SG耐药的乳腺癌细胞系中，研究者观察到BCRP（由ABCG2基因编码）的过表达，使用ABCG2的抑制剂有助于克服对SG的耐药性[28]。

2.4.2 载荷作用靶点相关突变

肿瘤细胞可以通过载荷作用靶点的突变而获得ADC抗性。既往研究发现SG耐药患者组织样本构建的模型中存在TOP1 E418K突变，TOP1突变可导致SG的载荷SN38失去作用位点而产生耐药性[19]。除载荷作用靶点突变外，载荷诱导细胞凋亡过程中，其他相关蛋白突变同样会导致细胞耐药性的产生。DAISY试验的生物标志物分析中，14%的T-DXd耐药组织样本出现肿瘤抑制蛋白SLX4突变，该突变在治疗前样本中、癌症基因组图谱乳腺癌数据库中检测的突变率分别为3%和1.5%。T-DXd载荷属于TOP1抑制剂，可以阻断脱氧核糖核酸（deoxyribonucleic acid，DNA）复制和转录，从而诱导肿瘤细胞凋亡。SLX4在DNA交联的修复、重组中间体的分离过程中发挥重要作用。研究者发现，敲除乳腺癌细胞中的SLX4基因后，肿瘤细胞抑制率为80%所需的DXd浓度分别增加了20倍和5倍，该突变可能诱导T-DXd的继发性耐药，但涉及的具体分子机制以及该突变是否能作为生物标志物指导临床用药仍需进一步验证[18]。

2.4.3 细胞周期蛋白缺陷介导获得性耐药

Cyclin B1/CDK1复合物参与细胞周期G2-M期转变，能够促进有丝分裂过程中的染色体聚集和纺锤体的形成，确保染色体的准确分离[29]。T-DM1的载荷是美登素类毒素的衍生物DM1，可抑制微管蛋白聚合从而诱导M期有丝分裂停滞及细胞凋亡[30]。临床前研究发现，在大多数（12/18，66.6%）T-DM1敏感的HER2阳性人乳腺癌外植体中，T-DM1诱导cyclin B1表达增加，而耐药细胞中并未观察到此现象。通过敲低亲本细胞中的cyclin B1可以诱导T-DM1耐药性，而增加耐药细胞中cyclin B1的水平使部分细胞系恢复对T-DM1的敏感性[31]。ADC的耐药机制总结见图1。



A: Inadequate antigen-antibody binding: the decreased antigen expression and the diminished binding affinity of antibody to antigen. B: The impaired cell internalization pathways and transport efficiency of ADC: defective endocytosis of the antigen-antibody complex and rapid recycling of endocytosed ADC, resulting in a decrease in the number of ADC transported to the lysosomes. C: Lysosomal dysfunction: the elevated lysosomal pH resulting in the impaired function of proteolytic enzymes, and the reduced expression of lysosomal membrane proteins obstructing the transfer of payloads to the cytoplasm. D: Abnormal release of payloads and lack of insensitivity to payloads: efflux pumps expel the payloads from the cytoplasm of tumor cells and mutations in proteins associated with sites of action resulting in resistance to ADC, and deficiencies of cyclin expression inducing acquired resistance.

图1 ADC的耐药机制

Figure 1 Mechanisms of ADC resistance

3 ADC耐药的应对策略

目前，为应对ADC药物耐药情况，ADC药物联合应用策略[化疗药物、抗HER2靶向药物和免疫检查点抑制剂(immune checkpoint inhibitor，ICI)]、新药研发成为重中之重。

3.1 联合策略

3.1.1 联合化疗

化疗可能与ADC具有协同作用，导致细胞周期停滞，抑制DNA修复，或导致肿瘤表面抗原上调。一项Ⅰb/Ⅱa期临床试验，探讨T-DM1联合多西他赛加或不加帕妥珠单抗对LABC或mBC的有效性及毒性，联合疗法在两种适应证中均取得了不错的疗效，mBC患者中ORR达80%，60%的LABC患者达病理完全缓解(pathological complete response，pCR)[32]。一项Ⅰb/Ⅱa期研究评估了T-DM1联合紫杉醇加或不加帕妥珠单抗治疗HER2阳性mBC的安全性/耐受性，42例患者的ORR为50.0%，临床获益率(clinical benefit rate，CBR)为56.8%[33]。在两项研究中，一半以上患者因发生不良反应事件(adverse event，AE)需要减少剂量或停止使用紫杉烷。考虑到ADC本质上是化疗，因此在设计组合策略时不仅需考虑ADC载荷和联合的化疗药物之间的协同作用，同样要关注到药物组合对相同系统AE的叠加效果[34]。

3.1.2 联合靶向药物

帕妥珠单抗是一种靶向HER2细胞外结构域的大分子单克隆抗体，可有效抑制HER2与其他HER家族成员形成二聚体，从而抑制HER2介导的信号通路的激活。研究者对T-DM1和帕妥珠单抗联合方案相关的临床研究进行汇总分析发现，相比T-DM1±紫杉烷，T-DM1±紫杉烷联合帕妥珠单抗未见明显疗效优势[35]。DESTINY-Breast07研究旨

在探索T-DXd单药或与其他抗肿瘤药物联合用于既往未经治疗的HER2阳性mBC的疗效及安全性。在最新公布的剂量扩展中期分析中，T-DXd联合帕妥珠单抗组ORR优于T-DXd单药组（84.0% *vs*. 76.0%），证明了T-DXd、帕妥珠单抗联合方案的治疗潜力，期待后续随访数据的公布[36]。

酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI）已被证明可调节表面抗原，促进ADC活性。拉帕替尼是一种与表皮生长因子受体（epidermal growth factor receptor，EGFR）/HER2可逆结合的双重TKI，可以促进HER2转录上调和减少细胞表面HER2蛋白的泛素化。拉帕替尼+T-DM1和化疗联合使用在早期和晚期HER2阳性乳腺癌中均产生了显著疗效。TEAL研究是一项随机、对照的Ⅱ期试验，评估标准紫杉醇、曲妥珠单抗和帕妥珠单抗（THP）新辅助方案与T-DM1、拉帕替尼和白蛋白紫杉醇（KLT）联合方案在HER2阳性乳腺癌患者中的疗效，KLT组和THP组中残余肿瘤负荷（residual cancer burder，RCB）为0或1的患者比例分别为100.0% *vs*. 62.5%（*P*=0.003 5）[37]。奈拉替尼是第2代TKI，与EGFR、HER2和HER4不可逆结合，可以刺激靶抗原-抗体内吞作用。两项研究探讨了T-DM1联合奈拉替尼治疗HER2阳性乳腺癌患者的疗效及安全性：Ⅱ期TBCRC022研究报告了该方案用于既往未经治疗的乳腺癌脑转移患者（breast cancer with brain metastasis，BCBM）（4A）、中枢神经系统（central nervous system，CNS）局部治疗后进展的BCBM［其中又分为既往未接受（4B）/接受过（4C）T-DM1治疗］的疗效，3组的CNS ORR分别为33.3%（队列4A）、35.3%（队列4B）和28.6%（队列4C），mOS分别为30.2个月（队列4A）、23.3个月（队列4B）和20.9个月（队列4C）[38]。Ⅰb/Ⅱ期的单臂NSABP FB-10研究中，该联合方案用于曲妥珠帕妥珠双靶治疗进展后的HER2阳性患者的ORR为32%（7/22）[39]。图卡替尼是一种选择性HER2抑制剂，Ⅲ期HER2 CLIMB-02结果表明，相比T-DM1加安慰剂组，T-DM1与图卡替尼的联合方案能够显著延长经过治疗的HER2阳性mBC的PFS（9.5个月*vs*.7.4个月），进展或死亡风险降低了24.1%（HR=0.759，95%CI：0.607~0.950，*P*=0.016 3）[40]。

3.1.3 联合免疫治疗

ADC和ICI具有协同作用。临床前模型中，联合T-DM1和程序性细胞死亡蛋白-1（programmed death protein 1，PD-1）抗体较单药更为有效。但是KATE2研究中，T-DM1加入阿替利珠单抗不改善PFS（mPFS为8.2个月 *vs*. 6.8个月，*P*=0.33），并与更严重的AE相关，但是在PD-L1表达阳性患者亚组中观察到可能的OS获益[41]。Ⅰb/Ⅱ期BEGONIA研究队列旨在评价度伐利尤单抗联合ADC用于不可切除的LABC/mTNBC一线治疗的疗效和安全性。Dato-DXd+度伐利尤单抗治疗组ORR为79%，mPFS为13.8个月[42-43]。SCI-IO研究比较了SG单药对比SG联合帕博利珠单抗在既往经过治疗的HR阳性/HER2阴性mBC中的疗效。结果显示，SG联合用药组和SG单药组的mPFS分别为8.12个月 *vs*. 6.22个月（HR=0.76，95%CI：0.47~1.23，*P*=0.26）。虽然联合用药组在mPFS上有所改善，但并未达到统计学意义[44]。因此，ADC联合ICI的协同治疗是否真正有增益效果还需更多临床研究来验证。

联合疗法相关临床研究见表2。

3.2 新药研发

目前Ⅲ期临床开发中的ADC主要分为两大类：第1类靶向新的抗原和/或采用不同作用机制的载荷；第2类利用已知的靶点和载荷组合，但对递送组件，如抗体、连接子、偶联方法等进行优化，以达到最优[45]。德帕瑞妥单抗（patritumab deruxtecan，U3-1402）靶向新靶点HER3，属于第1类，在不同亚型患者中表现出持久的抗肿瘤活性。U3-1402在HR阳性/HER2阴性、TNBC、HER2阳性患者中，ORR分别为30.1%、22.6%、42.9%[46]。SKB264与SG具有相同的靶点和相同作用机制的载荷，但其差异化2-甲磺酰嘧啶连接子提高了循环稳定性，属于第2类。一项在经治mTNBC中开展的Ⅱ期研究数据显示，SKB264的ORR为40%，≥3级AE发生率为56%。这优于SG在类似患者群体中报告的ORR（21%）和AE发生率（74%）[47]。临床前/临床早期阶段研究进一步提升ADC疗效及安全性的关键点包括：非内化ADC可以通过靶向肿瘤细胞外基质来实现药物的定向输送和释放。例如，PYX-201靶向肿瘤基质中的纤维连接蛋白，抗原抗体结合后，有效载荷就会被肿瘤基质中的组织蛋白酶B切割并扩散到相邻的肿瘤细胞膜和周围的肿瘤组织，实现“旁观者效应”。避免了潜在的低内化效率，同时大大扩展了肿瘤靶标的范围[48]。双特异性ADC、条件激活型抗体前药偶联物（probody-drug conjugate，PDC）等通过工程化改造抗体以改变其对抗原结合的亲和力，可以降低ADC对非靶向组织的毒性并增加肿瘤特异性暴露[49-50]。聚焦于载荷创新的下一代ADC包括蛋白

表2 联合治疗相关临床研究

Table 2 Clinical trials related to combination therapy

Drugs combined with ADC	Clinical trial	Efficacy	Safety
Chemotherapy drugs	Phase Ⅰb/Ⅱa(NCT00934856),T-DM1 + docetaxel ± pertuzumab for HER2 - positive LABC or mBC（*n*=98）：mBC（*n*=25），LABC（*n*=73）	The ORR in mBC patients（*n*=25）was 80.0%（20/25，95%CI：59.3%-93.2%）；the mPFS is 13.8 months（range 1.63-33.5 months） The pCR rate in LABC patients（*n*=73）was 60.3%（44/73，95% CI：48.1%-71.5%）	Neutropenia was the most common grade 3-4 AE（mBC，72%；LABC，29%）.48%（12/25）of patients with mBC and 47%（34/73）of patients with LABC experienced AE that required dose adjustment
	Phase Ⅰb/Ⅱa（NCT00951665),T-DM1 + paclitaxel ± pertuzumab for HER2 - positive mBC：phase Ⅰb（*n*=104），phase Ⅱa（*n*=60）	Among the 42 phase Ⅱa patients with measurable disease，the ORR was 50.0%（95% CI：34.6%-65.4%）；CBR was 56.8%（95% CI：41.6%-71.0%）	77.3% of patients experienced grade ⩾ 3 AE，the most common being neutropenia（25.0% and peripheral neuropathy（18.2%）
Targeted drugs	Phase Ⅰb/Ⅱ DESTINY-Breast07 trial（NCT04538742），T-DXd±pertuzumab for HER2-positive mBC first-line therapy：T-DXd monotherapy（*n*=75），T-DXd+pertuzumab（*n*=50）	The ORR of T - DXd was 77.3%（80% CI：70.0%- 83.6%）. The ORR of T - DXd + pertuzumab was 82.0%（80%CI：73.1%-88.8%）	Nausea was the most common AE in the T-DXd and T-DXd+ pertuzumab，with incidence rates of 70.7% and 68.0%，res-pectively The incidence of diarrhea was 34.7% and 60.0%，respectively
	Phase Ⅱ TEAL trial（NCT02073487），paclitaxel，trastuzumab，and pertuzumab（THP）and T-DM1，lapatinib，and nab - paclitaxel（KLT）；neoadjuvant therapy for HER2 -positive breast cancer（*n*=30）	The proportion of patients with RCB 0 or 1 in the KLT and THP groups was 100% *vs.* 62.5%，res - pectively（*P*=0.003 5） In the ER - positive subgroup，100% of patients in the KLT group achieved RCB 0-1 compared to 25% in the THP group（*P*=0.003 5）	Common adverse events in the KLT and THP groups included elevated liver function（64.3% *vs.* 56.3%），diarrhea（50.0% *vs.* 43.8%），and fatigue（42.9% *vs.* 50.0%）. There was no statistically significant difference in AE between treatment groups
	Phase Ⅱ TBCRC 022 trial（NCT01494662），T - DM1 + neratinib for cohort 4A - previously untreated BCBM，cohorts 4B and 4C-BCBM progressing after local CNS-directed therapy without（4B）and with（4C）prior exposure to T-DM1（*n*=44）：4A（*n*=6），4B（*n*=17），4C（*n*=21）	The CNS ORR in cohorts 4A，4B，and 4C was 33.3%（95%CI：4.3%-77.7%），35.3%（95% CI：14.2%-61.7%），and 28.6%（95%CI：11.3%-52.2%），respectively	Diarrhea was the most common grade 2（31.8%）and grade 3（22.7%）AE；grade 2 fatigue occurred in 12（27.3%）patients
	Phase Ⅰb/Ⅱ NSABP FB - 10 trial（NCT02236000），T - DM1 + neratinib for HER2 - positive metastatic breast cancer patients who progressed on treatment with trastuzumab + pertuzu - mab（*n*=49）：Ⅰb（*n*=27）；Ⅱ（*n*=22）	In phase Ⅰb，the ORR was 12/19（63%）. The ORR in phase Ⅱ was 7/22（32%），and the CBR was 45%（10/22）	Diarrhea was the most common grade 2（27%）and grade 3（36%）AE. Other grade 3/4 toxicities included thrombocytopenia（10%），elevated aminotransferase（15%）and pneumonia（5%）

（续表2）

Drugs combined with ADC	Clinical trial	Efficacy	Safety
	Phase Ⅲ HER2CLIMB-02 trial（NCT 03975647），T-DM1±tucatinib for patients with previously treated HER2-positive LABC/mBC（*n*=463）：the tucatinib arm（*n*=228）；the placebo arm（*n*=235）	Median PFS was 9.5 months *vs.* 7.4 months for the tucatinib and control arms，respectively，HR=0.759（95% CI：0.607−0.950，*P*=0.016 3）	The most common AE included nausea（65.4% in the tucatinib arm *vs.* 49.4% in the control arm），diarrhea（56.7% *vs.* 26.6%）and fatigue（48.9% *vs.* 37.3%） The most common grade ≥3 AE in the tucatinib arm was elevated alanine and aspartate aminotransferase
Immune checkpoint inhibitors	Phase Ⅱ KATE2 trial（NCT02924883），T-DM1±atezolizumab for previously treated，HER2-positive advanced breast cancer（*n*=202）：the atezolizumab arm（*n*=133）；the placebo arm（*n*=69）	Median PFS was 8.2 months（95% CI：5.8−10.7）for patients assigned atezolizumab versus 6.8 months（95% CI：4.0−11.1）for those assigned placebo（HR=0.82，95% CI：0.55−1.23；*P*=0.33）	The most common grade ≥3 AE was thrombocytopenia（13% in the atezolizumab arm and 4% in the placebo arm）. Serious AE occurred in 33% of patients treated with atezolizumab and 19% of patients treated with placebo. One patient receiving atezolizumab died from a treatment-related adverse event（hemophagocytic syndrome）
	Phase Ⅰb/Ⅱ BEGONIA trial（NCT 03742102），Arm 7：datopotamab deruxtecan（Dato-DXd）+ durvalumab as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer（a/mTNBC）（*n*=62）	Confirmed ORR was 79%（95% CI=67%− 88%）；median PFS was 13.8 months（95% CI：11−not calculable）	Grade 3/4 AE occurred in 17 patients（36%），and severe AE occurred in 7 patients（15%）.The most common all-Grade AE was gastrointestinal（nausea in 26 patients（55%）and stomatitis in 24 patients（51%）
	Phase Ⅱ SACI-IO HR+ trial（NCT04448886），sacituzumab govitecan±pembrolizumab in patients with metastatic hormone receptor-positive/HER2-negative breast cancer：the pembrolizumab arm（*n*=52）；the placebo arm（*n*=52）	Median PFS was 8.4 months in the sacituzumab govitecan+pembrolizumab arm *vs.* 6.2 months in the sacituzumab govitecan arm（HR=0.76，95% CI：0.47−1.23；*P*=0.26）	The most frequent treatment-related toxicities（≥G2）in the sacituzumab govitecan+pembrolizumab arm were neutropenia（67.3%），fatigue（36.5%），alopecia（36.5%）and anemia（32.7%）；in the sacituzumab govitecan arm，neutropenia（59.6%），alopecia（38.5%），diarrhea（34.6%），nausea（32.7%）and fatigue（32.7%）

AE：adverse event；CBR：clinical benefit rate；CI：confidence interval；CNS：central nervous system；ER：estrogen receptor；HER2：human epidermal growth factor receptor-2；HR：hazards ratio；LABC：locally advanced breast cancer；mBC：metastatic breast cancer；mPFS：median progression-free survival；ORR：objective response rate；pCR：pathological complete response；RCB：residual cancer burden；a/mTNBC：unresectable locally advanced/metastatic triple-negative breast cancer.

质降解ADC（antibody-degrader conjugate，ADeC）、免疫刺激ADC（immune stimulating antibody conjugate，ISAC）和双载荷ADC，其中ADeC因其高特异性、皮摩尔级的效力以及能够针对肿瘤相关的细胞内蛋白而备受关注[51]。下一代连接子技术专注于控制有效载荷的释放，而不依赖于内源性酶介导的裂解作用。其中，“点击释放”技术能够通过触发分子的点击化学反应来诱导药物的可控释放，受控的载荷释放可以限制组织外毒性，降低AE发生率[45]。传统ADC采用随机偶联技术，其均一性差，稳定性低，影响药效及治疗窗。下一代ADC将引入非天然氨基酸、工程化半胱氨酸以及N-糖基重构等方法实现定点偶联[52-53]。

4 小结与展望

ADC通过其独特的结构设计，实现对肿瘤的精

准靶向和高效杀伤能力，显著提高乳腺癌患者的生存获益。但随着ADC的广泛应用，显露出的ADC耐药性意味着出现更严峻的挑战。为逆转ADC耐药，ADC本身组件的优化以及联合用药方案是当下ADC开发的关注重点。对于ADC药物未来研究方向的展望：①“万物皆可偶联”概念提供了新的研究思路。鉴于ADC技术平台的灵活性和可扩展性，理论上任何功能性的分子都可以被设计成ADC的载药，包括但不限于双载荷或多载荷药物、放射性药物、免疫调节剂等。②ADC打破了传统乳腺癌分型的局限性，需要开发新的生物标志物(如循环肿瘤标志物、靶点或载荷相关基因突变)以识别可能受益于特定ADC的患者人群，实现精准医疗，进一步提高药物的临床响应率和疗效。③ADC研发及生产成本高昂，未来其相关研究需要进一步优化临床前期和临床研究路径、改良生产工艺，以求降低生产成本，为更多患者带来治疗选择和生存希望。

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卢蓉蓉负责稿件的撰写起草、稿件的修改，瞿菲负责稿件的撰写起草；李薇提出研究方案、监督研究实施、修改论文及提供资金。

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LU Rongrong was responsible for writing original draft, reviewing and editing. QU Fei was responsible for writing original draft. LI Wei was responsible for conceptualization, supervision, revising the manuscript and funding acquisition.

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