专家述评·“乳腺癌精准靶向与转化”重点号

乳腺癌抗体偶联药物耐药的机制解析与应对策略

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[摘要] 抗体偶联药物(antibody-drug conjugate,ADC)已深刻重塑乳腺癌的治疗格局,尤其在HER2阳性和HER2低表达晚期乳腺癌中展现出确切的生存获益,但其广泛临床应用亦使原发耐药、继发耐药及交叉耐药问题日益突出。耐药已成为乳腺癌患者追求长期生存获益的硬性瓶颈。乳腺癌ADC耐药的多维分子机制诸如:第一,肿瘤相关抗原表达下调、空间异质性改变及抗原基因突变可削弱ADC与肿瘤细胞的结合能力;第二,内吞受体及相关蛋白表达和功能异常、溶酶体功能受损等可导致ADC内吞与转运障碍;第三,药物外排泵上调、DNA修复增强及拓扑异构酶1突变等是载荷耐药的关键因素;第四,PI3K/AKT/mTOR、MAPK等经典信号通路的异常激活可促进肿瘤细胞存活;第五,肿瘤相关巨噬细胞与成纤维细胞等抑制性免疫微环境组分亦在ADC耐药中发挥重要作用。克服乳腺癌ADC耐药的阶梯式破局策略:第一,研发具有新型靶点、创新载荷及可裂解连接子的“下一代ADC”;第二,将现有ADC与免疫检查点抑制剂、不可逆酪氨酸激酶抑制剂等药物联合应用,以协同增效并逆转耐药,其中ADC联合免疫检查点抑制剂已展现出最具潜力的临床前景;第三,依托类器官技术与人工智能平台实现精准个性化用药方案制定与药物研发。尽管联合方案的临床验证与新药转化仍需较长时日,但采用多技术融合的方式对肿瘤耐药微环境及其异质性进行深度解析,可为突破ADC疗效瓶颈、实现乳腺癌精准个体化治疗指明方向。未来将微环境特征解析与AI驱动的新药研发、类器官技术临床转化相结合,有望为突破ADC耐药瓶颈提供关键支撑,从而推动乳腺癌治疗格局的实质性进步。

[关键词] 肿瘤耐药;乳腺肿瘤;免疫偶联物;分子靶向治疗;抗肿瘤药物;肿瘤生物标志物
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Resistance to antibody-drug conjugates in breast cancer: mechanism and strategies for overcoming

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[**Abstract**] Antibody-drug conjugates (ADCs) have profoundly reshaped the treatment landscape of breast cancer, demonstrating definite survival benefits especially in HER2-positive and HER2-low advanced

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breast cancer. However, their widespread clinical application has also made primary resistance, acquired resistance, and cross-resistance increasingly prominent. Drug resistance has become a critical bottleneck in achieving long-term survival benefits for breast cancer patients. The multidimensional molecular mechanisms of ADC resistance in breast cancer include: First, downregulation of tumor-associated antigen expression, altered spatial heterogeneity, and antigen gene mutations can weaken the binding of ADCs to tumor cells; Second, aberrant expression and function of endocytic receptors and related proteins, as well as impaired lysosomal function, can lead to defects in ADC internalization and trafficking; Third, upregulation of drug efflux pumps, enhanced DNA repair, and topoisomerase I mutations are key factors underlying payload resistance; Fourth, abnormal activation of classical signaling pathways such as PI3K/AKT/mTOR and MAPK can promote tumor cell survival; Fifth, immunosuppressive microenvironment components such as tumor-associated macrophages and fibroblasts also play important roles in ADC resistance. Stepwise strategies for overcoming ADC resistance in breast cancer include: First, developing "next-generation ADCs" with novel targets, innovative payloads, and cleavable linkers; Second, combining existing ADCs with agents such as immune checkpoint inhibitors and irreversible tyrosine kinase inhibitors to achieve synergistic efficacy and reverse resistance, among which ADCs combined with immune checkpoint inhibitors has shown the most promising clinical prospects; Third, leveraging organoid technology and artificial intelligence (AI) platforms to enable precision personalized medication design and development. Although clinical validation of combination regimens and translation of novel drugs still require considerable time, in-depth analysis of the drug-resistant tumor microenvironment and its heterogeneity by multi-technology integration may provide direction for breaking the efficacy bottleneck of ADCs and achieving precision individualized treatment for breast cancer. In the future, integrating microenvironmental feature profiling with AI-driven drug development and clinical translation of organoid technology is expected to provide critical support for overcoming the bottleneck of ADC resistance, thereby driving substantial progress in the treatment landscape of breast cancer.

[**Key words**] drug resistance in neoplasms; breast neoplasms; immune conjugates; molecular targeted therapy; anti-tumor drugs; tumor biomarkers

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抗体偶联药物(antibody-drug conjugate,ADC)是由靶向肿瘤细胞相关抗原的单克隆抗体和高效细胞毒性药物通过可控化学连接子连接而成的大分子药物,兼具靶向性和肿瘤细胞杀伤作用。目前ADC在临床的广泛应用,使得包括HER2阳性/低表达乳腺癌在内的多数晚期恶性肿瘤患者极大地从中获益,然而随着ADC在乳腺癌晚期解救及前线治疗中作为优选方案的地位不断提升,伴随广泛应用而出现的耐药问题也日益突出,且已逐渐成为患者追求长期生存获益的硬性瓶颈。本文对乳腺癌ADC耐药的多维机制进行重点梳理,并结合最新临床试验数据、转化研究、类器官及AI技术的进展,为建立抗耐药精准治疗体系提供初步的学术框架。

1 乳腺癌ADC治疗现状及耐药挑战

ADC在乳腺癌领域的应用始于HER2阳性晚期乳腺癌,在过去6年间已基本完成了对我国乳腺癌(特别是晚期乳腺癌)临床治疗格局的重塑。首款靶向HER2的ADC恩美妥珠单抗(trastuzumab emtansine,T-DM1)于2013年在FDA获批(2020年在NMPA获批)用于HER2阳性晚期乳腺癌[1],成为HER2阳性乳腺癌二线治疗的标准方案。随后,第二代ADC德曲妥珠单抗(trastuzumab deruxtecan,T-DXd)凭借高药物抗体比(DAR≈8)、可裂解连接子以及强烈的旁观者效应,在DESTINY-Breast03研究中展现出卓越的疗效:中位无进展生存期(progression-free survival,PFS)显著优于T-DM1(中位PFS:28.8 *vs* 6.8个月,*HR*=0.33)。更具里程碑意义的是,DESTINY-Breast04研究证实T-DXd可显著延长HER2低表达(IHC 1^+或IHC 2^+/$FISH^-$)晚期乳腺癌患者的PFS与总生存期(overall survival,OS),使得乳腺癌的分子分型与治疗范式迎来深刻的变革[2-3]。

在非HER2靶点方面,靶向TROP2的新型ADC戈沙妥珠单抗(sacituzumab govitecan,SG)也紧随其后获批用于晚期三阴性乳腺癌,显著延长接受后线治疗患者的生存期,并在近期进一步获批用于(基于ASCENT03研究)晚期三阴性乳腺癌的一线治疗方案[4-5]。此外,国产新型TROP2-ADC芦康沙妥珠单抗已于2024年获批用于不可切除局部晚期或转移性三阴性乳腺癌三线及以上的治疗[6];新型TROP2-ADC德达博曲妥珠单抗(datopotamab deruxtecan,Dato-DXd)也在2025年获批应用于激素受体阳性/HER2阴性晚期乳腺癌[7]。ADC发展至今,尚有数十款采用不同靶点、不同载荷、不同连接子设计的新型ADC正在各大临床试验中进行疗效探索,极具应用潜力。目前HER2 ADC和TROP2 ADC已获批的临床适应证,已经实现对"分型而治"理念下几乎所有类型乳腺癌的全方位覆盖。无论靶向HER2或TROP2,ADC都在晚期乳腺癌的一线用药场景广泛应用,成为晚期乳腺癌患者的"最后防线"。

然而,随着ADC在临床的广泛应用及治疗线数前移,原发耐药与获得性耐药已为追求长期疗效带来挑战。既往多种获批ADC的注册临床试验结果报告及后续生存分析显示,绝大多数经ADC治疗后获益的晚期乳腺癌患者,在首次给药后数月至2年内出现了疾病进展[2,5,8-9]。DAISY研究[10]结果显示,HER2过表达、低表达、零表达队列对T-DXd的无响应率分别为29.4%、62.5%、70.3%,提示ADC治疗耐药形势严峻。此外,在真实世界高度经治人群中,ADC耐药后换用相同载荷但不同靶点的第二种ADC治疗后,高达77.4%患者的第二程ADC至治疗失败时间(time to treatment failure,TTF)短于第一程ADC,且在交叉耐药患者中发现了TOP1、TOP3A/3B基因突变,突变直接作用于SG和T-DXd的结合位点,或为交叉耐药的直接原因[11]。这种"交叉耐药"现象提示,除抗原特异性改变外,对载荷本身的耐药也起到了重要作用。

原发耐药、继发耐药以及交叉耐药是当前临床实践中乳腺癌ADC耐药机制的主要分类,用于指导具体临床治疗策略的制定、方案优化以及针对ADC治疗失败后的临床研究设计。深入解析ADC耐药的具体分子机制,不仅是延长患者生存的临床迫切需求,更是研发下一代ADC的核心科学指引。

2 乳腺癌ADC的多维耐药机制

无论是"盲目杀伤"的传统化疗药物,还是"精准靶向杀伤"的ADC,都无法避免耐药的发生。目前学界对ADC耐药机制的认识可大致分为以下5类(图1)。

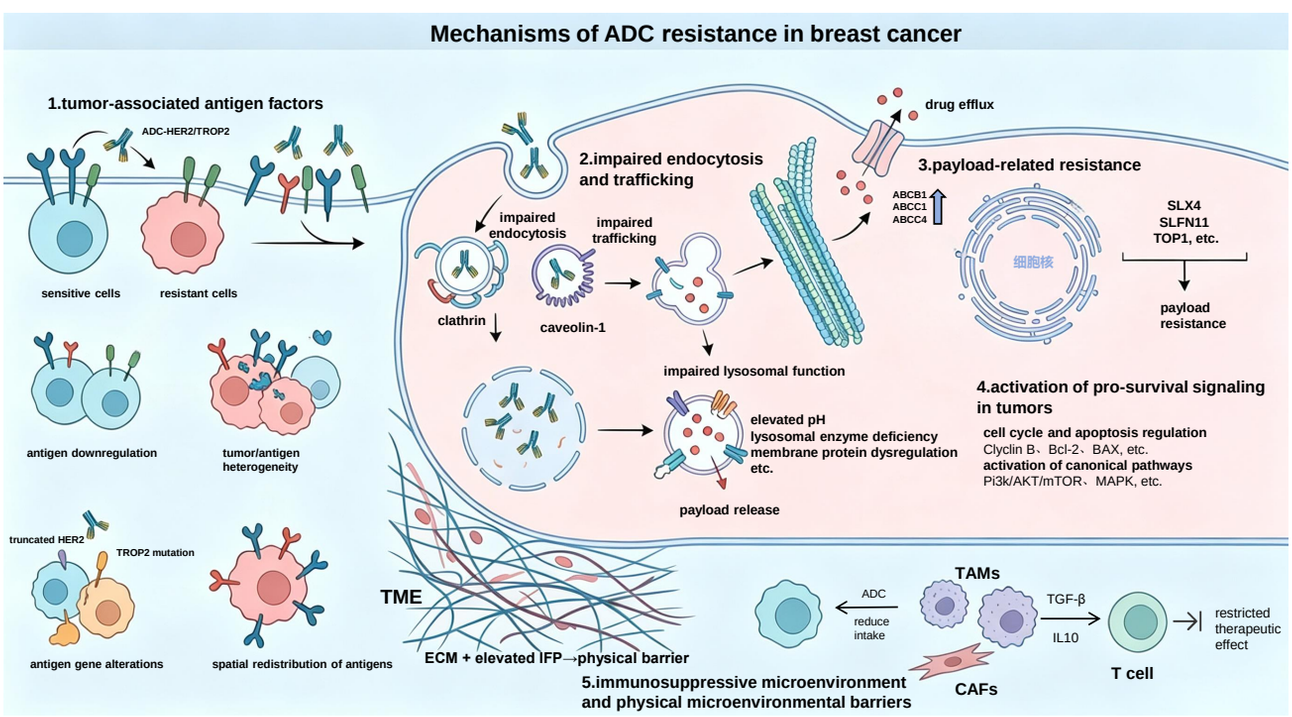


图1 乳腺癌ADC耐药机制示意图

Figure 1 Schematic diagram of the mechanisms of antibody-drug conjugate (ADC) resistance in breast cancer

2.1 肿瘤相关抗原因素

肿瘤相关抗原表达状态是ADC发挥作用的关键因素。抗原表达水平的改变直接影响ADC与肿瘤细胞结合,进而可能导致ADC耐药[12]。而肿瘤异质性(肿瘤相关抗原水平表达不一)、抗原基因突变、经治后抗原下调、抗原空间重分布等因素是导致抗原表达水平改变的直接原因[13];在基于T-DM1治疗的Ⅱ期临床研究中,基线肿瘤的HER2异质性与无法达到病理学完全缓解密切相关[14]。DAISY研究中的生物标志物分析结果也提示,T-DXd的抗肿瘤活性与HER2表达水平密切相关,在T-DXd初始治疗有效但后续疾病进展的患者样本中也发现,HER2表达较治疗前呈下调趋势[10]。不过,该研究中所出现的耐药也并非仅由HER2表达水平降低的所致,即使肿瘤细胞依旧正常表达HER2且内吞ADC,抗肿瘤效应依然受限,这也提示肿瘤抗原、ADC转运及载荷均在整体ADC耐药背景下发挥着各自的作用。目前已经明确证实影响ADC结合的抗原基因突变有$TROP2^{T256R}$(基于TROP2靶点的SG)和HER2截短蛋白P95HER2(基于HER2靶点的T-DM1和T-DXd)[15-16]。

2.2 ADC的内吞与转运障碍

肿瘤细胞对ADC的内吞障碍、胞内运输障碍以及肿瘤细胞的溶酶体功能受损使得ADC的内吞和转运受限,进而影响载荷发挥肿瘤杀伤作用。参与ADC内吞过程的内吞受体及其相关蛋白表达量或活性降低是导致内吞障碍的主要因素。例如,肿瘤细胞通常利用低密度脂蛋白受体、转铁蛋白受体以及内吞相关蛋白(网格蛋白、衔接蛋白等)内吞ADC,这些蛋白的表达和功能改变直接导致ADC与肿瘤细胞结合却无法内吞进入肿瘤细胞[17]。

对于靶向HER2的ADC而言,可能仅发挥抗HER2的抗肿瘤作用,无法发挥载荷的杀伤作用;而对于靶向TROP2的ADC而言,则可能几乎无法发挥抗肿瘤效应。近期转化研究发现,胃癌中的小窝蛋白1表达与T-DM1摄取呈负相关,进一步研究证实小窝蛋白1包被的囊泡是ADC内吞的替代途径,但效率较常规途径更低,而在异种移植模型中抑制小窝蛋白的表达,可增强T-DM1的摄取并提升疗效[18-19]。此外,即使ADC顺利经内吞和转运进入肿瘤细胞,仍需依赖健全的溶酶体功能以便释放载荷。而多项研究显示,在T-DM1耐药细胞株中,ADC内吞及转运功能与正常细胞株无异,但溶酶体pH值显著上升,这直接导致了蛋白酶解活性的下降,进而阻碍载荷的释放[20]。除pH之外,溶酶体酶缺乏、溶酶体膜蛋白失调等多种因素均可通过损伤溶酶体功能引起ADC耐药。

2.3 载荷相关耐药

肿瘤细胞对载荷的耐药大体上有着与对传统化疗药物耐药相似的机制。目前应用于乳腺癌的ADC普遍选用拓扑异构酶抑制剂或微管类抑制剂作为载荷,载荷相关耐药主要围绕这2类药物的作用机制产生。药物外排泵的表达上调是抗肿瘤药物耐药的经典机制之一。患者样本的多组学分析和二代测序的结果提示经典外排泵ABCB1和ABCC1蛋白上调可介导T-DXd耐药,同时ABCC1和ABCC4蛋白上调则可致SG耐药[21-22]。同样基于临床研究入组患者的肿瘤样本,基因组分析显示SLX4突变驱动的DNA修复增强、SLFN11缺失以及更直接的拓扑异构酶1(TOP1)突变均可导致肿瘤细胞对ADC常见载荷拓扑异构酶1抑制剂耐药[16,23-24]。

2.4 促肿瘤细胞存活的信号激活

多项临床前和临床研究表明,PI3K/AKT/mTOR、MAPK等经典信号通路以及EGFR受体酪氨酸激酶家族的激活与乳腺癌细胞对T-DM1或T-DXd的获得性耐药密切相关[25]。研究显示细胞周期蛋白B(cyclin B)水平降低可导致乳腺癌细胞系产生对T-DM1的耐药,上调其表达水平则可使部分耐药细胞恢复对T-DM1的敏感性[26]。此外,抗凋亡蛋白Bcl-2上调和促凋亡蛋白BAX下调协同促进肿瘤细胞存活,也在ADC耐药中发挥重要作用[27]。

2.5 免疫抑制性肿瘤微环境和微环境物理屏障

肿瘤微环境中的致密细胞外基质、高间质液压(interstitial fluid pressure,IFP)所构成的物理屏障以及多种免疫抑制性细胞,在一定程度上阻碍了药物的递送及疗效的发挥。肿瘤相关巨噬细胞(tumor associated macrophages,TAMs)和肿瘤相关成纤维细胞(cancer associated fibroblasts,CAFs)是肿瘤微环境中的重要促癌细胞组分,同时也能以抗原特异性或非抗原特异性的方式内化ADC,导致肿瘤细胞对ADC的摄取降低,削弱ADC的肿瘤杀伤效应[25-28]。临床研究及人源肿瘤异种移植模型的研究数据显示,CAFs和TAMs的特定亚群均可诱导HER2阳性乳腺癌产生对T-DXd和T-DM1的获得性耐药[29-31]。此外,TAMs还可通过分泌TGF-β、IL10等免疫抑制信号抑制T细胞功能,进一步削弱ADC疗效[13]。临床研究证实乳腺癌组织中透明质酸的累积使得组织间液压显著升高,扰乱药物渗透动力学并改变其生物分布模式[32]。值得注意的是,针对抑制性免疫微环境可能导致的ADC耐药,目前已有初步临床研究数据提示,ADC联合ICIs相较ADC单药治疗可显著提升疗效。

3 克服乳腺癌ADC耐药的阶梯式破局策略

3.1 新型靶点和设计的ADC

长远来看,设计开发功能全面的新型ADC有望从根源上解决耐药问题,为ADC经治的晚期乳腺癌患者提供更多治疗选择,同时还有望提高早期乳腺癌患者的治愈率、延长无病生存期。新型ADC的设计主要围绕抗体、载荷、连接子以及偶联策略4个方面创新,更可靠的抗体、更可控的连接子、更有效的载荷是“下一代ADC”研发的重点。

当前乳腺癌领域极具前景的ADC靶点主要包括HER2、TROP-2、HER3、Nectin-4、B7H4、LIV-1、B7-H3、PTK7等[33]。除选用新抗体外,下一代ADC的靶点设计还包括了多靶点策略,即靶向同一抗原不同表位或双抗原的双特异性ADC,这有望提升其结合、内化效率及肿瘤杀伤效能[34-36]。连接子设计需兼顾在循环系统中的稳定性及载荷在肿瘤细胞内的释放效率,由于T-DXd的旁观者效应已经展现出明显更优的抗肿瘤作用,而恶性肿瘤普遍存在的肿瘤异质性在肿瘤复发、转移、耐药中发挥着重要作用。因此,采用具有旁观者效应的可裂解连接子设计依旧是未来新型ADC(肿瘤细胞杀伤载荷)的主流设计方向[37]。根据肿瘤细胞、血液循环与正常细胞的酸碱性、谷胱甘肽水平及蛋白酶表达差异,可匹配选择酸裂解、还原裂解、酶裂解等多种裂解机制的连接子[34]。目前临床应用于乳腺癌的ADC主要基于微管抑制剂或拓扑异构酶抑制剂设计,针对这2类细胞毒性药物介导的耐药,开发搭载其他杀伤机制的新载荷ADC,其疗效将具有重大潜力。新型细胞毒药物以及RNA聚合酶2抑制剂、激酶抑制剂、甚至免疫刺激分子等新型载荷已在临床前研究和临床研究中取得不错疗效,未来有望改变临床实践[34,36,38]。

3.2 基于现有ADC的联合疗法

新型ADC从实验室落地临床实践往往需要相当长的周期,而当前ADC的广泛应用已经产生了不小的耐药患者群体,如何切实解决耐药问题、延长疾病控制时间和总生存时间对于乳腺癌ADC耐药的患者而言具有紧迫性。乳腺癌领域的前沿制药企业和研究者正在就已获批ADC的序贯治疗、ADC与其他药物联合等治疗方案开展临床试验,探索其疗效和安全性。相较于开发全新ADC并获批临床应用,将现有ADC与成熟的临床抗癌药物(如免疫检查点抑制剂、酪氨酸激酶抑制剂、PARP抑制剂、抗血管生成药物、抗HER2单抗等)联合应用是克服当前临床实践中ADC耐药困境最高效的手段。

其中最具潜力且有望短期内见证疗效的方案是ADC联合免疫检查点抑制剂。研究者发现,ADC所发挥出的抗肿瘤效应并不只源于对肿瘤细胞的直接杀伤,还包含了ADC及其游离载荷对免疫微环境的重塑,增强抗肿瘤免疫[39-40]。具体而言,在细胞学机制方面,ADC内吞后释放细胞毒性载荷破坏微管或损伤DNA,诱导肿瘤细胞发生免疫原性死亡;死亡的肿瘤细胞向胞外释放损伤相关分子模式(damage-associated molecular patterns,DAMPs)及大量新抗原(含肿瘤相关抗原),这些信号吸引并激活树突状细胞及其他抗原呈递细胞,促进其成熟并向引流淋巴结迁移,将抗原交叉呈递给初始$CD8^+$T细胞;成熟DC分泌趋化因子(如CXCL9/CXCL10),定向招募激活的细胞毒性T淋巴细胞及NK细胞侵入肿瘤组织;带有功能性Fc端的ADC结合靶抗原后,可结合NK细胞表面的FcγRⅢa(CD16a)触发抗体依赖性细胞毒作用,或结合巨噬细胞表面的FcγR触发抗体依赖性细胞吞噬作用,进一步加速肿瘤细胞裂解与碎片清除[41]。在分子机制方面,ADC可通过激活cGAS-STING通路,建立引导T细胞归巢的趋化因子浓度梯度,通过IFN-γ/JAK-STAT1通路介导PD-L1代偿性上调调控抗肿瘤免疫。因此ADC联合免疫检查点抑制剂可产生显著的治疗协同作用,提升肿瘤杀伤效果[42]。

多项探索ADC联合免疫检查点抑制剂用于早期乳腺癌新辅助、辅助治疗以及晚期乳腺癌解救治疗的临床研究正先后进行中,如ASCENT-04、NeoSTAR、BEGONIA、TROPION-Breast03、TROPION-Breast05、TroFuse-012等研究,其中NeoSTAR、BEGONIA、ASCENT-04已取得部分阳性结果。NeoSTAR研究中SG联合帕博利珠单抗新辅助治疗组的pCR率达34%,4名(8%)患者治疗中接受SG剂量减量,3/4级不良事件发生率为40%,常见不良事件主要为恶心、脱发、疲劳和腹泻[43];在BEGONIA研究中,采用DATO-DXd联合度伐利尤单抗方案晚期一线解救治疗的2个治疗组确认客观缓解率(cORR)分别为79%(PFS中位数为13.8个月,不论PD-L1表达)和81.8%(PD-L1高表达),3/4级不良事件发生率分别为48%和24%,和既往应用ADC或免疫单药治疗的不良反应特征基本一致,总体安全性可控[44],提示ADC联合免疫检查点抑制剂极具临床治疗潜力。1项Ⅲ期RCT研究ASCENT-04的结果亦显示,在既往未经治疗的PD-L1阳性晚期三阴性乳腺癌中,SG联合帕博利珠单抗相较于化疗联

合帕博丽珠单抗,可以带来显著的PFS获益(中位数为11.2 *vs* 7.8个月;*HR*=0.65,95%*CI*:0.51~0.84;*P*<0.001),提示ADC联合免疫治疗在PD-L1阳性晚期三阴性乳腺癌一线治疗中的巨大潜力[45]。

除免疫检查点抑制剂以外,不可逆TKI可以提升ADC的内吞效率,进而提升ADC的疗效,例如针对HER2表达水平降低所致内吞效率低下进而导致耐药,ADC联合不可逆TKI或能逆转耐药,恢复ADC抗肿瘤效应;在采用该治疗策略的转化研究中,T-DM1经治耐药的晚期乳腺癌患者使用T-DM1联合不可逆TKI实现疾病的进一步控制,提示TKI逆转耐药的潜力[46-47]。不过目前采用这一策略的HER2CLIMB04单臂Ⅱ期研究数据显示联合方案并未优于历史T-DXd单药数据,安全性可控,未来仍需进一步研究细化其适宜的应用场景[48]。其他联合策略如ADC联合抗HER2单抗、PARP抑制剂、抗血管生成药物亦有潜力改善对ADC耐药患者中特定群体的预后。

3.3 基于个性化耐药机制的联合策略及临床样本耐药机制深度解析

关于ADC耐药问题的讨论早已远离"是否会耐药"的范畴。如何定义、预测耐药的发生以及系统破解不同层次的耐药,是未来ADC在临床合理应用的关键。当前对ADC耐药机制的解析主要集中在肿瘤细胞本身,如肿瘤细胞ERBB2半合子缺失或可导致T-DXd原发耐药[10];HER2截短蛋白(p95HER2)促进肿瘤细胞表达PD-L1、分泌IL-6,驱动免疫抑制性微环境,使得T-DXd的疗效大打折扣[15];$TROP2^{T256R}$和$TOP1^{E418K}$突变分别导致肿瘤细胞对SG的抗体和载荷的耐药[16]。这些基于临床耐药患者肿瘤样本的转化研究,为未来在临床实践中早期识别耐药患者提供了可靠的生物标志物参考及耐药应对思路。比如针对表达p95HER2的HER2阳性乳腺癌患者,联合靶向p95HER2及其下游分子的靶向药物,可以恢复抗肿瘤免疫及T-DXd疗效。

然而肿瘤微环境结构及微环境基质、免疫细胞是ADC耐药的重要参与者甚至核心调控因素,目前关于ADC耐药乳腺癌患者的肿瘤微环境特征尚未被充分解析。基于当前临床耐药患者基线和耐药后的肿瘤组织+血液样本的多组学分析解析ADC耐药的肿瘤微环境特征、微环境异质性、全身免疫景观,挖掘ADC疗效、耐药相关的关键分子和潜在机制,将为规避、逆转耐药策略的制定以及下一代ADC研发,提供至关重要的指引。

3.4 新技术助力ADC耐药破局

基于乳腺癌患者来源类器官平台的ADC敏感性分析,将显著提升识别临床耐药患者的可靠性,指导制定更精准的ADC耐药逆转策略。尤其在近年来类器官技术快速进步的背景下,血管化类器官芯片、气液界面类器官(air-liquid interface organoids,ALI-PDO)以及肿瘤组装体等先进类器官技术,使得免疫细胞、基质细胞、内皮细胞甚至血流所产生的物理剪切力得以保留,可以更好地模拟肿瘤原生状态[49-50]。未来新型肿瘤类器官的临床应用将有力支撑ADC耐药难题的破解,用于高通量测试患者对不同ADC药物及联合方案的敏感性。然而先进类器官技术尚处于"部分从事类器官研究的团队专属"的阶段,作为新技术尚未普及应用,临床应用仍需较长时间。而常规PDO培养普及程度更高,但该技术易丢失基质与免疫成分,难以完全真实再现ADC介导的ADCC效应与免疫协同效应;患者肿瘤亦存在高度异质性,基于局部活检组织的类器官可能缺乏代表性;此外,建库培养周期需2~4周,与晚期患者紧迫的治疗时间窗存在冲突。这些类器官应用的现实问题,使得该技术赋能ADC耐药患者的治疗策略尚仅见于极少数探索场景。

近年来人工智能(artificial intelligence,AI)的飞速发展使得药物的研发效率得到显著提升。ADCNet模型可以提取抗体和抗原的蛋白序列特征、Linker和payload的化学结构特征,用以预测ADC针对特定细胞系的抗肿瘤杀伤活性[51]。此外Dumpling GNN和Linker-GP模型在对载荷和Linker的预测和筛选中表现亮眼,亦有较大潜力助力新型ADC研发[52-53]。不过AI辅助的ADC研发尚处于前沿技术的早期探索阶段,目前AI预测模型的训练集高度依赖体外细胞系及回溯性小样本数据,缺乏大规模临床耐药多组学数据的验证;深度学习的"黑盒"属性使其缺乏明确的生物学可解释性,模型跨非经典靶点、跨创新载荷预测的泛化能力与外推可靠性仍需严格的临床前与临床验证。

4 展望

目前广泛应用于乳腺癌的ADC因载荷普遍为单一细胞毒药物且抗体仅结合单一靶点,多数场景下被临床定位为一种更精准、高效的化疗平台。随着现有ADC的临床应用线数前移,未来会逐步进入可预见的疗效瓶颈阶段,ADC与多种临床疗效确切的药物多药联合及"下一代ADC"有望保障ADC经治耐药患者获益,提升疗效延长生存期,但其临床应用潜能仍有待设计合理的临床试验进行验证。与此同时,对当前乳

腺癌ADC耐药患者肿瘤微环境的解析,可随AI技术的快速迭代而变得更可靠和高效,有望显著提升新型ADC研发效率;同时肿瘤类器官关键技术的迭代与普及,也为解决乳腺癌ADC耐药问题提供有力支撑。

利益冲突 本文所有作者声明不存在利益冲突

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