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·综 述·

# 晚期胃癌分子靶向药物研发的研究进展

**Advances in research and development of molecular targeted drugs for advanced gastric cancer**

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[摘 要] 近年来,化疗基础上加用抗表皮生长因子受体2药物、抗血管生成药物及免疫检查点抑制剂,不仅可提高晚期胃癌(GC)患者治疗的有效率,而且可明显改善患者预后。然而,目前晚期GC患者治疗后的生存获益远落后于肺癌、结直肠癌及乳腺癌等实体肿瘤,靶向治疗仍需进一步探索。随着分子生物学技术的发展,新的治疗靶点如Claudin 18.2、基质金属蛋白酶(MMP)、Dickkopf相关蛋白1(DKK-1)、RAD3相关蛋白激酶(ATR)被发现在GC细胞中表达,针对这些靶点的药物逐渐在临床治疗中崭露头角,并显示出较好的临床应用前景。阐述晚期GC治疗中靶点的作用机制及靶向药物的研究进展,对提高GC的临床治疗疗效具有重要意义。

[关键词] 胃癌;Claudin18.2;基质金属蛋白酶;Dickkopf1相关蛋白;人表皮生长因子受体2;RAD3相关蛋白激酶;抗体偶联药物
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胃癌(gastric cancer,GC)是最常见的恶性肿瘤之一。2020年,全球GC新发病例约为108.9万,中国新发病例占全球新发病例的43.9%[1]。氟尿嘧啶联合铂类化疗是晚期GC(advanced gastric cancer,AGC)患者的首选治疗方案[2]。近年来,分子靶向药物和免疫检查点抑制剂(immune-checkpoint inhibitor,ICI)已成为肿瘤治疗药物研究的热点。表皮生长因子受体2(human epithelial growth factor receptor-2,HER-2)扩增的AGC患者,采用化疗基础上联合曲妥珠单抗治疗,可使客观缓解率(objective response rate, ORR)从35%提高到47%,患者中位总生存期(median overall survival,mOS)延长2.7个月,死亡风险降低26%[3]。因此,曲妥珠单抗联合化疗已成为HER-2阳性AGC患者的一线标准治疗方案。

在ORIENT-16 Ⅲ期临床试验[4]中(NCT03745170),化疗联合信迪利单抗一线治疗AGC患者,其mOS较单用化疗患者延长2.9个月($P$=0.009)。信迪利单抗联合化疗作为一线治疗使AGC患者有较好的生存获益。对于PD-L1阳性的联合阳性评分分数(combined positive score,CPS)≥5的AGC患者,采用化疗联合纳武利尤单抗作为一线治疗可使患者mOS达到14.4个月,较单纯化疗组患者的mOS延长约3个月($P$<0.000 1)[5]。因此,ICI联合化疗已成为AGC患者尤其是PD-L1高表达患者的一线标准治疗方案。雷莫芦单抗为抗血管内皮生长因子受体-2(vascular endothelial growth factor receptor-2,VEGFR-2)抗体,是首个在AGC患者二线治疗中取得成功的抗血管生成药物。在二线化疗基础上联合雷莫芦单抗,可使得AGC患者mOS延长1.4个月[6]。虽然ICI及抗血管生成药物的应用改善了AGC患者的预后,但AGC患者的mOS仍不足2年,亟待研发新的治疗药物。本文就当前对AGC治疗具有潜在临床应用价值的新药研究现状进行综述,为AGC临床治疗提供新思路。

## 1 Claudin 18.2的靶向药物

Claudin是介导紧密连接的四次穿膜蛋白,参与维持细胞极性和细胞间的黏附[7]。Claudin 18.2由Claudin 18基因编码,仅存在于胃黏膜细胞的紧密连接中。在GC中,胃黏膜细胞间的紧密连接被破坏,导致细胞表面的claudin 18.2蛋白表位暴露,成为GC患者特异性治疗的靶点[8]。目前,对于Claudin 18.2靶向药物的研究主要包括单克隆抗体和双特异型抗体。

### 1.1 单克隆抗体zolbetuximab

Zolbetuximab是一种针对Claudin 18.2的嵌合型IgG1单克隆抗体,通过引发抗体依赖性细胞毒性效应和补体依赖性细胞毒性效应杀灭肿瘤细胞[9]。在一项针对化疗后进展的Claudin 18.2阳性AGC患者,给予zolbetuximab抗体联合唑来膦酸和白细胞介素2治疗的临床Ⅰ期试验中(NCT01671774)[10],患者的mOS达到40周,中位无进展生存期(median progression-free survival,mPFS)为12.7周,初步显示了Claudin 18.2抗体治疗AGC患者的疗效。在MONO临床Ⅱa期临床试验中(NCT01197885),针对Claudin 18.2阳性率≥50%的AGC和食管腺癌(esophageal adenocarcinoma,EAC)患

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者，Zolbetuximab单药作为二线及多线治疗患者的ORR为9%，mPFS为14.5周[11]。在FAST Ⅱb期临床试验中（NCT01630083），选取癌组织中Claudin 18.2高表达的AGC和EAC患者，分别接受zolbetuximab联合EOX方案（表柔比星+奥沙利铂+卡培他滨）治疗（试验组）或EOX方案治疗（对照组）。试验组mPFS和mOS分别为7.5和13.0个月，对照组mPFS和mOS分别为5.3和8.3个月，两组均具有显著的统计学差异（均$P$<0.000 5）[12]。SPOTLIGHT等[13]的Ⅲ期临床试验（NCT03504397）观察了Zolbetuximab联合mFOLFOX6（氟尿嘧啶+亚叶酸钙+奥沙利铂）或安慰剂联合mFOLFOX6作为一线方案治疗Claudin 18.2阳性、HER-2阴性AGC患者的临床疗效，结果显示，Zolbetuximab组患者的mOS为18.2个月，mPFS为10.6个月；而安慰剂组患者的mOS为15.5个月，mPFS为8.7个月，两组间具有明显的统计学差异（$P$<0.05）。试验结果表明，对比单用化疗，化疗联合Zolbetuximab治疗可进一步改善患者预后。

### 1.2　靶向CD3及Claudin 18.2的双特异性抗体

CD3双特异性抗体是通过同时结合T细胞表面的CD3和肿瘤表面抗原，形成免疫突触，从而直接激活T淋巴细胞，进而释放细胞因子和细胞毒素来杀伤肿瘤细胞[14]。目前已上市的CD3双特异性抗体catumaxomab和blinatumomab主要用于治疗血液肿瘤[14-15]。研究[16]表明，靶向CD3及Claudin 18.2的双特异性抗体可能是治疗GC和胰腺癌的有效手段，其有效性和安全性在动物活体模型中得到了验证。目前，靶向CD3及Claudin 18.2的双特异性抗体AMG-910已进入Ⅰ期临床试验阶段（NCT04260191），未来前景值得关注。

## 2　基质金属蛋白酶（matrix metalloproteinase，MMP）抑制剂

MMP是钙依赖性含锌内肽酶家族，可降解和重塑细胞外基质。在恶性肿瘤中MMP的表达量和活性均增加，使癌细胞能够穿透基质，发生浸润和远处转移[17]。MMP-9是MMP家族中分子量最大的酶，有60.7%的GC患者的癌组织中存在MMP-9高表达，MMP-9高表达的患者生存期（约40个月）较低表达患者（约88个月）明显缩短[18-19]。因此，MMP-9是治疗GC的潜在靶点。Andecaliximab（ADX）是一种重组嵌合型免疫球蛋白G4单克隆抗体，可特异性抑制MMP-9活性。在一项Ⅰ/Ⅰb期临床试验中（NCT01803282）[20]，给予HER-2阴性AGC患者ADX联合mFOLFOX6方案治疗，患者的mPFS达到7.8个月，ORR为48%。其中一线治疗患者的mPFS达到9.9个月，ORR为50%。然而，在之后进行的Ⅲ期GAMMA-1临床研究中（NCT02545504），化疗联合ADX和化疗联合安慰剂治疗患者的mOS分别为12.5和11.8个月，mPFS分别为7.5和7.1个月，两组间并无统计学差异（$P$=0.56）[21]。mFOLFOX6加用ADX作为一线治疗能否改善HER-2阴性AGC患者的预后仍有待进一步研究。除了与化疗药物联合使用外，ADX与ICI的联合治疗方案也在逐步探索中。一项Ⅱ期临床试验（NCT02864381）[22]观察了AGC患者在纳武利尤单抗治疗基础上加用ADX的疗效，ADX联合纳武利尤单抗组患者的ORR为10%，mOS为7.1个月，纳武利尤单抗单药组患者的ORR为7%，mOS 5.9个月，两组的差异无统计学意义（均$P$>0.05），ADX的加入并未明显改善AGC患者预后。因此，明确哪些患者可以从ADX治疗中获益仍需进一步研究。

## 3　VEGFR抑制剂

肿瘤细胞通过分泌大量促血管生成因子，促进肿瘤组织血管生成，维持肿瘤细胞的新陈代谢[23-24]。VEGF是最重要的促血管生成因子，在多种实体瘤中过度表达；VEGFR家族成员包括VEGFR-1、VEGFR-2和VEGFR-3，其中VEGFR-1和VEGFR-2主要在血管内皮细胞中表达，VEGFR-3主要在淋巴管内皮细胞中表达[25]。当VEGF与VEGFR结合后，VEGFR胞内信号转导区的酪氨酸发生磷酸化，激活细胞内信号通路，促进血管内皮生长和血管生成[26]。因此，阻断VEGF和VEGFR的结合能有效抑制肿瘤血管生成[27]。

### 3.1　仑伐替尼

仑伐替尼是针对VEGFR、成纤维细胞生长因子受体（fibroblast growth factor receptor，FGFR）、血小板衍生生长因子受体（platelet derived growth factor receptor，PDGFR）等多受体的酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI）[28]。仑伐替尼已被FDA批准用于治疗甲状腺癌、肝细胞癌和肾癌[29]。一项Ⅱ期临床研究（NCT03609359）[30]显示，仑伐替尼联合帕博利珠单抗用于AGC一线或二线治疗时，患者的ORR为69%，mPFS为7.1个月。

### 3.2　呋喹替尼

呋喹替尼是靶向VEGFR-1、VEGFR-2和VEGFR-3的TKI，在中国已被批准用于治疗转移性结直肠癌[31]。在一项Ⅰb/Ⅱ期临床试验中（NCT02415023），呋喹替尼联合紫杉醇作为AGC患者的二线治疗，患者的mOS为8.5个月，mPFS为4个月，ORR为25.9%[32]。FRUTIGA研究是一项在中国开展的随机双盲的Ⅲ期临床试验（NCT03223376），旨在评估呋喹替尼联合紫杉醇对比紫杉醇单药二线治疗AGC患者的疗效和安全性，后续结果令人期待[33]。

## 4 Dickkopf相关蛋白1(dickkopf related protein 1, DKK1)抑制剂

WNT信号通路突变经常导致发育缺陷和癌症，DKK1是WNT通路的强效拮抗剂，通过拮抗WNT通路抑制细胞增殖、凋亡，导致肿瘤生长[34]。研究[35]表明，GC患者血清DKK1水平显著高于健康人群，且血清DKK1水平增加与GC组织中的DKK1过表达密切相关，血清表达水平≥60 pg/mL的患者生存期显著缩短。DKN-01是一种可与DKK1特异性结合的人源化单克隆抗体，有望成为靶向DKK1的新型药物[36]。一项P102/KEYNON-731 Ⅰb期试验(NCT02013154)[37]，给予AGC患者DKN-01联合帕博利珠单抗治疗，DKK1高表达患者的ORR为50%，疾病控制率(disease control rate，DCR)为80%，mPFS为22.1周，mOS为31.6周，而DKK1低表达患者的ORR为0%，DCR为20%，mPFS为5.9周，mOS为17.4周。此外，DISTINGUISH Ⅱa期临床试验(NCT04363801)[38]评估了DKN-01联合替雷利珠单抗及CAPOX方案(卡培他滨+奥沙利铂)一线治疗AGC患者的疗效，患者DCR达96%，ORR为68.2%，其中DKK1高表达患者的ORR达到90%。DKN-01抗体显示出良好的抗肿瘤活性，其对DKK1高表达患者的疗效更为突出，有望成为AGC患者的一线治疗药物。

## 5 靶向HER-2的抗体偶联药物(antibody-drug conjugate，ADC)

人类表皮生长因子(human epidermal growth factor，hEGF)与其受体(HER)特异性识别结合后，促进靶细胞DNA合成及有丝分裂；HER家族包括HER-1、HER-2、HER-3、HER-4四个成员[39]。1986年在GC细胞中首次发现了HRE-2的过表达[40]，其过表达促进肿瘤侵袭和转移[41]。由于曲妥珠单抗治疗失败后，AGC患者后线抗HER-2治疗药物缺乏，新型抗HER-2药物一直在研究中。ADC由重组抗克隆抗体与细胞毒性药物共价结合。抗体与肿瘤表面的特异性抗原结合后被内化，细胞毒性药物被精准释放到肿瘤细胞内，引起肿瘤细胞的损伤和死亡，减少对正常细胞的伤害[42]。

### 5.1 曲妥珠单抗-美坦新(T-DM1)

曲妥珠单抗-美坦新(trastuzumab emtansine，T-DM1)是一种针对HER-2阳性GC的ADC药物，由曲妥珠单抗和小分子微管抑制剂结合而成，T-DM1已被美国FDA批准作为HER-2阳性晚期乳腺癌的二线治疗药物[43]，因此不少实验探究其在GC中的疗效。GATSBY Ⅱ/Ⅲ期临床试验(NCT01641939)[44]结果显示，在既往接受过化疗或靶向治疗后进展的HER-2阳性AGC患者中，T-DM1的疗效并不优于紫杉类药物(mOS为7.9 *vs* 8.6个月，*P*=0.86)，这可能与HER-2阳性转阴有关[45]。

### 5.2 曲妥珠单抗-德鲁替康(T-DXd)

曲妥珠单抗-德鲁替康(trastuzumab deruxtecan，T-DXd；DS-8201)由曲妥珠单抗和人拓扑异构酶Ⅰ抑制剂组成。T-DXd作为三线或多线治疗，应用于既往接受氟嘧啶、铂类药物和曲妥珠单抗治疗失败的HER-2阳性GC患者。T-DXd组患者的mOS为12.5个月，ORR为51%，化疗组患者的mOS为8.4个月，ORR为14%，差异具有统计学意义(*P*<0.05)[46]。在DESTINY-Gastric01 Ⅱ期针对HRE-2低表达患者的探索性队列临床研究中(NCT03329690)，将HER-2低表达且既往接受氟嘧啶、铂类药物，但未接受过抗HER-2治疗的GC/食管胃交界腺癌的患者分为2组。队列1为HER-2免疫组化表达为2+、原位杂交结果阴性的患者；队列2为HER-2免疫组化表达为1+的患者；每组患者均接受每3周一次的T-DXd治疗。结果表明，队列1患者的DCR为89.5%，mOS为7.8个月；队列2患者的DCR为71.4%，mOS为8.5个月[47]，提示T-DXd对HER-2低表达患者可能同样存在临床疗效。

### 5.3 维迪西妥单抗

维迪西妥单抗是由中国自主研发的ADC药物，在一项Ⅱ期临床试验中(NCT03556345)[48]，维迪西妥单抗作为HER-2过表达的AGC患者三线或多线治疗时，患者的ORR为24.8%，mPFS和mOS分别为4.1个月和7.9个月，表现出较好的生存获益，并被批准用于中国HER-2阳性GC患者的三线治疗方案。

尽管ADC药物在治疗GC中取得初步疗效，给AGC患者抗HER-2治疗带来了新曙光，但其安全性及有效性仍有待进一步验证。

## 6 成纤维细胞生长因子受体2(FGFR2)抑制剂

FGFR是一种酪氨酸激酶受体，具有调控细胞生长和迁移、调节血管生成及胚胎发生，维持组织稳态和促进伤口修复的作用，其家族成员包括FGFR1、FGFR2、FGFR3、FGFR4四种受体；FGFR基因突变会导致肿瘤发生，并促进疾病进展[49]。中国GC患者中FGFR-2基因扩增频率约4.6%，且与预后不良相关[50]。因此，FGFR-2可作为GC患者的潜在治疗靶点。贝马里妥珠单抗(bemarituzumab，FPA144)是首个可选择性结合FGFR-2的人源化IgG1单克隆抗体，通过阻断FGF与FGFR-2的结合，抑制下游信号转导，促进FGFR-2内化和降解[51]。在FPA144-001 Ⅰ期临床试验中(NCT02318329)，给予FGFR-2高表达AGC患者单药bemarituzumab治疗，患

者的ORR为17.9%[51]。在FIGHT（FPA144-004）Ⅱ期探索性临床试验中（NCT03694522）[52]，针对FGFR-2过表达的AGC患者，分别给予mFOLFOX6联合Bemarituzumab（试验组）和mFOLFOX6联合安慰剂（对照组）作为一线治疗，以评价Bemarituzumab的疗效。试验组和对照组的mPFS分别为9.5个月和7.4个月，ORR分别为53%和40%，两组均无统计学差异（均$P$=0.073）。该初期试验表明，化疗联合Bemarituzumab单抗治疗虽未明显改善AGC患者的生存，但显示出一定前景的临床疗效。关于Bemarituzumab的FIGHT Ⅲ期验证性试验正在进行中，包括FORTITUDE-101（NCT05052801）和FORTITUDE-102（NCT05111626），有望为AGC患者的治疗带来新的希望。

## 7　RAD3相关蛋白激酶（ataxia telangiectasia and RAD3-related kinase，ATR）抑制剂

DNA损伤修复（DNA damage repair，DDR）基因的改变可导致基因修复障碍，DDR突变对肿瘤的发生发展至关重要[53]。ATR是DDR的关键激酶，ATR在DNA损伤后激活细胞应答，阻滞细胞周期并修复损伤的DNA，避免细胞凋亡[54]。Ceralasertib（AZD6738）是一种选择性的ATR抑制剂，可引起细胞损伤或凋亡[55]。研究[56]表明，ceralasertib联合化疗治疗晚期/转移性黑色素瘤取得了良好的疗效。在一项治疗AGC的Ⅱ期临床试验中（NCT03780608）[57]，ceralasertib联合度伐利尤单抗作为AGC患者二线及多线治疗方案，患者的ORR为22.6%，mPFS为3.0个月，mOS为6.7个月，初步显示了针对AGC患者治疗的疗效。

## 8　结　语

近些年来，尽管化疗联合曲妥珠单抗等分子靶向药物及信迪利单抗、纳武利尤单抗等ICI类药物的治疗，使得AGC患者的预后得到明显改善，但当前更多相关新型药物的研发仍面临很大的挑战，以及由于患者难以耐受的毒性而推进缓慢甚至以失败告终，因此对于AGC患者的治疗仍然是肿瘤科医生面临的难题。本文回顾了目前GC治疗的新靶点及相关药物研究的现状，许多药物也已初步显示出良好的临床疗效及临床应用价值，未来前景可期。

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