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文献综述 REVIEW

胃癌抗血管生成药物治疗的研究进展

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■背景资料
胃癌是消化系统最常见的恶性肿瘤, 居我国恶性肿瘤死亡率的第1位, 传统的手术治疗和化疗预后较差, 分子靶向治疗是近年来肿瘤治疗领域中的研究热点, 其中针对VEGF及VEGFR的抗血管生成治疗在胃癌综合治疗方面取得了较大进展.

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Advances in research of antiangiogenic drugs for gastric cancer

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Abstract
Gastric cancer is the most common cancer of the digestive system and the first leading cause of cancer deaths in China. Conventional surgery and chemotherapeutic regimens can not significantly improve the poor prognosis of gastric cancer. In recent years, molecular targeted therapy has become a hot topic in the treatment of cancers, and many antiangiogenic drugs for treatment of gastric cancer have been developed, including monoclonal antibodies or soluble receptors that bind and neutralize vascular endothelial growth factor (VEGF), tyrosine kinase receptor inhibitors, and antibodies against VEGF receptors (VEGFRs).

Key Words: Gastric cancer; Anti-angiogenesis; Drugs

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摘要
胃癌是消化系统最常见的恶性肿瘤, 居我国恶性肿瘤死亡率的第1位, 传统的手术治疗和化疗预后较差. 分子靶向治疗是近年来肿瘤治疗领域中的研究热点, 其中抗肿瘤血管生成药物的应用在胃癌综合治疗方面取得了较大进展, 包括血管内皮生长因子(vascular endothelial growth factor, VEGF)为靶点的单克隆抗体、可溶性受体、酪氨酸激酶受体抑制剂、血管内皮生长因子受体(vascular endothelial growth factor receptor, VEGFR)为靶点的抗体等.

关键词: 胃癌; 抗血管生成; 药物

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0 引言
尽管新细胞毒性药物的开发利用在一定程度上提高了胃癌的疗效, 但进展期患者的预后仍然较差, 发生远处转移和局部进展的胃癌患者的中位总生存期(overall survival, OS)分别只有9 mo和14 mo[1]. 近年来, 分子靶向药物在胃癌治疗中显示出一定的临床应用价值, 其中针对血管内皮生长因子(vascular endothelial growth factor, VEGF)及VEGFR的抗血管生成治疗在胃癌综合治疗方面取得了较大进展, 本文对此综述如下.

1 VEGF/VEGFR
目前已知的VEGF成员有VEGF-A、VEGF-B、VEGF-C、VEGF-D、VEGF-E以及胎盘生长因子[2], 具有促进内皮细胞增殖和分化、增加微血管通透性、诱导血管生成等多种功能[3].

VEGFR家族主要有VEGFR1、VEGFR2、VEGFR3和Neuropilins, 他们本质上属于酪氨酸蛋白激酶受体. VEGFR1主要存在于单核细胞和内皮细胞中, 与VEGF-A、VEGF-B以及PIGF结合, 促进正常的血管生成和造血功能; VEGFR2与VEGF-A、VEGF-C、VEGF-D结合, 是VEGF发挥促血管生成效应的主要受体, 存在于内皮细胞中, 可调节内皮细胞的增殖, 分化以及微血管的通透性; VEGFR3主要与VEGF-C、VEGF-D结

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合, 是特异表达在淋巴内皮细胞中的另一种酪氨酸激酶受体, 动脉、静脉、毛细血管内皮中基本没有表达. VEGFR3可促进淋巴管的生成, 也可以通过调节VEGFR2信号通路维持脉管系统结构的完整性[2,4]. Neuropilins是VEGF特异性共同受体, 可与VEGFR相互作用, 增强VEGF与VEGFR的亲和力. 有研究表明针对VEGF和Neuropilins的双重靶向治疗比单一用药疗效更好[5].

有研究显示, 与正常胃组织相比, VEGF在胃癌组织中的表达率较高, 并与肿瘤的浸润深度、淋巴结转移、远处转移及临床分期呈正相关, 血清中VEGF浓度升高的胃癌患者预后较差[6-8].

2 抗血管生成药物

抗血管生成治疗是通过抑制肿瘤血管的生成, 从而阻断肿瘤生长和转移必需的氧气和营养供应, 是主要的分子靶向治疗之一. 此外, 抗血管生成还可以诱导肿瘤血管正常化, 使血管结构变得规则、基底膜完整、血管周围支持细胞增多, 这减少了肿瘤出血和转移的机会, 同时增加了肿瘤的氧供和治疗药物的灌注量[9,10].

2.1 VEGF为靶点的单克隆抗体 贝伐单抗(bevacizumab)是世界上首个批准上市的重组抗人VEGF单克隆抗体, 他通过阻断VEGF的分泌及VEGFR家族成员中的VEGFR1和VEFGR2的信号传递来阻止VEFG诱导的细胞增殖和转移, 从而具有抗血管生成作用[11,12]. 临床试验显示贝伐单抗与化疗药物联合能够显著提高晚期结直肠癌有效率, 延长生存期[13].

在胃癌方面一些学者也进行了有益地探讨. 2006年Shah等[14]报道了一项多中心Ⅱ期临床研究的结果. 对手术无法切除、转移性胃腺癌及胃食管连接部腺癌患者给以贝伐单抗联合伊立替康和顺铂, 34例可评价患者的总有效率为65%, 其中20例部分缓解(partial remission, PR), 2例完全缓解(complete remission, CR), 中位无进展生存期(progress free survival, PFS)8.3 mo, 生存期12.3 mo. 2011年Shah等[15]又报道了一项Ⅱ期临床试验的结果. 对转移性胃食管腺癌给以贝伐单抗联合多西他赛、氟尿嘧啶和顺铂, 39例可评价患者的有效率为65%, 6 mo无进展生存率为79%, 中位PFS 12 mo. 随访26 mo, OS和2年生存率分别为16.8 mo和37%. 尽管贝伐单抗与化疗联合能够明确地提高有效率和PFS, 但是否对总生存产生影响尚有一定争议. Ohtsu等[16]报道的一项随机对照、双盲的Ⅲ期临床试验(AVAGAST)结果显示, 774例无法手术的局部晚期或转移性胃癌、胃食管连接部腺癌患者, 在卡培他滨+顺铂一线化疗基础上加入贝伐单抗, 与加入安慰剂相比, PFS由5.3 mo延长至6.7 mo(P = 0.0037); 客观有效率(objective response rate, ORR)由29.5%提高至38%(P = 0.0121), 但未能延长OS(12.1 mo *vs* 10.1 mo, P = 0.1002). 亚组分析显示, 加入贝伐单抗后的生存获益具有一定的种族差异: 美洲人组中位生存期从6.8 mo延长至11.5 mo(HR = 0.63), 欧洲人组从8.6 mo延长至11.1 mo(HR = 0.85), 亚洲或太平洋地区人组从12.1 mo延长至13.9 mo(HR = 0.97). 作者认为不同地区患者在疾病进展后接受二线治疗的比例明显不同, 可能是出现这种差异的主要影响因素(入组患者中接受二线治疗的比例: 亚洲患者66%; 美洲患者21%).

2.2 可溶性受体 Aflibercept是一种可溶性重组诱饵型VEGFR, 是将VEGFR1的第2免疫球蛋白(Ig)域与VEGFR2的第3 Ig域融合后再与人IgG1的一恒定区Fc融合而成的完全人融合蛋白, 可与VEGF-A的所有亚型和相关胎盘生长因子结合[17]. 动物研究显示aflibercept对小鼠肿瘤模型的原发病灶和肺部转移病灶都有一定疗效[18,19]. Ⅰ期临床试验也显示aflibercept单药或联合化疗治疗恶性实体瘤的耐受性和安全性较好, 并能延长患者稳定期[20,21]. aflibercept单药或联合化疗的Ⅱ/Ⅲ期临床试验在晚期或转移性非小细胞肺癌、肾细胞癌等肿瘤中相继展开, 但在胃癌方面还没有类似研究[22].

2.3 酪氨酸激酶抑制剂 索拉非尼(Sorafenib)为口服多靶点酪氨酸激酶抑制剂, 能够抑制VEGFR、血小板衍生生长因子受体、B-Raf、Raf-1以及c-Kit, 进而阻断血管生成[23]. 有研究表明, 索拉非尼单药治疗肝细胞癌转移患者, 能够提高其OS[24], 并且作为二线治疗药物能提高肾细胞癌转移患者PFS[25]. 在胃癌方面, 索拉非尼联合卡培他滨和顺铂治疗进展期胃癌的Ⅰ期临床研究显示[26], 21例入组患者的ORR为62.5%, 中位PFS和OS分别为10.0 mo(95%CI, 7.4-13.8 mo)和14.7 mo(95% CI, 12.0-20.0 mo). Sun等[27]报道了一项Ⅱ期临床试验结果. 对进展期胃腺癌或胃食管连接部腺癌患者给以索拉非尼联合多西他赛和顺铂, ORR为41%, 中位PFS为5.8 mo, 中位OS为13.6 mo[28], 提示索拉非尼与化疗药物联合具有一定的协同作用.

舒尼替尼(Sunitinib)是一类选择性靶向多

■研发前沿
近年来随着对胃癌分子生物学研究的不断深入, 使分子靶向治疗研究成为胃癌治疗的一种新手段, 其中抗血管生成治疗是诸多学者的研究热点.

■相关报道
Liu等研究显示, 与正常胃组织相比, VEGF在胃癌组织中的表达率较高; 同时, VEGF的表达与肿瘤的浸润深度、淋巴结转移、远处转移、临床分期及预后有关.

种受体酪氨酸激酶的新型药物, 能够抑制血小板衍生生长因子受体及VEGFR, 已被FDA批准用于转移性肾癌及对伊马替尼不能耐受或耐药的胃肠间质肿瘤患者的治疗[29,30]. 但舒尼替尼在胃癌治疗中的价值尚待明确. 一项无对照的Ⅱ期临床试验显示, 舒尼替尼单药二线治疗进展期胃腺癌或胃食管连接部腺癌患者的有效率为2.6%, 中位PFS及OS分别为2.3、6.8 mo[31], 与化疗药物单药治疗的临床试验结果相似[32,33].

范得它尼(Vandetanib, ZD6474)是一种合成的苯胺喹唑啉化合物, 为口服小分子酪氨酸激酶抑制剂, 可同时作用于肿瘤细胞表皮生长因子受体、VEGFR及RET酪氨酸激酶, 能够下调肿瘤细胞的血管生成因子以及抑制表皮生长因子对肿瘤血管内皮细胞的信号传导, 进而抑制血管的生成[34]. 临床前的体内实验表明, 范得它尼联合紫杉醇或吉西他滨能更为显著地抑制肿瘤生长[35,36]. 体外和动物试验也表明: 范得它尼能够抑制细胞增殖, 降低肿瘤的微血管密度, 从而抑制肿瘤生长[37-39]. 目前正在进行其与奥沙利铂和多西他塞联合的Ⅱ/Ⅲ临床试验.

SU6668是一种口服多靶点酪氨酸激酶抑制剂, 对VEGFR-2、血小板衍生生长因子和碱性成纤维生长因子受体均有抑制作用. Tokuyama等[40]应用SU6668成功抑制胃癌细胞荷瘤裸鼠肿瘤新生血管生成和腹膜播散. 但SU6668面世时间较短, 其疗效还有待进一步探索.

2.4 VEGFR为靶点抗体 Ramucirumab(IMC1121B)为抗VEGFR-2的完全性人类IgG1单克隆抗体, 具有抗血管生成的作用[41]. 2010年Spratlin等[42]报道了一项有关ramucirumab的Ⅰ期临床试验结果. 试验共入组37例既往治疗失败的晚期实体瘤患者, 给以ramucirumab剂量递增的每周用法, 11例(30%)获PR(包括1例胃癌)或疾病稳定超过6 mo. 目前一项对既往化疗失败的晚期胃癌给以ramucirumab单药或联合紫杉醇的临床试验正在进行[43].

2.5 其他 AMG-386是首个获批的重组Fc-肽融合蛋白类药物, 可以通过中和Tie2受体与促血管生成素1和2之间的相互作用抑制血管生成. 一项Ⅰ期临床试验显示, AMG-386单药或联合化疗在抗实体肿瘤方面有一定的疗效, 且不良反应较轻, 主要为乏力和水肿等[44]. AMG-386联合化疗治疗胃癌或胃食管连接部癌的Ⅱ期临床试验正在进行, 预计2013年7月完成[45]. Alphastatin是由staton等合成的人纤维蛋白原α链末端的24个氨基酸片断, 能够抑制血管的生成, 其机制还不清楚[46]. 体外研究显示, alphastatin能够抑制人脐静脉来源内皮细胞管状结构的形成[47]. 动物模型试验证实, alphastatin可明显抑制人胃癌细胞裸鼠移植瘤的血管生成[48].

■创新盘点
本文就针对VEGF及VEGFR的抗血管生成治疗在胃癌综合治疗方面取得的较大进展进行了综述, 探讨国内外抗血管生成药物治疗的研究进展.

3 结论

血管生成是实体肿瘤生长不可或缺的一部分, 是决定肿瘤生长、转移、复发及预后的关键因素之一. 从1971年哈佛大学医学院Folkman博士[49]提出阻断血管的“饿死肿瘤”假说开始, 抗血管生成治疗受到越来越多的关注, 并取得较大进展, 给胃癌的治疗带来了新的选择. 大量研究证实, 抗血管生成治疗在胃癌治疗中具有广泛的临床应用前景. 但与其他一些肿瘤相比, 如肺癌、结直肠癌, 肾癌等, 胃癌抗血管生成治疗的疗效仍然有限, 特别是在延长总生存期方面, 疗效并不显著. 而且胃癌抗血管生成治疗的研究起步较晚, 需要更多的临床前和临床试验去证实其在胃癌治疗中的作用.

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■应用要点
本文总结了近年来抗血管生成药物治疗的研究进展, 有利于进一步了解抗血管生成治疗并指导临床治疗.

■名词解释
抗血管生成治疗是指通过抑制血管的生成, 从而减少肿瘤细胞的氧气和营养供应, 进而抑制肿瘤生长和转移.

■同行评价
本文就抗血管生成药物在胃癌治疗中的应用做了一简单综述, 重点阐述了以VEGF和VEGFR为靶点的药物, 有助于我们更好的了解胃癌抗血管生成药物的治疗.

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