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文献综述 REVIEW

S-1治疗进展期胃癌的研究进展

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■背景资料
我国为胃癌高发区, 近50%的患者确诊时已为局部晚期或远处转移. 化疗是进展期胃癌治疗不可或缺的手段, 人们也不断寻求着高效低毒的化疗药物. S-1作为在胃癌治疗经典药物-5-氟尿嘧啶基础上研发的新药, 其使用安全性、有效性及适用性被广泛探讨.

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Role of S-1 in treatment of advanced gastric cancer

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Abstract
Gastric cancer is the fourth most common malignancy worldwide. More than 50% of gastric cancer patients have unresectable disease at diagnosis, and there is a high rate of local or distant recurrence, even in patients with an operable tumor. Chemotherapy is regarded as a significant and basic treatment that can provide a longer symptom-free period and improve quality of life. S-1 is a novel oral derivative of 5-FU. Compared with 5-FU, S-1 is more tolerable and effective, and will be more convenient to use for patients with advanced gastric cancer. Recent phase II randomized trials of S-1 based chemotherapy have achieved encouraging results with regard to objective response rate and overall survival. This paper aims to review the efficacy of S-1 in treating advanced gastric cancer, molecular markers that can predict efficacy, and the prospect for therapy with S-1 in combination with new chemotherapeutic drugs or molecularly targeted drugs.

Key Words: S-1; Gastric cancer; Chemotherapy

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摘要
在世界范围内胃癌为第4大常见恶性肿瘤, 我国亦为高发区, 且在确诊时, 约50%的患者已为局部进展或有远处转移, 失去了手术机会. 全身的系统性化疗能够显著延长患者的无进展生存期和总生存时间, 提高生存质量. S-1为口服氟尿嘧啶类新药, 与5-氟尿嘧啶(fluorouracil, 5-FU)安全性、耐受性良好的特点, 且使用方便. 近来一些Ⅱ、Ⅲ期随机临床试验对以S-1为基础的方案进行了研究, 也取得了令人鼓舞的客观缓解率、总生存率. 本文旨在综述S-1在治疗进展期胃癌的疗效、预测疗效相关分子标志物, 并展望S-1与新一代化疗药物、分子靶向药物联合治疗胃癌的前景.

关键词: S-1; 胃癌; 化疗

核心提示: S-1无论单药还是联合其他化疗药物、靶向治疗药物, 均显示出了较高的疗效. 随着对S-1疗效相关分子标志物的不断研究, 相关的基因监测能更好地指导S-1的临床应用.

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0 引言
在世界范围内胃癌为第4大常见恶性肿瘤, 死亡

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率居所有恶性肿瘤第2位. 2008年全球胃癌新发病例数为989600, 死亡病例数为738000[1]. 不同国家甚至同一国家的不同地区胃癌发病差异大, 高、低发区发病率相差近10倍. 胃癌是我国常见的恶性肿瘤之一, 居各类癌症病死率的第一位, 严重威胁人民健康. 目前手术是治疗胃癌最有效的手段, 但大多数患者最终因为肿瘤局部复发或远处转移而死亡. 且在确诊时, 约50%的患者已为局部进展或有远处转移, 失去了手术机会. 对于这类患者, 单纯的最佳支持治疗只有3-5 mo的中位生存时间[2,3].

化疗在进展期胃癌治疗中具有重要地位, 相对于最佳支持治疗, 全身的系统性化疗能够显著延长患者的无进展生存期和总生存时间, 提高生活质量[4,5]. 第一代化疗方案代表为FAM方案(5-FU、多柔比星、丝裂霉素), 此方案不良反应大, 临床已将其淘汰. 第二代化疗方案主要有FAMTX方案(5-FU、多柔比星、甲氨蝶呤)、FP方案(5-FU、顺铂)、ELF方案(依托泊苷VP-16、甲酰四氢叶酸、5-FU)、ECF方案(表柔比星、顺铂、5-FU)等, 有效率为30%-40%. 以上方案在随机对照的III期临床试验中, 仅ECF方案被证实具有可比有效性[6], 已被NCCN指南列为进展期胃癌一线治疗方案之一. 而该方案中位总生存时间约为9-10 mo, 且存在较大毒性, 亚洲地区人种往往不能耐受, 在日本, 仍提倡两药联合方案用于治疗进展期胃癌. 故目前世界范围内缺乏治疗进展期胃癌的标准化疗方案. 高效低毒的联合化疗方案亟待证实. 自2005年以来, 新的化疗药物不断被应用于进展期胃癌的治疗, 临床新药主要包括: 口服氟尿嘧啶类药物、第三代铂类、紫杉类药物以及拓扑异构酶Ⅰ抑制剂. 氟尿嘧啶作为胃癌治疗的基础药物, 经改良为口服制剂, 提高疗效、降低毒性, 且方便使用, 在临床上被广泛应用.

S-1即为口服氟尿嘧啶类新药, 由5-FU前体药物替加氟(Tegafur, FT)及生化调节剂吉美嘧啶(Gimeracil, CDHP)、黏膜保护剂奥替拉西钾(Potassium oxonate, OXO)混合而成. FT在体内经P-450酶作用生成5-FU[7], 肝内二氢嘧啶脱氢酶(dihydropyrimidine dehydrogenase, DPD)可使5-FU失活. 而CDHP是一种DPD抑制剂, 能减缓5-FU的分解代谢, 明显提高5-FU的血药浓度[8,9]. OXO可抑制胃肠道内氟尿嘧啶磷酸化, 从而降低FU的胃肠道毒性[10]. 近来一些Ⅱ期随机临床试验对以S-1为基础的方案进行了研究, 也取得了令人鼓舞的客观缓解率、总生存. 例如Koizumi等[11]以S-1联合顺铂方案治疗进展期胃癌患者, 获得了76%的客观缓解率和383 d的中位总生存时间. 本文旨在综述S-1在治疗进展期胃癌的疗效、预测疗效相关分子标志物, 并展望S-1与新一代化疗药物、分子靶向药物联合治疗胃癌的前景.

■研发前沿
近年来针对胃癌高效低毒的联合化疗方案亟待证实. 临床新药主要包括: 口服氟尿嘧啶类药物、第3代铂类、紫杉类药物以及拓扑异构酶Ⅰ抑制剂. S-1为改良口服氟尿嘧啶类药物, 如何在临床合理应用, 以提高疗效, 改善患者生活治疗, 被广泛研究.

1 S-1单药治疗进展期胃癌的疗效与安全性

S-1单药治疗进展期胃癌患者的疾病控制率约为21%-44%, 中位无进展生存时间(progression free survival, PFS)约为3.9-5.7 mo, 中位总生存时间(overall survival, OS)约为10.8-15.7 mo, 主要III-Ⅳ度血液学不良反应为中性粒细胞减少、贫血, 发生率在5%-10%、10%-20%, III-Ⅳ度非血液学毒性反应主要为乏力、厌食、恶心等, 发生率低[12,13]. 研究表明, S-1单药一线治疗老年进展期胃癌患者的疗效较为可靠、不良反应轻[14]. 但随着年龄的增长, 有效率、PFS、OS逐步降低[15].

近年来, S-1均采用每日给药方案. 但已有文献证实, S-1隔日给药比每日给药能减轻不良反应, 并且能获得较好的临床疗效[16]. 一项前瞻性研究发现在对进展期胃癌的治疗中, S-1隔日给药能获得25%的客观缓解率(overall response ratio, ORR), 及338 d的OS[17]. 在小鼠模型研究中, S-1隔日给药方式与S-1每日给药方式在对肿瘤生长的抑制疗效类似[18]. 对于S-1给药方式值得进一步商榷.

2 以S-1为基础的化疗方案治疗进展期胃癌的疗效及安全性

2.1 S-1联合铂类 在日本, 已把S-1联合顺铂作为一线治疗进展期胃癌的标准方案[19]. 该方案ORR为45%-74%, 中位PFS为5.2-7.8 mo, 中位OS为11-19 mo. III-Ⅳ度不良反应主要有: 中性粒细胞减少16.7%-29%, 贫血10%-20%, 厌食12%-30%, 恶心7%-20%, 乏力6%-13%[20,21].

由于S-1联合顺铂方案存在较大的不良反应, 一些研究尝试S-1联合低剂量顺铂治疗方案, Tsuji等[22]采用S-1 80 mg/(m^2·d), 分两次使用, 顺铂6 mg/(m^2·次), 每周一、四, 持续实行4 wk, 休息2 wk方案, 结果ORR为78.1%, OS为12 mo; Nakata等[23]采用S-1 80-120 mg/(m^2·d), d1-28, 同时顺铂10 mg/(m^2·次), 2次/wk方案, 结果ORR为47.1%, OS为11 mo. S-1联合低剂量顺铂的治疗

■相关报道
随着分子肿瘤学的发展, 化疗药物疗效相关基因的监测, 为个体化治疗提供了依据. 我国学者Wang等就S-1治疗胃癌代谢途径中的关键基因多态性与疗效的关联性做了较为深入的研究, 为进一步探讨相关分子标志物提供了一定的思路.

似乎临床疗效可, 也降低了化疗的不良反应, 同时不需要水化治疗, 适合患者门诊化疗. 但这些均为小样本研究, 需要进一步大规模临床试验来验证.

另外, 研究者还尝试S-1联合奥沙利铂化疗方案[24], 结果ORR为59%, 疾病控制率为84%, PFS为6.5 mo, 1年生存率为71%, OS为16.5 mo. III-Ⅳ度不良反应主要有中性粒细胞22%, 血小板减少13%, 贫血9%, 厌食6%, 乏力6%, 周围神经病变4%. 该方案与S-1联合顺铂方案疗效相似, 但其消化系不良反应明显减轻, 值得进行进一步探讨.

2.2 S-1联合紫杉类 有文献表明[25], 紫杉醇类药物能调节影响S-1疗效的DPD、胸苷酸合成酶(thymidylate synthase, TS)、乳清酸磷酸核糖基转移酶(orotate phosphoribosyl transferase, OPRT)等的表达与活性, 被认为与S-1有协同作用. S-1与紫杉类药物联合在Ⅱ期临床试验中也取得了较好的结果. 一项来自日本的回顾性研究[26]共纳入86例患者, 多西他赛40 mg/m^2, d1, S-1 80 mg/(m^2·d), d1-14, 每3 wk为一疗程, 结果显示ORR为52.4%, PFS为6.5 mo, OS为15.1 mo. 主要的III-Ⅳ度不良反应为中性粒细胞减少36%, 白细胞减少31.7%, 中性粒细胞减少性发热4.7%, 贫血1.2%, 厌食5.8%. 另一项Ⅱ期临床试验[27]共有54例入组, 方案为紫杉醇50 mg/m^2, d1、8、15, S-1 40 mg/m^2, bid, d1-14, 每4 wk为一周期, 结果发现ORR为46.3%, PFS为6 mo, OS为14.3 mo, 主要的III-Ⅳ度不良反应为中性粒细胞减少27.8%, 腹泻9.3%. 而Kunisaki等[28]采用多西他赛联合S-1一线治疗进展期胃癌, 则获得了57.8%的ORR、PFS为6.9 mo, OS为15.3 mo, 最常见的III-Ⅳ度不良反应为中性粒细胞减少40.4%, 其次为白细胞减少29.8%.

2.3 S-1联合拓扑异构酶I抑制剂 S-1与伊立替康均被认为是治疗进展期胃癌的有效药物, 一些研究也探讨了两者联合应用的价值. 一项来自韩国的II期临床试验[29]采用S-1 40 mg/m^2, bid, d1-14; 伊立替康150 mg/m^2, d1, 每3 wk为一疗程. 共有45例患者入组, 结果ORR为48.9%, 中位PFS为5.7 mo, OS为10.4 mo. III-Ⅳ度不良反应主要有中性粒细胞减少29.5%, 呕吐13.6%. 另一项来自日本的研究[30]则获得了54.2%的ORR及581 d的OS. 这些试验提示S-1与伊立替康联合治疗可能可以取得较好的疗效及可接受的不良反应. 但在GC0301/TOP002试验中[31], 该方案的ORR、1.5年生存时间及中位生存时间等指标均未优于S-1单药组, 而已有SPIRITS研究[32]证实S-1联合顺铂比S-1单药明显延长总生存时间, 故一些学者认为伊立替康可能并不是最适合与S-1联合应用于进展期胃癌的一线治疗[33].

2.4 以S-1为基础的三药联合方案 Sato等[34]采用S-1联合多西他赛及顺铂方案一线治疗进展期胃癌的Ⅱ期多中心临床试验显示了很高的有效率. 该试验共入组34例患者, S-1 40 mg/m^2, bid, d1-14; 顺铂 60 mg/m^2、多西他赛60 mg/m^2, d8, 每3 wk为1个周期, 结果ORR为87.1%, 中位PFS为226 d, OS为687 d. III-Ⅳ度不良反应主要有中性粒细胞减少77.4%, 厌食35.5%, 恶心32.3%. 虽然该方案疗效高, 但不良反应较重, 之后一些研究将多西他赛更换为紫杉醇[35-37]. 结果发现ORR为60%-67%, 中位PFS为8-9.4 mo, OS为11-18 mo. 而III-Ⅳ度不良反应主要为血液学毒性, 主要有中性粒细胞减少20%-30%, 血小板减少12.7%, 贫血11.1%, 而非血液学毒性主要有Ⅰ-Ⅱ度的恶心27.2%, 腹泻9.0%. 该方案似乎更为安全, 但两者在疗效及生存时间上的差异需要进一步研究. 另外, 一项来自韩国的研究[38]采用S-1、伊立替康、奥沙利铂联合一线治疗转移性胃癌, S-1 40 mg/m^2, bid, d1-14, 伊立替康150 mg/m^2、奥沙利铂85 mg/m^2, d1, 每3 wk为1个疗程, 其ORR为75%, OS为17.6 mo, 也取得了较好的疗效.

3 其他药物耐药后S-1的疗效与安全性

目前虽然有大量临床试验证实了以S-1为基础的化疗方案在一线治疗进展期胃癌中的疗效, 其在二线以上的治疗中能否获益尚未有肯定的结果.

一项Ⅱ期临床试验[39]评价了已对紫杉醇和顺铂耐药的进展胃癌患者再使用S-1单药解救化疗的疗效及安全性, 共有53例患者入组, 给药剂量为体表面积(BSA)<1.25 m^2, 80 mg/d; BSA<1.5 m^2, 100 mg/d; BSA>1.5 m^2, 120 mg/d, 每日分2次给药, 连续给药4 wk, 休息2 wk. 结果9.4%的患者部分缓解, 34%的患者病情稳定. 中位PFS为4.9 mo, OS为10.4 mo. III-Ⅳ度不良反应主要为中性粒细胞减少症, 发生率为11%, 而非血液学毒性均为Ⅰ-Ⅱ度.

另一项来自日本的回顾性研究[40]则并不推荐S-1作为二线以上治疗进展期胃癌的方案. 该研究纳入了21例患者, 对伊力替康联合顺铂或氟尿嘧啶耐药, 最终无患者获得完全缓解(com-

plete remission, CR)或部分缓解(partial remission, PR), 47.6%的患者病情稳定, 中位OS为271 d, 1年生存率为32%, 且有约20%的患者出现III-IV度贫血或中性粒细胞减少, 分别有9.5%与14.2%的患者出现III-IV度腹泻与厌食.

由于目前这些研究样本量均过小, 且S-1治疗之前耐药的药物不同, 可能对S-1二线以上治疗进展期胃癌的疗效及安全性的评估存在缺陷, 需要进一步的研究来指导临床用药.

4 S-1与靶向药物联合方案的探索

传统抗肿瘤药物最大的缺陷在于缺乏选择性, 在快速杀死肿瘤细胞的同时产生明显不良作用. 而靶向药物能提高恶性肿瘤治疗的特异性, 最大程度杀灭肿瘤细胞而不损伤机体正常细胞, 已成为当前研究热点. 在临床上, 化疗药物联合靶向药物已用于恶性肿瘤的治疗, 取得了较好的疗效, 大量基础及临床研究也在进行中.

Yashiro等[41]评估了Ki23057、舒尼替尼(sunitinib)、伊马替尼(glivec)、拉帕替尼(lapatinib)及SU11274, 这5种小分子靶向药物与S-1联合, 对胃硬癌细胞的生长抑制活性. 最终发现Ki23057与5-FU具有协同抗肿瘤作用. Ki23057作为一种成纤维细胞生长因子受体2抑制剂, 能降低DPD的表达, 增强细胞凋亡速率, 提高p21的表达水平. 其联合S-1比单药S-1显著提高原发灶及淋巴结转移灶的对药物的敏感性. Kobunai等[42]则评估了西妥昔单抗与S-1联合在裸鼠体内的抗肿瘤活性. 他们采用了EGFR高表达, 同时K-ras野生型的SC-2和SC-4两种胃癌细胞系. 结果发现西妥昔单抗与S-1联合应用比单用其中任何一种药物具有更高的抗肿瘤活性. 进一步研究发现, 西妥昔单抗能降低TS mRNA及蛋白表达量, 从而增强S-1的抗肿瘤疗效. 这些试验为进展期胃癌化疗联合靶向治疗方案提供了新的理论依据.

此外, 一些Ⅰ期与Ⅱ期S-1联合靶向药物的临床试验也在进行中. 如2011年第13届ESMO会议上汇报了S-1联合曲妥株单抗一线治疗HER-2阳性的进展期胃癌研究. 同年, 在亚洲肿瘤学高峰论坛中汇报了尼妥珠单抗联合S-1及顺铂方案一线治疗进展期胃癌的随机单中心研究. 另外, 舒尼替尼联合S-1及顺铂方案Ⅰ期临床试验也在进行中.

5 预测S-1治疗进展期胃癌疗效的分子标志物

近年来, 肿瘤的研究已向分子肿瘤学方向发展. 随着药物遗传学和基因组学研究的不断深入, 化疗药物疗效相关的基因监测, 为个体化化疗选择敏感药物提供了依据, 更好地指导临床用药.

由于S-1为复合制剂, CDHP与OXO并无抗肿瘤活性, 对S-1疗效相关分子标志物的研究主要集中在替加氟体内代谢途径相关作用酶上. 替加氟在人体肝脏内经由CYP2A6转化为5-FU, 一项来自中国的研究发现[43], CYP2A6的基因多态性与替加氟生物活化程度相关. CYP2A6*4限制了替加氟向5-FU的转化, 而CYP2A6*1B则能提高5-FU微粒体活性. 作者推测中国人群中CYP2A6*4和CYP2A6*1B为替加氟转化为5-FU个体差异的主要基因表型, 对S-1的疗效可能有一定预测作用, 需进一步的研究证实. 另外, Jeung等[44]分析了5-FU代谢及抗肿瘤途径基因, 包括DPD、OPRT、TS和胸腺嘧啶脱氧核苷磷酸化酶(thymidine phosphorylase, TP)mRNA在胃癌组织中的表达, 对S-1治疗进展期胃癌的预测作用, 结果发现*OPRT*基因高表达, 尤其是OPRT、TP同时高表达的患者, 对S-1的治疗具有较高的客观缓解率(40% *vs* 10%). OPRT高表达, 同时TS低表达能延长患者PFS与OS. 同样有研究发现[45], 患者肿瘤组织中OPRT蛋白高表达相较低表达, 能显著提高S-1治疗进展期胃癌的PFS(23.3 wk *vs* 14.1 wk)与OS (72.4 wk *vs* 55.4 wk), 而活检组织中OPRT与TS的比值则被认为可作为预测进展期胃癌患者行术前S-1新辅助化疗客观反应率的指标[46]. 另外, 由于SPIRITS试验认为S-1联合顺铂方案(PS-1)比S-1单药治疗显著提高患者总生存时间, 但伴随较高的不良反应, Koizumi等[47]试图寻找预测S-1单药比PS-1更具优势的生物标志物, 结果发现组织TP和TS mRNA同时低于其截断值时, S-1单药组的中位总生存时间比PS-1组延长(18.2 wk *vs* 9.4 wk).

此外, 人们还寻求更为简便的方法来预测S-1的疗效. 如有研究表明[48], 循环肿瘤细胞的监测在预测以S-1为基础的方案治疗进展期胃癌的疗效方面有一定的作用, 而作为能指示DPD活性的2-^{13}C-尿嘧啶呼吸试验, 也有研究表明其可用于预测S-1抗肿瘤的疗效[49].

6 结论

S-1无论单药还是联合其他化疗药物、靶向治疗药物, 均显示出了较高的有效率及较长的生存时间, 且以其为基础的化疗方案在其他药物治疗失败后仍有一定疗效, 是胃癌治疗中的一种

■创新盘点

本文旨在综述S-1在治疗进展期胃癌的疗效、预测疗效相关分子标志物, 并展望S-1与新一代化疗药物、分子靶向药物联合治疗胃癌的前景.

■应用要点
本文通过综述以S-1为基础的药物治疗方案在进展期胃癌中的疗效及不良反应, 为临床相关治疗提供了一定的参考, 并重点归纳了S-1个体化化疗初步探索的相关预测基因, 为临床进一步研究提供方向.

有益选择[50], 随着对S-1疗效相关分子标志物的不断研究, 相关的基因监测能更好地指导S-1的临床应用. 相信在对进展期胃癌不断的研究下, 临床医生有更多的治疗手段与方案, 并能最终实现个体化治疗的目标.

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■同行评价
本文对S-1在胃癌治疗中的作用、疗效做了较系统全面的综述, 为临床治疗方案的个体化选择提供了有益的探讨.

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