世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2010年9月8日; 18(25): 2685-2689
ISSN 1009-3079 CN 14-1260/R

文献综述 REVIEW

晚期胰腺癌的化疗进展

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国家自然科学基金资助项目, No. 30770993
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收稿日期: 2010-07-04 修回日期: 2010-07-26
接受日期: 2010-08-03 在线出版日期: 2010-09-08

Advances in chemotherapy of advanced pancreatic cancer

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Received: 2010-07-04 Revised: 2010-07-26
Accepted: 2010-08-03 Published online: 2010-09-08

Abstract
Most patients with pancreatic cancer are diagnosed at advanced stage and have to undergo chemotherapy-based comprehensive therapy. Gemcitabine is still the standard chemotherapeutic drug for pancreatic cancer. Although gemcitabine-based combination therapy has certain curative effects on pancreatic cancer, combined application of targeted drugs can enhance the efficacy of chemotherapy in superiority crowd. This paper reviews the recent advances in chemotherapy of advanced pancreatic cancer.

Key Words: Pancreatic cancer; Chemotherapy; Radiotherapy; Targeted therapy

Xu L, Liu YP. Advances in chemotherapy of advanced pancreatic cancer. Shijie Huaren Xiaohua Zazhi 2010; 18(25): 2685-2689

摘要
胰腺癌在诊断时多数为晚期, 采用以化疗为主的综合治疗. 吉西他滨仍然是化疗的标准用药, 吉西他滨为基础的联合治疗取得了一定的疗效, 靶向药物的应用使优势人群的疗效进一步提高. 本文就多种治疗策略在晚期胰腺癌中的进展作一总结.

关键词: 胰腺癌; 化疗; 放疗; 靶向治疗

徐玲, 刘云鹏. 晚期胰腺癌的化疗进展. 世界华人消化杂志 2010; 18(25): 2685-2689
http://www.wjgnet.com/1009-3079/18/2685.asp

■背景资料
胰腺癌的治疗是当前研究的热点, 以化疗为主的综合治疗是局部晚期及转移性胰腺癌的主要治疗手段. 吉西他滨是目前的标准治疗, 以吉西他滨为主的联合方案的疗效有越来越多的循证医学证据支持. 化疗与靶向药物的联合应用也使部分优势人群的疗效进一步提高.

0 引言
胰腺癌的发病率逐年升高, 在欧美居常见恶性肿瘤的第4位, 在我国位于恶性肿瘤死亡的第9位. 胰腺癌的治疗首选手术治疗, 但由于胰腺解剖位置特殊, 症状缺乏特异性, 早期诊断困难, 80%的患者在确诊时为中晚期, 能够进行根治性手术者仅10%-15%, 术后5年生存率仅15%-20%. 进展期胰腺癌患者的生存期不到3 mo, 5年生存率不到1%. 因此, 晚期胰腺癌多数采用化疗为主的综合治疗.

1 传统化疗
在胰腺癌的传统化疗中, 5-FU是治疗的首选. 2003年ASCO报告了化疗对晚期胰腺癌生存获益的Meta分析[1], 研究纳入29个临床试验的3 458例患者, 比较5-FU为基础的联合方案(262例)和最佳支持治疗(434例)的疗效. 结果显示, 两组总生存期(overall survival, OS)分别为6.38 mo和3.87 mo(P<0.0001). 与最佳支持治疗相比, 5-FU为基础的联合方案延长了患者的生存.

2 吉西他滨单药
吉西他滨的出现使胰腺癌的化疗取得了突破性的进展. 1997年Burris等[2]进行了一项对比吉西他滨和5-FU治疗126例晚期胰腺癌的III期临床研究, 吉西他滨组的OS为5.65 mo, 长于5-FU组的4.41 mo, 1年生存率为18%(P = 0.0009). 结果表明, 吉西他滨单药化疗的疗效明显优于传统

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■研发前沿
放疗在胰腺癌治疗中的作用一直存在争议. 目前的研究支持, 对于局部晚期胰腺癌患者, 同步放化疗优于单纯放疗. 同步放化疗时采用何种药物与放疗同步应用也在不断深入探讨.

化疗. 因此, 吉西他滨成为治疗局部晚期或转移性胰腺癌的金标准药物.

3 吉西他滨联合细胞毒药物化疗

随着吉西他滨治疗胰腺癌临床地位的确立, 在吉西他滨基础上联合细胞毒药物成为人们研究的方向. 但除铂类化合物及卡培他滨外, 大多数有效率并不优于单药. 2003年ASCO年会上, Heinemann等[3]报道了吉西他滨联合顺铂对比吉西他滨单药的III期临床试验, 共入组195例胰腺癌患者. 2组无进展生存期(progression free survival, PFS)分别为5.4 mo和2.8 mo(P<0.01). OS分别为8.3 mo和6.0 mo(P = 0.046). GP组更容易发生3/4度恶心、呕吐(20.9% *vs* 6.4%). 2006年ASCO报告了GERCOR/GISCAD研究机构组织的III期临床研究[4], 该研究比较了吉西他滨联合铂类药物与吉西他滨单药的治疗503例晚期胰腺癌患者的疗效. 2组PFS分别为5.5 mo和3.5 mo(P = 0.003), OS为8.3 mo和6.7 mo(P = 0.031). 单变量分析显示, 疾病分期、ECOG评分和含铂类药物治疗是疾病的独立预后因素. 2010年Poplin等[5]报道了吉西他滨联合顺铂对比吉西他滨单药的GIP-1研究, 该研究入组400例患者, 联合组和单药组的OS分别为7.2 mo和8.3 mo(P = 0.38), PFS分别为3.8 mo和3.9 mo(P = 0.8). 联合组没能提高疗效, 反而引起了更多的血液学毒性. 2005年ASCO报告了吉西他滨联合5-FU对比吉西他滨治疗晚期胰腺癌的III期临床研究[6], 该研究入组473例初治患者. 吉西他滨+5-FU和吉西他滨组的OS分别是5.85 mo和6.2 mo, 1年生存率分别是21%和22%(P = 0.68). 2组3/4度不良反应发生率相似. 结果表明, 在吉西他滨基础上联合5-FU没能延长患者的生存. 2007年Herrmann等[7]报道了比较吉西他滨联合卡培他滨与吉西他滨单药治疗晚期胰腺癌的III期临床研究, 该研究纳入319例患者, 2组OS无差异. 分析提示KPS评分好的患者中位生存期有提高, OS分别是10.1 mo和7.4 mo(P = 0.014). 最常见3/4度不良反应为中性粒细胞减少. 2010年Cunningham等[8]报道了吉西他滨联合卡培他滨对比吉西他滨单药的临床研究, 2组RR分别为19.1%和12.4%(P = 0.034). 2组OS的HR为0.86, P = 0.08; PFS的HR为0.78, P = 0.004. 该研究推荐吉西他滨联合卡培他滨方案治疗进展期胰腺癌. 2008年Heinemann等[9]报道了局部晚期和转移性胰腺癌化疗的Meta分析, 纳入16项研究中的4 465例患者. 结果显示, 与吉西他滨单药相比, 吉西他滨为基础的联合治疗只能使PS评分好的患者死亡风险下降, 而PS评分差的患者不能从联合化疗中获益. 吉西他滨与伊立替康和氟尿嘧啶为基础的联合治疗没显示出优势. 2010年Xie等[10]报道了吉西他滨联合化疗对比吉西他滨治疗晚期胰腺癌的Meta分析, 纳入18项研究中的4 237例患者. 结果显示, 吉西他滨联合奥沙利铂和卡培他滨组的6 mo死亡风险降低(P<0.05). 分析上述研究报道的数据, 尽管吉西他滨与铂类或卡培他滨联合化疗时取得了一定的疗效, 但患者的不良反应较重, 患者的耐受性和生活质量较差, 能够获益的多数是PS评分好的患者. 因此, 吉西他滨单药仍然是晚期胰腺癌一线治疗的标准方案. 吉西他滨与何种药物联合, 如何联合等问题, 尚需进一步研究.

4 吉西他滨联合放疗

放疗在胰腺癌治疗中的作用一直存在争议. 目前的研究支持, 对于局部晚期胰腺癌患者, 同步放化疗优于单纯放疗. 同步放化疗时采用何种药物与放疗同步应用也在不断深入探讨. 一项包括34例患者的随机对照研究发现[11], 吉西他滨同步放化疗在OS、PFS和生活质量方面均优于5-FU的同步放化疗, OS延长(14.5 mo *vs* 6.7 mo, P = 0.027), PFS延长(7.1 mo *vs* 2.7 mo, P = 0.019). 2008年ASCO会议报告了E4201研究[12], 以吉西他滨作为放射增敏剂, 研究放疗在局部晚期胰腺癌中的治疗价值. 研究组在吉西他滨化疗同时给予6 wk适形放疗, 总剂量50.4 Gy, 对照组接受吉西他滨化疗. 研究组和对照组的PFS分别是6.3 mo和6.1 mo(P = 0.34), OS分别为11 mo和9.2 mo(P = 0.044). 与吉西他滨单药相比, 虽然联合放疗显著延长患者生存期, 但由于该研究入组缓慢, 仅入组74例患者后被迫中止, 其结果还需要今后的研究进一步证实. FFCD/SFRO研究对比同步放化疗后序贯吉西他滨和吉西他滨单药的疗效[13], 结果显示序贯组的OS不及单药组(8.6 mo *vs* 13 mo, P = 0.03), 但3/4度不良反应却明显增加. 2010年ASCO报告了吉西他滨为基础的化疗对比同步放化疗治疗局部晚期/无法手术胰腺癌患者的临床研究[14], 结果显示两组疗效相似, OS分别为12.6 mo和12.4 mo(P = 0.36), PFS分别为6.2 mo和8.0 mo(P = 0.73). 从上述研究结果来看, 吉西他滨可作为同步放化疗治疗中的增敏剂, 但单纯化疗与同步放化疗孰优孰劣尚未明确.

■相关报道
最新的研究评价了564例胰腺癌患者的临床症状, 结果表明疲乏和疼痛是独立的生存预测指标, 这两种症状的改善能使胰腺癌患者从治疗中更多的获益.

5 吉西他滨联合生物靶向药物

随着分子靶向药物研究的进展, 近年来多种分子靶向药物尝试用于晚期胰腺癌的治疗, 但总体结果并不理想. 基于胰腺癌常有表皮生长因子受体过表达, SWOG的S0205研究比较了吉西他滨联合西妥昔单抗与吉西他滨单药治疗晚期胰腺癌的疗效[15]. 该研究入组735例患者, 结果显示, OS为6.5 mo *vs* 6.0 mo(P = 0.14), 有改善趋势的PFS为3.5 mo *vs* 3.0 mo(P = 0.058). 西妥昔单抗对晚期胰腺癌的疗效目前尚未获III期临床研究结果的证实. NCIC-CTG研究[16]纳入了569例晚期胰腺癌患者, 随机给予吉西他滨+厄洛替尼或吉西他滨+安慰剂治疗. 结果显示, 两组OS分别为6.24 mo和5.91 mo(P = 0.038). 接受厄洛替尼治疗患者的皮疹严重程度与生存期的延长相关. 然而, 吉西他滨与厄洛替尼联合治疗改善疗效的幅度很小, 治疗成本却大幅提高, 因此未被广泛认可. AViTA研究[17]将607例患者分成治疗组(吉西他滨+厄洛替尼+贝伐单抗)和对照组(吉西他滨+厄洛替尼). 结果显示, 研究组和对照组的OS分别为7.1 mo和6.0 mo(P = 0.2087), PFS为4.6 mo和3.6 mo(P = 0.0002). 由于AViTA研究没有根据分子生物学特征选择治疗策略, 这可能对结果有一定影响. 一项III期临床交叉研究[18]将279例患者分为2组, 一组接受吉西他滨+厄洛替尼, 治疗失败后接受卡培他滨治疗; 另一组接受卡培他滨+厄洛替尼, 治疗失败后接受吉西他滨治疗. 结果显示, 2组一线治疗失败时间(time to treatment failure of first-line therapy, TTF1)分别为3.4 mo和2.4 mo(P = 0.0036), OS为6.6 mo和6.9 mo(P = 0.78). 亚组分析显示, KRAS野生型患者的疗效优于突变型, OS为6.6 mo和8 mo(P = 0.011). 一项II期临床研究报告了吉西他滨加用索拉非尼治疗17例晚期胰腺癌患者的结果[19], 其中仅有2例疾病稳定, OS仅4 mo. 由于疗效较低, 中期分析后试验中止. 因此, 今后的临床研究如果根据患者的遗传学特征或分子标志物选择靶向药物, 有望获得更好的疗效.

6 吉西他滨治疗失败的二线化疗

对吉西他滨治疗后进展或原发耐药的患者, 采用何种二线治疗方案, 目前尚无一致意见. 2008年ASCO会议上报告了CONCO-003研究[20], 入组的均是对吉西他滨一线治疗失败的胰腺癌患者. 研究组为FF方案+奥沙利铂(OFF方案), 对照组为FU+亚叶酸钙(FF方案). 结果显示, OFF组和FF组的OS分别是26 wk和13 wk(P = 0.014), PFS分别为13 wk和9 wk(P = 0.012). 分层分析显示, KPS评分>90分更能从OFF方案中获益(P = 0.012). 因此, OFF方案对吉西他滨耐药的晚期胰腺癌患者是一个可行的二线治疗方案. FOLFIRI和FOLFOX作为二线治疗的II期随机临床研究提示[21], 两组OS分别是16.6 wk和14.9 wk, 疾病控制率(disease control rate, DCR)为23%和17%. XELOX二线治疗39例胰腺癌患者的结果显示[22], DCR为28%, PFS为9.9 wk, OS为23 wk. 一项II期临床研究采用卡培他滨+厄洛替尼二线治疗吉西他滨治疗失败后的30例胰腺癌患者[23]. 结果显示, 患者RR为10%, OS为6.5 mo. 常见的不良反应包括乏力、腹泻、皮疹及手足综合征. 卡培他滨+多西紫杉醇二线治疗胰腺癌的结果显示[24], DCR为32.3%, PFS为2.4 mo, OS为6.3 mo. 另有培美曲塞治疗吉西他滨失败胰腺癌的II期临床研究[25], 结果显示, DCR为23.1%, PFS为7 wk, OS为20 wk. S1治疗21例吉西他滨失败后的患者[26], DCR为52.5%, PFS为4.1 mo, OS为6.3 mo. 然而, 上述方案对晚期胰腺癌患者二线治疗的疗效尚未获得III期临床研究结果的支持.

随着胰腺癌治疗的不断进展, 一些疗效预测相关指标成为研究的热点. 最新的研究评价了564例胰腺癌患者的临床症状[27], 结果表明疲乏(HR: 1.01, P = 0.02)和疼痛(HR: 1.006, P = 0.01)是独立的生存预测指标, 这两种症状的改善能使胰腺癌患者从治疗中更多的获益. RTOG 9704研究的结果显示[28], 胰腺癌术后CA199的低水平(<180或≤90)均提示患者预后较好(P<0.0001). 人类扩展型核苷转运蛋白(human equilibrative nucleoside transporter, hENT)和人类富集型核苷转运蛋白(human concentrative nucleoside transporter, hCNT)均能转运吉西他滨进入细胞. 最近的多项研究均表明[29-31], hENT和hCNT的高表达能使胰腺癌患者从吉西他滨的辅助治疗中更多的获益(P<0.05), 而核糖核苷酸还原酶M1(ribonucleoside reductase subunit M1, RRM1)低表达有使患者从吉西他滨治疗中获益的趋势.

7 结论

目前众多的化疗药物中, 吉西他滨仍是治疗进展期胰腺癌的首选药物. 吉西他滨联合铂类或卡培他滨的方案可能更适合KPS评分好的患者. 靶向药物厄洛替尼联合吉西他滨在一定程度上提高了疗效, 但由于治疗成本大幅度提高, 没能

■创新盘点
本文紧扣晚期胰腺癌治疗以化疗为主这一特征, 围绕吉西他滨治疗金标准这一主线, 就多种治疗方案在晚期胰腺癌中的应用及进展进行了综述.

广泛应用. 尽管多种药物二线治疗胰腺癌取得了一定的疗效, 但标准方案的确立还需要更多III期临床研究结果的支持. 现已发现, hENT1和hCNT3的表达量与胰腺癌对吉西他滨的敏感性密切相关. 随着肿瘤分子生物学技术的迅速发展, 通过特定的分子生物学标志进行个体化治疗, 才能进一步提高胰腺癌的疗效.

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本文选题为热点问题，内容较全面，具有代表性，论述思路清晰，具有很好的可读性.

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