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SOX 方案与 FOLFOX4 治疗进展期胃癌的临床疗效、毒副作用及生存时间比较研究 *

翟宏芳¹ 胡万宁^{2Δ} 孙国贵¹ 陈明达¹ 孙 璐¹

(1 唐山市人民医院放化科 河北 唐山 063000; 2 唐山市人民医院头颈肿瘤外科 河北 唐山 063000)

摘要 目的:探讨 SOX 方案与 FOLFOX4 治疗进展期胃癌的临床疗效、毒副作用及生存时间。**方法:**选取 2013 年 10 月到 2014 年 10 月期间唐山市人民医院收治的进展期胃癌患者 90 例作为研究对象, 根据随机数字表法将其分为 SOX 组与 FOLFOX4 组, 两组均为 45 例。SOX 组患者给予奥沙利铂 + 替吉奥胶囊进行治疗, FOLFOX4 组给予奥沙利铂 + 亚叶酸钙 + 氟尿嘧啶进行治疗。比较两组患者的疾病缓解率、疾病控制率、毒副反应、1 年生存率、2 年生存率和 3 年生存率。**结果:**两组患者的疾病缓解率和疾病控制率经统计分析差异均无统计学意义 ($P>0.05$)。两组患者红细胞下降、血小板下降、腹泻、外周神经症状、手足综合征、肝功能异常发生率比较差异均无统计学意义 ($P>0.05$), FOLFOX4 组 I-II 级白细胞下降、恶心呕吐的发生率高于 SOX 组 ($P<0.05$), 两组 III-IV 级白细胞下降、恶心呕吐的发生率比较差异无统计学意义 ($P>0.05$)。两组患者的 1 年生存率、2 年生存率、3 年生存率经统计分析差异均无统计学意义 ($P>0.05$)。**结论:**SOX 方案与 FOLFOX4 治疗进展期胃癌的临床疗效相近, 且患者的生存时间无明显差异, 但 SOX 方案的白细胞下降、恶心呕吐等毒副反应程度较轻。

关键词:进展期胃癌; SOX 方案; FOLFOX4 方案; 疗效; 毒副作用; 生存时间

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Comparative Study of Clinical Efficacy of SOX and FOLFOX4 in Treatment of Advanced Gastric Cancer*

ZHAI Hong-fang¹, HU Wan-ning^{2Δ}, SUN Guo-gui¹, CHEN Ming-da¹, SUN Lu¹

(1 Department of Chemoradiation, Tangshan People's Hospital, Tangshan, Hebei, 063000, China;

2 Head and Neck Cancer Surgery, Tangshan People's Hospital, Tangshan, Hebei, 063000, China)

ABSTRACT Objective: To investigate the clinical efficacy, toxic side effects and survival time of SOX and FOLFOX4 in the treatment of advanced gastric cancer. **Methods:** A total of 90 patients with advanced gastric cancer, who were treated in Tangshan City people's Hospital from October 2013 to October 2014 were selected and randomly divided into SOX group (n=45) and FOLFOX4 group (n=45). The patients in SOX group were treated with oxaliplatin plus S1 capsule, and the patients in FOLFOX4 group were treated with oxaliplatin plus calcium folate plus fluorouracil. The disease remission rate, disease control rate, toxic side effects, 1 year of survival rate, 2 years of survival rate and 3 years of survival rate were compared between the two groups. **Results:** There was no statistical difference in the disease remission rate and disease control rate between the two groups by statistical analysis ($P>0.05$). There was no significant difference in the incidence of erythrocyte descen, thrombocytopenia, diarrhea, peripheral nerve symptoms, hand foot syndrome and liver dysfunction between the two groups ($P>0.05$). The incidence of I-II grade leucocyte descen and nausea and vomiting in FOLFOX4 group was higher than that in SOX group ($P<0.05$), and there was no significant difference in the incidence of III-IV grade leucocyte descen and nausea and vomiting between the two groups ($P>0.05$). There was no significant difference in 1 year of survival rate, 2 years of survival rate and 3 years of survival rate between the two groups by statistical analysis ($P>0.05$). **Conclusion:** The clinical efficacy of SOX regimen is similar to that of FOLFOX4 regimen in the treatment of advanced gastric cancer, and the survival time of patients is not significantly different. But the degree of toxic side effects such as leukocyte decline, nausea and vomiting is mild in the SOX regimen.

Key words: Advanced gastric cancer; SOX regimen; FOLFOX4 regimen; Efficacy; Toxic side effects; Survival time

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前言

胃癌是一种起源于胃黏膜上皮的恶性肿瘤, 相关文献显

示, 2015 年我国男性最常见的恶性肿瘤中, 胃癌排在第二位, 仅次于肺癌, 女性最常见的恶性肿瘤中, 胃癌排在第三位, 仅次于乳腺癌和肺癌, 由此可见, 胃癌在常见恶性肿瘤中均占有重

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作者简介: 翟宏芳 (1975-), 女, 硕士, 副主任医师, 从事消化系统肿瘤的临床治疗及基础方面的研究, E-mail: yanmwe@163.com

Δ 通讯作者: 胡万宁 (1964-), 男, 硕士, 主任医师, 从事头颈部肿瘤的临床治疗及基础方面的研究, E-mail: bwiege@163.com

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要的地位^[1,2]。临床上根据胃癌患者的病情发展情况可分为早期胃癌和进展期胃癌,其中早期胃癌是指癌组织存在于粘膜层和粘膜下层,而进展期胃癌是指癌组织浸润到胃壁肌层或浆膜层^[3-5]。由于胃癌患者在早期通常无显著的特异性症状,患者难以察觉并且常规体检难以发现,导致大部分患者在确诊时已进入进展期,并且大部分患者已经发生转移,手术治疗难以获得根治性的效果^[6-8]。化疗是临床上治疗进展期胃癌患者的重要方法,但目前尚无统一的用药方案,因此安全高效的治疗方案成为临床上研究的重点^[9,10]。SOX 方案和 FOLFOX4 方案均是临床上治疗进展期胃癌患者的常用方案,关于两个方案的疗效目前尚且存在一定的争议,鉴于此,本研究分析了 SOX 方案与 FOLFOX4 治疗进展期胃癌的临床疗效、毒副作用及生存时间,进一步的对比两种方案的临床价值,为临床治疗提供参考,现报道如下。

1 资料与方法

1.1 一般资料

选取 2013 年 10 月到 2014 年 10 月期间唐山市人民医院收治的进展期胃癌患者 90 例作为研究对象,纳入标准:(1)所有患者均通过胃镜活检和 CT 检查确诊为进展期胃癌;(2)患者预计生存时间大于 3 个月;(3)既往未接受手术治疗或放化疗等抗肿瘤治疗者;(4)无化疗禁忌症者;(5)患者及其家属对本研究知情同意并签署知情同意书。排除标准:(1)合并有其他恶性肿瘤者;(2)卡氏评分(Karnofsky,KPS)<60 分者;(3)心、肝、肾等重大脏器存在器质性病变者;(4)存在免疫系统疾病、血液系统疾病、精神系统疾病者;(5)胃部病变采取放疗者;(6)依从性不高,不配合治疗者。根据随机数字表法将其分为 SOX 组与 FOLFOX4 组,两组均为 45 例。SOX 组男性 25 例,女性 20 例;年龄 43-76 岁,平均(59.64±8.23)岁;KPS 得分 65-80 分,平均(73.26±6.34)分;肿瘤直径:>5 cm 共 24 例,≤5 cm 共 21 例;肿瘤部位:胃上部 11 例,胃中部 16 例,胃下部 18 例;国际抗癌联盟(UICC)分期:IIA 期 4 例,IIIA 期 14 例,IIIB 期 15 例,IIIC 期 12 例;病理类型:低分化腺癌 21 例,中分化腺癌 13 例,黏液腺癌 6 例,印戒细胞癌 5 例;肝转移 3 例,腹腔转移 4 例,卵巢转移 1 例,肺转移 1 例。FOLFOX4 组男性 27 例,女性 18 例;年龄 41-77 岁,平均年龄(60.23±8.56)岁;KPS 得分 64-83 分,平均(74.10±6.21)分;肿瘤直径:>5 cm 共 26 例,≤5 cm 共 19 例;肿瘤部位:胃上部 13 例,胃中部 12 例,胃下部 20 例;UICC 分期:IIA 期 3 例,IIIA 期 16 例,IIIB 期 14 例,IIIC 期 12 例;病理类型:低分化腺癌 23 例,中分化腺癌 12 例,黏液腺癌 5 例,印戒细胞癌 5 例;肝转移 4 例,腹腔转移 3 例,卵巢转移 1 例,肺转移 1 例。两组患者的一般资料经统计分析差异无统计学意义($P>0.05$),均衡可比。本次研究已通过唐山市人民医院伦理委员会的审批。

1.2 治疗方法

SOX 组患者给予 SOX 方案进行治疗,将奥沙利铂(江苏恒瑞医药股份有限公司,国药准字:H20000337,规格:50 mg/瓶)加入 5%的葡萄糖注射液静脉滴注,剂量为 130 mg/m²,第 1d;同时采用替吉奥胶囊(山东新时代药业有限公司,国药准字:H20080802,规格:20 mg)饭后口服治疗,体表面积 <1.25

m²,每次 40 mg;1.25 m²≤体表面积 <1.50 m²,每次 50 mg;体表面积 >1.50 m²,每次 60 mg,2 次/d,第 1d-14d,第 15d-21d 停药,21d 为一周期。FOLFOX4 组采用 FOLFOX4 方案进行治疗,奥沙利铂加入 5%的葡萄糖注射液静脉滴注,剂量为 85 mg/m²,第 1d;亚叶酸钙(哈尔滨三联药业股份有限公司,国药准字:H20034073,规格:100 mg)加入生理盐水中静脉滴注,剂量为 200 mg/m²,第 1d-2d;氟尿嘧啶(沈阳药大雷允上药业有限公司,国药准字:H21021858,规格:10 mL:0.25 g)静脉推注,剂量为 400 mg/m²,后续采用氟尿嘧啶加入生理盐水中静脉滴注 22h,剂量为 600 mg/m²,第 1d-2d,14d 为一周期。两组患者在化疗两个周期后评定疗效。

1.3 疗效评价标准

治疗后对两组治疗效果进行评估,参考标准为世界卫生组织制定的实体瘤疗效评价标准^[11],完全缓解(complete remission,CR):治疗后肿瘤病灶全部消失,并且持续时间超过 1 个月;部分缓解(partial remission,PR):肿瘤最大直径和最大垂直直径的乘积与治疗前比较缩小超过 50%,且持续时间超过 1 个月;疾病稳定(stable disease,SD):肿瘤最大直径和最大垂直直径的乘积与治疗前比较缩小低于 50%,或者增大低于 25%,持续时间超过 1 个月;疾病进展(disease progression,PD):肿瘤最大直径和最大垂直直径的乘积与治疗前比较增大超过 25%。疾病缓解率=(CR 例数+PR 例数)/总例数*100%。疾病控制率=(CR 例数+PR 例数+SD 例数)/总例数*100%。

1.4 毒副作用

参考世界卫生组织制定的抗癌药物急性及亚急性毒性反应分度标准进行毒副反应评估^[12],主要观察患者的白细胞下降、红细胞下降、血小板下降、恶心呕吐、腹泻、外周神经症状、手足综合征、肝功能异常等毒副作用的情况,根据严重程度给予 I-IV 级的分类,等级越高说明越严重。

1.5 生存时间

对所有患者均进行为期 3 年的随访,随访方式为电话随访或患者定期门诊复查,随访时间满 3 年或在 3 年内患者死亡则停止随访。记录患者的 1 年生存率、2 年生存率和 3 年生存率。

1.6 统计学方法

采用 SPSS22.0 进行统计分析,临床疗效、毒副作用、生存率等计数资料以[n(%)]的形式表示,采用 χ^2 检验,将 $\alpha=0.05$ 作为检验标准。

2 结果

2.1 两组患者的临床疗效比较

两组患者的疾病缓解率和疾病控制率经统计分析差异均无统计学意义($P>0.05$),见表 1。

2.2 两组患者的毒副作用比较

两组患者红细胞下降、血小板下降、腹泻、外周神经症状、手足综合征、肝功能异常发生率比较差异均无统计学意义($P>0.05$),FOLFOX4 组 I-II 级白细胞下降、恶心呕吐的发生率高于 SOX 组($P<0.05$),两组 III-IV 级白细胞下降、恶心呕吐的发生率比较差异无统计学意义($P>0.05$),见表 2。

2.3 两组患者的生存时间比较

两组患者的 1 年生存率、2 年生存率、3 年生存率经统计分

析差异均无统计学意义($P>0.05$),见表3。

表 1 两组患者的临床疗效比较[n(%)]
Table 1 Comparison of clinical efficacy between two groups [n (%)]

Groups	n	CR	PR	SD	PD	Disease remission rate	Disease control rate
FOLFOX4 group	45	5(11.11)	15(33.33)	18(40.00)	7(15.56)	20(44.44)	38(84.44)
SOX group	45	3(6.67)	18(40.00)	16(35.56)	8(17.78)	21(46.67)	37(82.22)
χ^2						0.045	0.080
P						0.832	0.777

表 2 两组患者的毒副作用比较[n(%)]
Table 2 Comparison of toxic and side effects between two groups [n (%)]

Groups	n	Grade	Leukocyte descent	Erythrocyte descent	Thrombocytopenia	Nausea and vomiting	Diarrhea	Peripheral nerve symptom	Hand foot syndrome	Liver dysfunction
FOLFOX4 group	45	I-II	20(44.44)*	15(33.33)	7(15.56)	25(55.56)*	7(15.56)	3(6.67)	9(20.00)	5(11.11)
		III-IV	4(8.89)	0(0.00)	0(0.00)	5(11.11)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
SOX group	45	I-II	10(22.22)	18(40.00)	12(26.67)	12(26.67)	5(11.11)	4(8.89)	10(22.22)	3(6.67)
		III-IV	2(4.45)	0(0.00)	0(0.00)	3(6.67)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

Note: compared with I-II grade in the SOX group, * $P<0.05$.

表 3 两组患者的生存时间比较[n(%)]
Table 3 Comparison of survival time between two groups[n (%)]

Groups	n	1 year survival rate	2 years survival rate	3 years survival rate
FOLFOX4 group	45	37(82.22)	29(64.44)	20(44.44)
SOX group	45	35(77.78)	28(62.22)	21(46.67)
χ^2		0.278	0.049	0.045
P		0.598	0.827	0.832

3 讨论

胃癌是消化系统最常见的恶性肿瘤,其发病率受到地域环境和当地饮食习惯的影响,幽门螺杆菌感染和遗传易感性也是胃癌的重要影响因素^[13,14]。近年来,我国胃癌的发病率得到了明显的控制,已趋于稳定状态,但仍然是最为常见的恶性肿瘤,对人民群众的生命健康影响巨大。手术治疗是治疗早期胃癌患者的最有效的方法,然而大部分胃癌患者在确诊疾病时已进入进展期,其在行手术后体内仍保留有微小转移肿瘤细胞,导致患者在术后易出现复发现象,因此在围手术期的综合化疗具有重要的意义^[15-17]。胃癌患者的化疗方式主要分为四种:新辅助化疗、辅助化疗、姑息化疗以及局部化疗,目前临床上尚无统一的化疗方案,如欧美等国家通常是用 DCF 化疗方案(多西他赛+顺铂+氟尿嘧啶)治疗胃癌患者,而我国和日本、韩国等国家则多用 SOX 方案及 FOLFOX4 方案^[18-20]。

在本次研究中,两组患者的疾病缓解率和疾病控制率、1 年生生存率、2 年生生存率、3 年生生存率方面比较差异均无统计学意义($P>0.05$),这说明两种化疗方案的近期疗效和远期疗效相当,对患者的疾病控制能力和远期生存能力的影响无明显的差

异。奥沙利铂是一种二氨环己烷的铂类化合物,为第 3 代铂类抗癌药,其具有较好的水溶性,并且毒性较低,可与多种化疗药物联用,在临床上被广泛用于消化系肿瘤的治疗^[21,22]。奥沙利铂可以与 DNA 形成铂链加合物,在 DNA 内部的两个鸟嘌呤或相邻的腺嘌呤和鸟嘌呤之间插入铂原子,进而导致 DNA 链出现断裂,影响其进行有效的复制和转录,进而抑制肿瘤细胞的增殖,起到抗肿瘤的作用^[23]。氟尿嘧啶是一种抗代谢抗肿瘤药,其在细胞内可通过转化为能有效抑制脱氧胸苷酸合成酶产生的氟尿嘧啶脱氧核苷酸后,对脱氧尿苷酸甲基化转变为脱氧胸苷酸这一过程发挥阻断作用,进而干扰肿瘤细胞中 DNA 的合成^[24]。此外,氟尿嘧啶对 RNA 的合成也具有一定的干扰作用。替吉奥是一种氟尿嘧啶前体药物,是由替加氟和两类调节剂(吉美嘧啶、奥替拉西钾)组成,其中替加氟经患者口服后在其体内将转变为氟尿嘧啶,进而产生抗肿瘤作用,而吉美嘧啶是一种氟尿嘧啶分解代谢酶(dihydropyrimidine dehydrogenase,DPD)的选择性抑制剂,可与 DPD 发生拮抗作用,进而增加氟尿嘧啶的浓度和作用时间,增强化疗效果^[25,26]。目前临床上关于 SOX 方案及 FOLFOX4 方案的化疗效果尚有争议,如翁伟明^[27]等人的研究显示,SOX 方案对于进展期胃癌患者的治疗效果要优

于 FOLFOX4 方案,而黄东宁^[29]等人的研究则显示两种方案对于胃癌患者的治疗效果相似。这可能是因为不同研究选取的病例数存在一定的差异,且大部分研究的病例数均较少,会在一定程度上影响结果。此外,进展期胃癌患者的肿瘤分期仍然较广,而选取病例数中不同分期所占比例不同也促进研究结果的差异化。本研究结果还显示,两组患者红细胞下降、血小板下降、腹泻、外周神经症状、手足综合征、肝功能异常发生率比较差异均无统计学意义 ($P>0.05$),FOLFOX4 组 I-II 级白细胞下降、恶心呕吐的发生率高于 SOX 组 ($P<0.05$),两组 III-IV 级白细胞下降、恶心呕吐的发生率比较差异无统计学意义 ($P>0.05$)。这说明两组患者均未出现严重的毒副反应现象,且 SOX 方案给患者带来的白细胞下降、恶心呕吐等毒副反应较小,这主要是因为替吉奥胶囊相较于氟尿嘧啶给人体带来的不良反应较为轻微,替吉奥胶囊中的奥替拉西钾被口服吸收后主要分布在人体肠胃道区域,该药物可有效抑制替加氟转变的氟尿嘧啶磷酸化,进而减少氟尿嘧啶磷酸化产物的生成,降低肠胃道不良反应,这在 Li Z 等人的研究报道中可以加以佐证^[29,30]。

综上所述,SOX 方案及 FOLFOX4 方案对于进展期胃癌患者的治疗效果和生存时间的影响无明显差异,而 SOX 方案可有效降低白细胞下降、恶心呕吐等毒副反应,可适当降低患者的化疗痛苦,利于提高患者的治疗依从性。

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