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乌苯美司胶囊联合 SOX 化疗对晚期胃癌患者的临床疗效研究 *

李 炜 姚忠强 柳仲秋 贺启华 喻小静 范志刚

（西安交通大学附属汉中 3201 医院 肿瘤内科 陕西 汉中 723000）

摘要 目的：探讨乌苯美司胶囊联合 SOX 化疗对晚期胃癌患者的临床疗效及安全性。**方法：**选择 2013 年 9 月至 2015 年 9 月我院接诊的 90 例晚期胃癌患者，通过随机数表法分为观察组(n=45)和对照组(n=45)。对照组给予 SOX 化疗方案，观察组在此基础上联合乌苯美司胶囊。比较两组治疗前后 CD_4^+、CD_8^+、CD_4^+/CD_8^+、血清基质金属蛋白酶(MMP)-2、MMP-9 水平、临床疗效、不良反应发生情况以及 6 个月、12 个月生存率。**结果：**治疗后，观察组 CD_4^+、CD_4^+/CD_8^+ 显著高于对照组(P＜0.05)，血清 MMP2、MMP-9 水平明显低于对照组(P＜0.05)；临床疗效总有效率高于对照组[68.89%(31/45)vs48.89%(22/45)](P＜0.05)，血小板下降、白细胞下降、恶心呕吐、肝功异常的发生率均显著低于对照组(P＜0.05)。观察组在 6 个月、12 个月时生存率均高于对照组[93.33%(42/45)vs77.78%(35/45)，82.22%(37/45)vs57.78%(26/45)](P＜0.05)。**结论：**与单用 SOX 方案相比，乌苯美司胶囊联合 SOX 化疗方案治疗晚期胃癌患者的效果显著，可有效改善免疫功能，提高远期生存率，且安全性更高。

关键词：晚期胃癌；乌苯美司胶囊；替吉奥；奥沙利铂

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Clinical Effect of Ubenimex Capsules Combined with SOX Chemotherapy on Treatment of Advanced Gastric Cancer*

LI Wei, YAO Zhong-qiang, LIU Zhong-qiu, HE Qi-hua, YU Xiao-jing, FAN Zhi-gang

(Department of oncology, the 3201 Affiliated Hospital of Xi'an Jiao Tong University, Hanzhong, Shaanxi, 723000, China)

ABSTRACT Objective: To study the clinical effect and safety of ubenimex capsules and SOX chemotherapy on the advanced gastric cancer. **Methods:** 90 patients with advanced gastric cancer who were treated in our hospital from September 2013 to September 2015 were selected and randomly divided into the observation group (n=45) and the control group (n=45). The patients in the control group were treated with SOX chemotherapy, while the patients in the observation group were treated with ubenimex capsules on the basis of control group. Then the serum levels of MMP-2 and MMP-9, the immune functions, the clinical efficacy, the adverse reactions and survival rate of two groups were observed and compared before and after the treatment. **Results:** After treatment, the CD_4^+, $CD_4^+/CD8^+$ in the observation group were higher than those of the control group (P<0.05); The levels of MMP2 and MMP-9 in the observation group were lower than those of the control group (P<0.05); The total effective rate of the observation group was higher than that of the control group [68.89%(31/45) vs 48.89%(22/45)] (P<0.05); The incidence of thrombocytopenia, leukopenia, nausea and vomiting and abnormal liver functions in the observation group was lower than that of the control group (P<0.05); The survival rate of the observation group was higher than that of the control group at 6 months and 12 months [93.33% (42/45) vs 77.78% (35/45), 82.22% (37/45) vs 57.78% (26/45)](P<0.05). **Conclusion:** Compared with SOX chemotherapy alone, ubenimex capsules and SOX chemotherapy could effectively improve the immune function, enhance the long-term survival rate with high safety of patients with advanced gastric cancer.

Key words: Advanced gastric cancer; Ubenimex capsules; Tegafur; Oxaliplatin

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前言

胃癌是临床上发病率较高的恶性肿瘤，手术是首选治疗方案，但由于多种因素的影响，单纯手术难以达到预期效果，且多数患者在发现使已处于晚期，没有了根治性手术的机会，化疗对此类患者显得极未重要[1,2]。近年来，替吉奥联合奥沙利铂(SOX)化疗方案在临床上表现出较好的抗肿瘤活性，尤其适用于储备能力较差的晚年胃癌患者，但其防止肿瘤细胞侵袭转移的效果仍不尽人意[3]。乌苯美司胶囊具有诱导肿瘤细胞凋亡的作用，并可提高免疫功能，目前也逐渐应用于肿瘤的治疗[4,5]。本研究在 SOX 化疗方案的基础上联合应用乌苯美司胶囊治疗晚期胃癌患者，探讨其临床疗效及安全性。

1 资料与方法

1.1 一般资料

选择 2013 年 9 月至 2015 年 9 月我院接诊的晚期胃癌患

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作者简介：李炜(1980-)，男，本科，主治医师，主要从事肿瘤放化疗方面的研究，电话：13319156612

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者 90 例。纳入标准[6]:① 符合胃癌诊断标准,且经过病理学检查得以确诊,TNM 分期Ⅲ~Ⅳ期;② 化疗、放疗初治者;③ 预计生存时间>3 个月;④ 患者及其家属对此次研究知情同意。排除标准[7]:① 存在神经系统转移;② 合并重症感染;③ 无法耐受化疗;④ 对研究药物过敏;⑤ 存在肿瘤相关出血病史、或其余恶性疾病。通过随机数表法分为观察组和对照组,各 45 例。观察组男 25 例,女 20 例;年龄 60~83 岁,平均(56.89± 1.36)岁;其中腺癌 34 例,粘液癌 10 例,未分化癌 1 例;TNM 分期Ⅲ期 15 例,Ⅳ期 30 例。对照组男 27 例,女 18 例;年龄 61~84 岁,平均(56.96± 1.34)岁;其中腺癌 36 例,粘液癌 8 例,未分化癌 1 例;TNM 分期Ⅲ期 17 例,Ⅳ期 28 例。本次研究已获得我院伦理委员会批准,两组患者一般资料比较差异均无统计学意义 (P>0.05),具有可比性。

1.2 治疗方法

对照组应用 SOX 化疗方案,在化疗 1~14 d 使用替吉奥胶囊 (规格 20 mg,厂家:山东新时代药业有限公司,国药准字 H20080802)的口服,剂量根据体表面积(S)计算:S>1.5 m^2,60 mg/ 次;1.5 m^2≥ S>1.25 m^2,50 mg/ 次;S≤ 1.25 m^2,40 mg/ 次;2 次 /d;化疗第 1d,使用 130 mg/ m^2 奥沙利铂(规格 50 mg,厂家:南京制药厂有限公司,国药准字 H20000686) 的静脉滴注,时间>2 h。以 21 d 为 1 个周期。观察组在对照组基础上,在化疗第 1 d,清晨顿服乌苯美司胶囊(规格 30 mg,厂家:四川绿叶宝光药业股份有限公司,国药准字 H20123287),30 mg/ 次,1 次 /d。使用周期和对照组相同。两组均连续治疗 3 个周期。

1.3 观察指标

① 免疫功能:检测 CD_3^+、CD^{4+}、CD_8^+、CD_4^+/CD_8^+ 水平;② 使用酶联免疫吸附法对基质金属蛋白酶 (MMP)-2、MMP-9 检测,试剂盒购于上海研卉生物科技有限公司;③ 记录治疗过程中不良反应;④ 对患者进行 1 年随访,记录生存率。

1.4 疗效评定标准

根据世界卫生组织实体瘤客观疗效评价标准 (RECIST)[8],完全缓解(CR):肿瘤完全消失,且维持时间>4 周;部分缓解(PR):肿瘤病灶直径缩小>50%,无新病灶出现,且维持时间>4 周;稳定(SD):肿瘤直径缩小 35%~50%,无新发病灶,且维持时间>4 周;进展(SD):肿瘤直径缩小<25%,或增加>25%,或存在新发病灶。总有效率 =(CR+PR)/ 总例数× 100%。

1.5 统计学分析

数据处理使用 spss18.0 软件包,计量资料表示以均数± 标准差($\bar{x}$± s)表示,采用 t 检验,计数资料以例(%)表示,采用 x^2 检验,以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后免疫功能的比较

两组治疗前 CD_3^+、CD_4^+、CD_8^+、CD_4^+/CD_8^+ 水平比较差异无统计学意义(P>0.05);治疗后,两组 CD_3^+、CD_8^+ 无显著变化(P>0.05),CD_4^+、CD_4^+/CD_8^+ 均较治疗前显著升高,且观察组 CD_4^+、CD_4^+/CD_8^+ 明显高于对照组(P<0.05),见表 1。

表 1 两组治疗前后免疫功能指标的对比($\bar{x}$± s)

Table 1 Comparison of the immune function index between the two groups before and after treatment($\bar{x}$± s)

Groups		CD_3^+	CD_4^+	CD_8^+	CD_4^+/CD_8^+
Observation group(n=45)	Before treatment	64.53± 3.48	27.45± 2.34	25.48± 2.42	0.94± 0.21
	After treatment	63.84± 3.40	37.95± 2.68*#	25.84± 2.47	1.58± 0.32*#
Control group(n=45)	Before treatment	64.43± 3.53	27.56± 2.28	25.50± 2.41	0.92± 0.23
	After treatment	63.90± 3.27	30.85± 2.49*	25.76± 2.2.45	1.20± 0.27*

Note: Compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

2.2 两组治疗前后血清 MMP2、MMP-9 水平的比较

治疗前,两组血清 MMP2、MMP-9 水平比较差异无统计学意义(P>0.05);治疗后,两组血清 MMP2、MMP-9 水平均较治疗前显著降低,且观察组 MMP2、MMP-9 水平明显低于对照组(P<0.05),见表 2。

表 2 两组治疗前后血清 MMP-2、MMP-9 水平比较($\bar{x}$± s,ng/L)

Table 2 Comparison of the serum levels of MMP-2 and MMP-9 between the two groups before and after treatment ($\bar{x}$± s)

Groups		MMP-2	MMP-9
Observation group(n=45)	Before treatment	4758.34± 775.95	2485.93± 454.34
	After treatment	4018.23± 644.12*#	1875.43± 244.26*#
Control group(n=45)	Before treatment	4768.21± 771.92	2491.12± 442.12
	After treatment	4458.93± 701.25*	2184.99± 317.85*

Note: Compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

2.3 两组临床疗效的比较

观察组总有效率为 68.89%,明显高于对照组(48.89%,P<0.05),见表 3。

2.4 两组不良反应发生情况的比较

观察组血小板下降、白细胞下降、恶心呕吐、肝功异常发生率均显著低于对照组低(P<0.05),两组外周静脉炎、口腔黏膜炎的发生率比较差异无统计学意义(P>0.05),见表 4。

2.5 两组生存率的比较

观察组在 6 个月、12 个月时生存率分别为 93.33%、77.78%,均显著高于对照组(82.22%、57.78%)(P<0.05),见表 5。

表 3 两组临床疗效比较(例,%)

Table 3 Comparison of the clinical efficacy between the two groups (n, %)

Groups	CR	PR	SD	PD	Total effective rate
Observation group(n=45)	5(11.11)	26(57.78)	8(17.78)	6(13.33)	31(68.89)*
Control group(n=45)	2(4.44)	20(44.44)	12(26.67)	11(24.44)	22(48.89)

Note: Compared with the control group, *P＜0.05

表 4 两组不良反应发生情况的比较(例,%)

Table 4 Comparison of the incidence of adverse reactions between the two groups (n, %)

Groups	Thrombocytopenia	Leukopenia	Nausea and vomiting	Abnormal liver function	Peripheral phlebitis	Oral mucositis
Observation group(n=45)	6(13.33)*	5(11.11)*	7(15.56)*	4(8.89)*	5(11.11)	6(13.33)
Control group(n=45)	15(33.33)	14(31.11)	17(37.78)	13(28.89)	8(17.78)	8(17.78)

Note: Compared with the control group, *P＜0.05.

表 5 两组生存率的比较(例,%)

Table 5 Comparison of the survival rate between the two groups (n, %)

Groups	Six months	Twelve months
Observation group(n=45)	42(93.33)*	37(82.22)*
Control group(n=45)	35(77.78)	26(57.78)

Note: Compared with the control group, *P＜0.05.

3 讨论

恶性肿瘤的发生、发展和患者的免疫功能衰退存在着密切的关系,再加上多数化疗药物会产生较多毒副反应,在一定程度上也会损伤到免疫功能,影响疗效及预后[9,10]。乌苯美司是一种橄榄网状链霉菌低分子产物,具有免疫调节的作用,其主要作用机制是通过与细胞表面的亮氨酸氨基肽酶之间互相结合,直接刺激淋巴细胞及单核细胞,并间接抑制单核细胞、淋巴细胞上促吞噬肽分解代谢的氨基肽酶[11,12]。乌苯美司可使白细胞介素(IL)-2 敏感性及 IL-2 产物增加,通过刺激 T 淋巴细胞、骨髓干细胞、激活吞噬细胞而达到抗肿瘤效果[13]。Wang X 等[14]的研究现实乌苯美司可有效改善肿瘤缓解 T 细胞亚群,使其恢复到正常水平,修复患者损伤的细胞免疫功能。

在机体细胞免疫中,T 细胞亚群起着重要作用，而癌细胞可对机体免疫功能造成损伤，且随着疾病的不断发展,CD_3^+、CD_4^+ 等指标也会逐渐呈下降趋势,而在化疗药物中,虽然会对患者免疫功能造成一定影响,但在大量消灭癌细胞后,可解除细胞免疫抑制,促进免疫功能的提高[15]。本次研究中,联合乌苯美司的患者在治疗后 CD_4^+、CD_4^+/CD_8^+ 水平明显比单用 SOX 化疗方案的患者更优异,进一步提示联合用药可更有效的解除细胞抑制,改善细胞免疫功能。在联合用药患者治疗后总有效率高达 68.89%，明显比单独 SOX 化疗的 48.89%更具有优势,且在血小板下降、白细胞下降、恶心呕吐、肝功异常发生率上也较低,显示出联合用药不仅可提高疾病治疗效果,还可减少化疗所产生的毒副反应。与 Liu S 等[16]的研究具有相似性。

在肿瘤侵袭转移过程中,肿瘤细胞首先突破细胞基质和毛细血管基底膜,侵袭到周围组织,或在血循环、淋巴系统中存在,随后在循环系统的迁移,逃逸机体免疫监视系统,进入远处组织或器官中,生成肿瘤血管,在远处产生转移病灶[17,18]。相关研究表明 MMP-2、MMP-9 是肿瘤侵袭转移转移中关系最密切的MMPs,胃癌细胞及组织可分泌 MMP-2、MMP-9,二者也是与胃癌侵袭转移高度相关的重要分子[19]。Soni P 等[20]研究证实在伴有淋巴结和(或)远处转移的患者中,MMP-2、MMP-9 表达明显较高,且和疾病严重程度存在着密切的关系,在判断预后中具有积极意义。本研究显示联合乌苯美司的患者在治疗后 MMP-2、MMP-9 的下降程度明显由于单用 SOX 化疗的患者,提示联合用药在一定程度上可对胃癌细胞的侵袭转移进行抑制,这也可能是患者生存率较高的原因之一。

综上所述，乌苯美司胶囊联合 SOX 化疗方案治疗晚期胃癌患者的效果显著,可有效改善免疫功能,且可减轻化疗毒副反应,提高远期生存率。

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