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西黄胶囊联合 GP 方案对中晚期乳腺癌患者血清 TNF-α,VEGF,MMP-2,MMP-9 水平的影响 *

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摘要 目的:研究西黄胶囊联合 GP 方案对中晚期乳腺癌患者血清肿瘤坏死因子 -α(TNF-α)、人血管内皮细胞生长因子(VEGF)、基质金属蛋白酶 -2(MMP-2)、基质金属蛋白酶 -9(MMP-9)的影响。**方法:**入选 2014 年 3 月至 2015 年 2 月我院收治的 88 例中晚期乳腺癌患者,按照患者入院顺序分为观察组和对照组,44 例每组。对照组使用 GP 方案进行治疗,观察采取西黄胶囊联合 GP 方案进行治疗。比较两组患者治疗前后血清 TNF-α、VEGF、MMP-2、MMP-9 水平的变化、临床疗效和不良反应的发生情况。**结果:**观察组的总有效率显著高于对照组[84.09%(37/44) vs 50.00%(22/44)](P<0.05)。治疗前,两组患者血清 TNF-α、VEGF、MMP-2、MMP-9 水平比较差异无统计学意义(P>0.05);治疗后,两组患者的血清 TNF-α、VEGF、MMP-2、MMP-9 水平均较治疗前显著降低(P<0.05),观察组的血清 TNF-α、VEGF、MMP-2、MMP-9 水平均明显低于对照组(P<0.05)。两组患者恶心呕吐等不良反应率比较差异无统计学意义(P>0.05),观察组脱发、腹泻、肝功能异常、食欲下降、贫血、白细胞下降发生率明显低于对照组(P<0.05)。**结论:**西黄胶囊联合 GP 方案较单用 GP 方案能更有效降低中晚期乳腺癌患者血清 TNF-α、VEGF、MMP-2、MMP-9 水平,临床疗效更好,安全性更高。

关键词:西黄胶囊;GP 方案;乳腺癌;血管内皮细胞生长因子;基质金属蛋白酶 -2;基质金属蛋白酶 -9

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Effect of Xihuang Capsule Combined with GP Regimen on Serum Levels of TNF-α, VEGF, MMP-2 and MMP-9 of Patients with Advanced Breast Cancer*

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ABSTRACT Objective: To study the effect of Xihuang Capsule combined with GP regimen on the serum levels of tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) of patients with advanced breast cancer. **Methods:** 88 patients with advanced breast cancer admitted in our hospital from March 2014 to February 2015 were selected and divided into the observation group and the control group according to the order of admission. The control group was treated by the GP program, the observation group was given Xihuang capsule combined with GP regimen. The serum levels of TNF-α, VEGF, MMP-2 and MMP-9 in the two groups were compared before and after treatment. The clinical efficacy and incidence of side effects were analyzed. **Results:** The total effective rate of observation group was significantly higher than that of the control group [84.09% (37/44) vs 50.00% (22/44)] (P<0.05). There was no significant difference in the serum levels of TNF-α, VEGF, MMP-2 and MMP-9 between the two groups before treatment (P>0.05). After treatment, the serum TNF-α, VEGF, MMP-2 and MMP-9 levels were significantly lower than those before treatment (P<0.05). The serum levels of TNF-α, VEGF, MMP-2 and MMP-9 of observation group were significantly lower than those of the control group (P<0.05). There was no significant difference in the incidence rate of nausea and vomiting between the two groups (P>0.05). The incidence of alopecia, diarrhea, abnormal liver function, decreased appetite, anemia and leukopenia in the observation group were significantly lower than those of the control group (P<0.05). **Conclusion:** Xihuang Capsule combined with GP regimen could more effectively reduce the levels of serum TNF-α, VEGF, MMP-2 and MMP-9 of patients with advanced breast cancer than GP regime alone with higher safety.

Key words: Xihuang capsule; GP regimen; Breast cancer; Vascular endothelial growth factor; Matrix metalloproteinase -2; Matrix metalloproteinase -9

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前言

当前临床治疗中晚期乳腺癌中主要以化疗等保守治疗方式为主,尽可能使得患者的病情发展得到控制,生存时间得到延长,然而也有研究者提出经通过单纯化疗方案部分患者难以取得满意的临床疗效,严重者可能伴有恶化反应,不利于患者预后[1,2]。西黄胶囊主要来自于古方犀黄丸改剂型,属于纯中药制剂的抗癌药,具有止痛、活血化瘀、消肿散结、清热解毒的作用[3]。研究表明乳香、麝香、没药、牛黄等提取物能有效抑制肿瘤的发展,对化疗的毒副反应起着缓解性作用[4]。为给临床在治疗中晚期乳腺癌提供更多可借鉴之处,本研究就西黄胶囊联合GP方案对中晚期乳腺癌患者血清肿瘤坏死因子-α(TNF-α)、人血管内皮细胞生长因子(VEGF)、基质金属蛋白酶-2(MMP-2)、基质金属蛋白酶-9(MMP-9)的影响进行分析,报道如下。

1 资料与方法

1.1 临床资料

入选2014年3月至2015年2月期间在我院进行治疗的88例中晚期乳腺癌患者。纳入标准:① 患者的临床诊断和《Berek&Novak妇科学》[5]中的诊断标准相符;② 预计存活期在3个月及其以上;③ 临床资料完善者;④ 无相关治疗禁忌症。排除标准:① 合并听力障碍、意识障碍、精神障碍及语言障碍的患者;② 合并心肺功能障碍、肝肾功能不全、恶性肿瘤、脑血管疾病者;③ 在进行本次研究前1个月进行过其他药物治疗的患者;④ 患者处于哺乳期、孕期。本次研究已获得患者及其家属的知情同意,同时取得了我院伦理委员会的批准和实施。

按照患者入院顺序将其分为观察组和对照组两组,44例每组。其中,观察组中年龄为35~51岁,平均(43.21± 2.23)岁;病程为0.3~1.5年,平均(1.03± 0.21)年;病灶数:单灶者11例,多灶者33例;乳腺癌类型:6例患者为浸润性小叶癌,2例患者为髓样癌,34例患者为浸润性导管癌,1例为乳头状癌,1例为硬癌;13例为复发,23例为转移,8例为复发及转移。观察组中年龄为36~49岁,平均(43.29± 2.31)岁;病程为0.4~1.4年,平均(1.04± 0.19)年;病灶数:单灶者13例,多灶者31例;乳腺癌类型:4例患者为浸润性小叶癌,3例患者为髓样癌,33例患者为浸润性导管癌,2例为乳头状癌,2例为硬癌;15例为复发,22例为转移,7例为复发及转移。两组患者年龄、病灶数、乳腺类型等临床资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组使用GP方案进行治疗,第1天、第6天,静脉滴注1000 mg/m² 的吉西他滨(生产厂家:江苏豪森药业股份有限公司,规格:200 mg,生产批号:20140211)持续时间为30 min;第1~5天,静脉滴注20 mg/m² 的顺铂(生产厂家:澳大利亚 Hospira Australia Pty Ltd,规格:50 mg/瓶,生产批号:20140214),持续时间为30 min,均以3周为1个治疗疗程。观察组在对照组治疗基础上联合西黄胶囊(生产厂家:陕西爱民药业股份有限公司,规格:0.25 g/粒,生产批号:20140121)进行治疗,1 g/次,2次/天,同样以3周为1个治疗疗程。所有患者均需连续治疗2个疗程。

1.3 观察指标

比较两组患者治疗前后血清TNF-α、VEGF、MMP-2、MMP-9水平的变化,分别在治疗前和治疗后抽取两组患者8 mL的空腹静脉血,转速3000 r/min,离心半径10 cm,离心15 min,分离血清后取出上清液,使用酶联免疫吸附法检测TNF-α水平,使用免疫组织化学法检测VEGF、MMP-2、MMP-9水平,由上海基免实业有限公司提供TNF-α试剂盒、VEGF试剂盒,上海通蔚生物科技公司提供MMP-2、MMP-9试剂盒,均根据说明书完成本次操作。

1.4 疗效评价标准

根据《乳腺癌诊治指南与规范》[6]中的相关标准对两组患者治疗后的临床疗效进行评价,包括完全缓解、部分缓解、稳定、进展,其中经治疗后,和治疗前相比患者的病灶完全消失,病情和体征好转则为完全缓解;和治疗前相比,病灶并没有完全消失,但缩小程度>30%,病情和体征有所好转则为部分缓解;和治疗前相比,病灶未完全消失,缩小程度和治疗前相比未达到30%,病情及体征有所好转则为病情稳定;和治疗前相比,病灶有所增大,病情及体征未出现明显好转则为病情进展。总有效=完全缓解+部分缓解。分析两组患者的不良反应情况。

1.5 统计学处理

实验数据处理使用SPSS11.5软件包完成,计量资料用($\bar{x}$± s)来表示,采用t检验,计数资料用[例(%)]来表示,采取x^2检验,用[例(%)]来表示等级资料,予以秩和检验,其P<0.05表明差异具有统计学意义。

2 结果

2.1 两组临床疗效比较

观察组总有效率为84.09%,显著高于对照组[84.09%(37/44)比50.00%(22/44)](P<0.05),见表1。

表1 两组临床疗效比较[例(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Cases	CR	PR	SD	PD	RR
Observation group	44	17(38.64)	20(45.45)	4(9.09)	3(6.82)	37(84.09)*
Control group	44	11(25.00)	11(25.00)	13(29.55)	9(40.45)	22(50.00)

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

2.2 两组治疗前后血清TNF-α、VEGF、MMP-2、MMP-9水平比较

治疗前,两组患者想TNF-α、VEGF、MMP-2、MMP-9水平比较无明显差异性(P>0.05),治疗后,两组患者血清TNF-α、VEGF、MMP-2、MMP-9水平均较治疗前显著降低(P<0.05),观察组的血清TNF-α、VEGF、MMP-2、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 TNF-α、VEGF、MMP-2、MMP-9 水平比较($\bar{x}\pm s$)

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

Item	Observation group(n=44)		Control group(n=44)	
	Before treatment	After treatment	Before treatment	After treatment
TNF-α(pg/mL)	912.32± 73.54	512.43± 23.56*#	913.03± 73.62	765.43± 54.32*
VEGF(pg/mL)	534.87± 52.09	285.43± 23.21*#	534.81± 52.01	378.32± 34.43*
MMP-2(mg/L)	77.32± 7.65	42.12± 4.02*#	77.29± 7.42	56.98± 4.32*
MMP-9(ng/mL)	97.41± 9.21	31.02± 3.22*#	97.48± 9.19	57.32± 5.26*

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

2.3 两组不良反应发生情况比较

两组患者的恶心呕吐的发生率比较差异无统计学意义(P>0.05),观察组脱发、腹泻、肝功能异常、食欲下降、贫血、白细胞下降的发生率明显比对照组低(P<0.05),见表 3。

表 3 两组不良反应发生情况的比较[例(%)]

Table 3 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	Hair loss	Diarrhea	Liver dysfunction	Loss of appetite	Nausea and vomiting	Anemia	White blood cell count decreased
Observation group(n=44)	11(25.00)*	12(27.27)*	2(4.55)*	5(11.36)*	32(72.73)	7(15.91)*	9(20.45)*
Control group (n=44)	28(63.64)	31(70.45)	11(25.00)	16(36.36)	35(79.55)	26(59.09)	35(79.55)

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

3 讨论

乳腺癌是临床中较为常见的一种恶性肿瘤,在女性恶性肿瘤中位居首位,发病率呈现出逐年升高的趋势,严重威胁女性健康[7]。乳腺癌的发病机制目前尚未完全阐明,与长期烟酒、未哺乳、未育、未婚、绝经迟、遗传、年龄等因素有关[9]。AT(阿霉素+紫杉醇)方案是治疗乳腺癌应用得较为广泛的化疗方案,研究表明二线治疗中晚期乳腺癌中使用 GP 方案也能获得较好的临床疗效[8]。为全面提高肿瘤治疗的临床疗效,人们开始应用中医毒副作用轻、标本兼治的特点以改善患者预后,从单纯的西医治疗转变为中西医结合治疗[10]。西黄胶囊主要为古方犀黄丸的改进剂型,属于纯中药抗癌药,主要由没药、乳香、麝香、牛黄等组合而成,其中没药、乳香具有活血祛瘀、消肿止痛的作用,麝香具有散淤血、行气滞、开经络、消痈疽肿毒的作用,牛黄具有化痰散结、清热解毒的作用[11,12]。西黄胶囊具备止痛、活血化瘀、消肿散结、清热解毒的作用,在痰核、横痃、乳岩 、累病等疾病中应用得较多。根据辨证施治的原则,西黄胶囊已在中晚期恶性肿瘤中得到广泛应用[13]。相关研究显示西黄胶囊能有效抑制乳腺癌细胞,通过对细胞周期发挥干扰性作用,诱导肿瘤细胞凋亡,进而缩小或消灭肿瘤。此外,西黄胶囊能发挥调节免疫功能的作用,有效缓解患者临床症状[14]。

本研究为探讨西黄胶囊联合 GP 方案治疗中晚期乳腺癌患者的有效性,将 88 例中晚期乳腺癌患者作为研究对象,发现经西黄胶囊联合 GP 方案治疗的患者总有效率明显比单纯 GP 方案治疗者高。研究表明西黄胶囊能有效促进肿瘤细胞的凋亡,具有明显的抗炎、促进血流灌注的作用,抑制新生血管的生成[15]。当西黄胶囊对机体主动脉内皮细胞发挥作用后,对血小板反应蛋白 1 的生成发挥着明显的促进性作用,阻碍内皮细胞增殖,使得 VEGF 表达水平有所降低,阻碍肿瘤新生血管的生成,对于癌细胞营养供应链具有阻碍的作用,使癌细胞代谢进一步凋亡[16,17]。TNF 是由单核巨噬细胞而产生的碱性多肽,在多种免疫和生理过程作为重要的介质, 发挥着参与性作用,TNF-α 对肿瘤能发挥双向性作用,不仅可抑制肿瘤的生长,还能促进癌转移。已有研究者表明乳腺癌的产生和 VEGF、MMP-2 存在着密切关联性,VEGF 和腺癌的恶性程度及肿瘤演变过程存在着密切关联性, 主要是因为 VEGF 诱导乳腺癌的血管形成,而新生的血管又给肿瘤生长提供营养并对肿瘤细胞增殖发挥着间接性促进作用,促使乳腺癌的转移和浸润[18]。MMP-2 可通过降解基膜中的胶原纤维以及细胞外基质进而打破肿瘤生存的微环境,促使肿瘤的转移及扩散,进而加重患者病情,使治疗难度加大。因此可将上述指标视为乳腺癌早期诊断及病情发展评估的标准,尽可能减少诊疗时间,给后续治疗工作创造有利的条件[19]。MMP-9 作为基质金属蛋白酶家族中的一员,通过酶原形式分泌,一旦激活后形成 IV 型胶原酶,肿瘤细胞朝着缺失的基底膜浸润至周围组织,进而导致肿瘤转移和浸润,不利于患者预后。而西黄胶囊能有效抑制 MMP-2 的表达,减慢肿瘤细胞扩散转移及生长的速度,进而控制病情的发展,使患者的生存时间有所延长[20]。除此之外,西黄胶囊不但对局部组织缺氧、缺血状态起着改善性作用, 还能有效抑制 TNF-α、VEGF、MMP-2、MMP-9 水平,促使患者的病情得到转归,进而提高患者预后质量。

此外,本研究结果显示西黄胶囊联合 GP 方案治疗的中晚期乳腺癌患者毒副反应发生率更低,提示西黄胶囊不但能阻碍肿瘤细胞增殖扩散,而且可中和化疗毒副反应,减轻患者痛苦,进而增强治疗的舒适度,改善患者的预后,此治疗方案对于免疫力低下、耐受力较差的患者尤为适用。

总之，西黄胶囊联合 GP 方案较单用 GP 方案能更有效降低中晚期乳腺癌患者血清 TNF-α、VEGF、MMP-2、MMP-9 水平，临床疗效更好，安全性更高。

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(上接第 4505 页)

2753-2765

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