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四磨汤对宫颈癌化疗患者胃肠功能的保护作用及对血清 IL-8、CEA、CA125 水平的影响 *

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摘要 目的:研究四磨汤对恩度联合力朴素治疗的宫颈癌患者胃肠功能的保护作用及对其血清白细胞介素 8(IL-8)、癌胚抗原(CEA)、糖类抗原 125(CA125)的影响。**方法:**选取 2015 年 9 月至 2016 年 8 月我院收治的 88 例宫颈癌患者,根据患者入院顺序分为观察组和对照组,每组 44 例。对照组在放疗基础上加以恩度联合力朴素完成化疗,观察组在对照组治疗基础上加以四磨汤。比较两组患者治疗前后血清 IL-8、CEA、CA125 水平及外周血 CD3⁺、CD4⁺、CD8⁺ 细胞比例的变化和胃肠道毒副反应、胃肠道放射性损伤的发生情况。**结果:**治疗后,两组患者血清 IL-8、CEA、CA125 水平均较治疗前显著降低($P<0.05$),且观察组的血清 IL-8、CEA、CA125 水平较对照组明显降低($P<0.05$);两组患者 CD3⁺、CD4⁺ 细胞比例较治疗前显著降低($P<0.05$),CD8⁺ 细胞比例较治疗前显著升高($P<0.05$),但观察组的 CD3⁺、CD4⁺、CD8⁺ 细胞比例显著高于对照组($P<0.05$)。观察组不良反应发生率、早期胃肠道放射性损伤发生率、II、III 级胃肠道放射性损伤率均显著低于对照组($P<0.05$)。**结论:**四磨汤用于恩度联合力朴素治疗的宫颈癌患者能有效保护患者胃肠功能,降低患者血清 IL-8、CEA、CA125 水平,增强患者免疫力。

关键词:四磨汤;宫颈癌;胃肠功能;白细胞介素 8;癌胚抗原;糖类抗原 125

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Protective Effect of Simo Tang on the Gastrointestinal Function of Endostar Combined with Paclitaxel Liposome-treated Cervical Cancer Patients and Effect on the Serum IL-8, CEA, CA125 Levels*

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ABSTRACT Objective: To study the protective effect of Simo tang on the gastrointestinal function of endostar combined with paclitaxel liposome-treated cervical cancer patients and effect on the serum interleukin 8 (IL-8), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125) levels. **Methods:** From September 2015 to August 2016, 88 patients with cervical cancer admitted in our hospital were divided into the observation group and the control group according to the order of admission. The control group was treated with endostar combined with paclitaxel liposome on the basis of radiotherapy, the observation group was given simo tang based on the treatment of control group. The serum levels of IL-8, CEA and CA125, the peripheral blood CD3⁺, CD4⁺, CD8⁺ cells, gastrointestinal toxicity and gastrointestinal radioactivity injury in the two groups were compared. **Results:** After treatment, the serum levels of IL-8, CEA and CA125 in both groups were significantly lower than those before treatment ($P<0.05$). Compared with the control group, the serum levels of IL-8, CEA and CA125 in the observation group were lower ($P<0.05$). After treatment, the ratio of CD3⁺, CD4⁺ cells in both groups were significantly lower than those before treatment ($P<0.05$), but the CD3⁺ and CD4⁺ cells in the observation group were significantly higher than those in the control group ($P<0.05$), the ratio of CD8⁺ cells in both groups were significantly higher ($P<0.05$), the ratio of CD8⁺ cells in the observation group was significantly higher than that in the control group ($P<0.05$). The incidence rate of adverse reaction, early gastrointestinal radioactive injury and gastrointestinal tract II and III in the observation group were significantly lower than those of the control group ($P<0.05$). **Conclusion:** Simo tang combined with paclitaxel liposome can effectively protect the gastrointestinal function, reduce the levels of serum IL-8, CEA and CA125 levels and enhance the immunity of patients with cervical cancer.

Key words: Simo decoction; Cervical cancer; Gastrointestinal function; IL-8; CEA; CA125

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前言

宫颈癌属于女性生殖系统恶性肿瘤,发病率较高,仅次于乳腺癌^[1]。宫颈癌发病早期缺乏典型的临床症状,患者确诊时基本上为宫颈癌中晚期,增加了治疗难度^[2]。放疗是治疗中晚期宫颈癌较为常见的治疗方式,尽管放疗技术手段和设施得到极大提高,但放疗效果不甚理想,患者易出现远处转移或局部复发^[3,4]。同步放化疗已在临床上广泛应用于治疗中晚期宫颈癌,但易发生胃肠道毒性副作用,如血便、腹泻、肠梗阻、肠粘连、腹胀、腹痛、便秘等症状,轻者可能影响疗效,重者会导致肠穿孔、肠梗阻,危及患者生命^[5]。为给临床治疗宫颈癌提供可借鉴之处,本研究主要探讨了四磨汤对恩度联合力朴素治疗宫颈癌患者胃肠功能的保护作用及对患者血清白细胞介素-8 (IL-8)、癌胚抗原(CEA)、糖类抗原 125(CA125)水平的影响,现将结果报道如下。

1 资料与方法

1.1 临床资料

将 2015 年 9 月至 2016 年 8 月我院收治的 88 例宫颈癌患者纳入本次研究。纳入标准:① 病理分期为 III-IV 期的患者;② 经病理学和阴道镜检查被诊断为中晚期宫颈癌;③ 无化疗禁忌症者;④ 预计生存期超过 6 个月。排除标准:① 肝肾功能异常者;② 其他恶性肿瘤合并者;③ 心电图异常者;④ 处于哺乳期或妊娠期。本次研究已取得我院伦理委员会批准及得到患者及家属同意。根据患者入院顺序分为观察组和对照组,44 例每组。观察组年龄为 34~58 岁,平均 (45.48 ± 3.17) 岁;体重为 $45.32 \sim 68.21$ kg,平均 (57.15 ± 3.02) kg;分化类型:3 例低分化型,25 例中分化型,16 例高分化型;病理分期:III 期 28 例,IV 期 16 例;病理类型:鳞癌 34 例,腺癌 10 例。对照组年龄为 33~59 岁,平均 (45.51 ± 3.14) 岁;体重为 $45.28 \sim 68.17$ kg,平均 (57.12 ± 3.09) kg;分化类型:4 例低分化型,27 例中分化型,13 例高分化型;病理分期:III 期 25 例,IV 期 19 例;病理类型:鳞癌 37 例,腺癌 7 例。两组患者年龄、体重、分化类型比较均无显著差异 ($P > 0.05$),具有可比性。

1.2 治疗方法

所有患者均实施单纯放射治疗,采取 BJ-6B 型直线加速器的 6MV-X 射线,盆腔外借助对穿式照射法近距离照射,照射范

围从患者第 4 腰椎体下缘到闭孔下缘,每周需照射 5 次,照射总量为 50Gy/25 f/5 W。盆腔内借助铱-192 后装治疗机完成近距离照射,腔外照射和腔内照射无需同步完成,每周照射 1 次。对照组在放疗基础上加以恩度联合力朴素完成化疗,在放疗开始静脉滴注 7.5 mg/m^2 的恩度(生产厂家:山东先声麦得津生物制药有限公司,生产批号:20150304,规格:15 mg/支),1 次/天;同时给予力朴素(生产厂家:南京绿叶制药有限公司;生产批号:20150218,规格:30 mg/瓶),静脉滴注, 135 mg/m^2 。观察组在对照组治疗基础上加以四磨汤口服液(生产厂家:湖南汉森制药股份有限公司,生产批号:20150214,规格:10 mL/支)完成治疗,20 mL/次,3 次/天,3 周为 1 个疗程,所有患者均需接受治疗 4 个疗程。

1.3 观察指标

分别在治疗前后抽取两组患者 5 mL 的空腹静脉血,转速为 3000 r/min,离心 15 min,分离血清,比较两组患者治疗前后 IL-8、CEA、CA125 水平及外周血 CD3^+ 、 CD4^+ 、 CD8^+ 细胞比例。采取双抗夹心酶联免疫法检测 IL-8、CA125 水平,由上海江莱生物科技公司提供试剂及检测试剂盒。使用电化学发光微粒子免疫分析法检测 CEA 水平,由瑞士 Roche 公司提供 Elec-sys1010 全自动电化学发光仪。采取贝克曼 Cyto FLEX 流式细胞仪检测外周血 CD3^+ 、 CD4^+ 、 CD8^+ 细胞比例。

按 WHO 统一抗癌毒副反应分度标准评判两组患者药物毒副反应。胃肠道放射性损伤根据欧洲放射肿瘤学会(EORTC)和美国放射肿瘤研究组(RTOG)^[6]中关于放射损伤分级标准予以评价。从放疗开始至结束 3 个月内放射损伤则视为早期放射反应,发生在放疗 3 个月后的放射损伤则视为晚期放射损伤。

1.4 统计学处理

选取 SPSS11.5 软件包对本次实验数据予以处理,用 $(\bar{x} \pm s)$ 对计量资料进行表示,进行 t 检验,用 $[n(\%)]$ 对计数资料进行表示,予以 χ^2 检验,以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者治疗前后血清 IL-8、CEA、CA125 水平的比较

治疗前,两组患者血清 IL-8、CEA、CA125 水平比较差异无统计学意义 ($P > 0.05$);治疗后,两组患者血清 IL-8、CEA、CA125 水平均较治疗前显著降低 ($P < 0.05$),且和对照组相比,观察组的血清 IL-8、CEA、CA125 水平较低 ($P < 0.05$),见表 1。

表 1 两组患者治疗前后血清 IL-8、CEA、CA125 水平比较 ($\bar{x} \pm s$)

Table 1 Comparison of the serum IL-8, CEA and CA125 levels between two groups before and after treatment ($\bar{x} \pm s$)

Items	Observation group(n=44)		Control group(n=44)	
	Before treatment	After treatment	Before treatment	After treatment
IL-8(ng/mL)	0.36 ± 0.04	$0.13 \pm 0.02^{*#}$	0.38 ± 0.05	$0.24 \pm 0.03^{*}$
CEA(ng/mL)	14.25 ± 1.36	$3.26 \pm 0.38^{*#}$	14.31 ± 1.28	$7.98 \pm 0.84^{*}$
CA125(U/mL)	88.53 ± 8.46	$13.21 \pm 1.28^{*#}$	88.49 ± 8.51	$29.45 \pm 2.76^{*}$

Note: Compared with before treatment, $^{*}P < 0.05$; Compared with the control group after treatment, $^{*#}P < 0.05$.

2.2 两组患者治疗前后外周血免疫细胞水平的比较

治疗前,两组患者 CD3^+ 、 CD4^+ 、 CD8^+ 细胞比例比较差异无统计学意义 ($P > 0.05$);治疗后,两组患者 CD3^+ 、 CD4^+ 细胞比例较治疗前显著降低 ($P < 0.05$),但观察组的 CD3^+ 、 CD4^+ 细胞比例

显著高于对照组 ($P < 0.05$),两组患者的 CD8^+ 细胞比例显著升高 ($P < 0.05$),观察组的 CD8^+ 细胞比例显著高于对照组 ($P < 0.05$),见表 2。

表 2 两组患者治疗前后外周血免疫细胞水平的比较($\bar{x} \pm s$)Table 2 Comparison of the peripheral blood immune cell levels before and after treatment between two groups($\bar{x} \pm s$)

Items	Observation group(n=44)		Control group(n=44)	
	Before treatment	After treatment	Before treatment	After treatment
CD3+(%)	58.12± 5.15	41.35± 4.26**	58.16± 5.18	23.45± 2.51*
CD4+(%)	45.23± 4.17	36.32± 3.25**	45.18± 4.19	27.43± 2.62*
CD8+(%)	28.15± 2.41	52.14± 5.32**	28.16± 2.39	39.25± 3.58*

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

2.3 两组胃肠道毒副反应发生情况的比较

对照组(P<0.05),见表 3。

观察组的恶心呕吐、便秘腹胀不良反应的发生率显著低于

表 3 两组胃肠道毒副反应发生情况的比较[例(%)]

Table 3 Comparison of the incidence of gastrointestinal side effects between two groups[n(%)]

Groups	Nausea and vomiting	Constipation bloating
Observation(n=44)	6(13.64)*	3(6.82)*
Control(n=44)	19(43.18)	14(31.82)

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

2.4 两组胃肠道放射性损伤发生情况的比较

观察组的早期胃肠道放射性损伤发生率显著低于对照组(P<0.05),但两者患者 I 级胃肠道放射性损伤发生率比较无显著差异(P>0.05),观察组的 II、III 级胃肠道放射性损伤发生率显

著低于对照组(P<0.05)。观察组和对照组的晚期放射损伤发生率比较无显著差异(P>0.05),同时两者患者的 I、II、III、IV 级晚期放射损伤发生率比较无显著差异(P>0.05),见表 3。

表 4 两组胃肠道放射性损伤发生情况的比较[例(%)]

Table 4 Comparison of the radiation damage of gastrointestinal tract between two groups[n(%)]

Groups	Early radiation injury					Advanced radiation injury				
	I	II	III	IV	Total	I	II	III	IV	Total
Observation group(n=44)	6(13.64)	2(4.55)*	1(2.27)*	0(0.00)	9(20.45)	5(11.36)	2(4.55)	1(2.27)	0(0.00)	8(18.18)
Control group(n=44)	10(22.73)	9(20.45)	6(13.64)	0(0.00)	25(56.82)	6(13.64)	3(6.82)	3(6.82)	0(0.00)	12(27.27)

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

3 讨论

宫颈癌是妇科三大恶性肿瘤的之一,发病率位居妇科肿瘤第一位^[7]。手术是治疗宫颈癌中较为常见的治疗方式,然而大部分患者就诊时已为晚期,再加上子宫本身结构的特殊性,会加大手术难度,因此难以获得良好的预期效果^[8,9]。在开展宫颈癌根治术前,予以 2~3 个疗程的化疗,能降低微转移、减小瘤体,进而提高整个手术疗效^[10]。因此,除手术外,同步放化疗是最为主要的治疗手段。虽然病理特征相同,但是对于不同的中晚期宫颈癌患者而言,使用同一种化疗药物会有着不同的治疗效果。因此,选取合理有效的化疗药物显得颇为关键。

恩度是一种新型重组人血管内皮生成抑制素,在阻碍形成血管内皮细胞增生的同时能阻滞肿瘤血管的形成,进而抑制机体给肿瘤细胞的营养供给,进而实现抑制肿瘤生长、肿瘤细胞增殖和转移的目的^[11,12]。力朴素作为紫杉醇的脂质体,在阻碍肿瘤细胞分裂的过程中同时能发挥抗肿瘤作用,且水溶性较好,不良反应率较低,有着较长的血浆半衰期,和常规紫杉醇类相比,抗肿瘤效果更为显著^[13,14]。但在盆腔放疗中,易出现胃肠道放射性毒性反应,化疗的过程中也会伴有腹泻、腹胀、呕吐、恶心等不良反应,不但会加大治疗的风险性,还可能会中断治疗,

影响疗效^[15-17]。

四磨汤主要由槟榔、乌药、枳壳、木香组合而成,具有消积止痛、通腑导滞、顺气降逆的效果^[18]。研究表明在化疗或腹部手术后患者中应用四磨汤能有效改善患者胃肠道功能^[19]。然而,关于四磨汤在盆腔放疗方面是否会发挥保护作用的研究甚少^[20]。本研究结果显示宫颈癌患者接受四磨汤、恩度联合力朴素治疗后,胃肠道不良反应得到显著缓解,其中恶心呕吐、便秘腹胀胃肠道不良反应率显著低于恩度联合力朴素治疗者,尽管晚期放射性胃肠道损伤无明显差异,但 II/III 级早期消化道损伤发生率明显低于恩度联合力朴素治疗者,提示在同步放化疗中,加以四磨汤改善宫颈癌放化疗阶段药物所致的胃肠道反应,同时能缓解放疗而导致的胃肠道受损程度。

在肿瘤细胞的生长过程中,部分蛋白会因为降解或激活作用而释放进入血液,在肿瘤的发生发展中对这些标志物进行检测有着极其重要的作用^[21,22]。IL-8 作为炎症因子,和宫颈癌的发生发展存在着密切关联性^[23]。CEA、CA125 在女性生殖系统肿瘤中作为首选的肿瘤标志物,常用于诊断和判断宫颈癌预后^[24]。本研究通过对宫颈癌患者予以四磨汤、恩度、力朴素治疗后,患者的血清 IL-8、CEA、CA125 水平均显著降低,且上述指标的降低效果显著优于恩度联合力朴素治疗者,提示四磨汤在恩度联

合力朴素治疗宫颈癌患者中,能有效降低患者血清 IL-8、CEA、CA125 水平。究其原因主要是因为恩度在阻碍形成肿瘤血管的内皮细胞增殖的同时,也能有效抑制肿瘤细胞营养供给,进而达到抗肿瘤的目的;力朴素在阻碍肿瘤细胞微管蛋白聚合的过程中,能抑制细胞有丝分裂,在抑制肿瘤细胞分化的同时能发挥抗肿瘤的目的;四磨汤具有消积止痛、顺气降逆的作用,在上述诸多药物作用下起着协同作用^[25-27]。

相关研究结果显示:力朴素在乏氧细胞二次氧合作用下能发挥放射增敏的作用,经同步放疗,能进一步杀灭肿瘤细胞^[28]。本研究结果显示:治疗后,患者的外周血 CD3⁺、CD4⁺ 细胞所占比例有所降低,CD8⁺ 细胞比例有所升高,但恩度联合力朴素治疗者的上述指标改善效果显著优于四磨汤、恩度联合力朴素治疗者,表明四磨汤、恩度联合力朴素治疗宫颈癌能有效改善患者 T 淋巴细胞,增强患者机体免疫力。可能主要因为放化疗尽管能在某种程度上抑制患者机体 T 淋巴细胞免疫功能,然而一旦四磨汤进入机体后,受到单核-吞噬细胞内皮系统吞噬后,会激活机体免疫系统,有利于患者机体免疫功能的改善^[29]。

总之,四磨汤用于恩度联合力朴素治疗的宫颈癌患者能有效保护患者胃肠功能,降低患者血清 IL-8、CEA、CA125 水平,增强患者免疫力。

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