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苦参碱注射液对宫颈癌患者化疗的增敏作用及 对 T 细胞亚群、CA125、IL-6 的影响 *

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摘要 目的:研究苦参碱注射液对宫颈癌患者化疗的增敏作用及对 T 细胞亚群、CA125、IL-6 的影响。**方法:**选择 2015 年 4 月至 2017 年 3 月在我院进行宫颈癌治疗的 76 例患者,随机将其均分为观察组(59 例)和对照组(59 例),对照组患者给予化疗,而观察组则在对照组化疗的基础上增加苦参碱注射液进行治疗,记录并比较两组患者治疗前后 T 细胞亚群、CA125 及 IL-6 水平的变化、肿瘤病灶面积的改善情况、临床疗效及不良反应的发生情况。**结果:**治疗后,观察组患者的肝肾功能损伤、骨髓抑制剂胃肠道反应等不良反应发生率、血清 CA125 及 IL-6 水平均明显低于对照组($P<0.05$),而总有效率(81.58%)显著高于对照组(50.00%)($P<0.05$), $CD3^+$ 、 $CD4^+$ 及 $CD4/CD8^+$ 水平也明显高于对照组($P<0.05$),而观察组患者 $CD8^+$ 水平则明显低于对照组($P<0.05$)。**结论:**苦参碱注射液辅助宫颈癌化疗的增敏效果显著,能有效降低患者 CA125 及 IL-6 水平,显著改善机体 T 细胞免疫功能。

关键词:苦参碱注射液;宫颈癌;化疗;T 细胞亚群;CA125;IL-6

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Chemotherapy Sensitization Effect of Matrine Injection on Patients with Cervical Cancer and Influence on the T Cell Subsets, Serum CA125 and IL-6 Levels*

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ABSTRACT Objective: To study the chemotherapy sensitization effect of matrine injection on the cervical cancer patients and influence on the T cell subsets, serum CA125 and IL-6 levels. **Methods:** Sixty-seven patients with cervical cancer treated in our hospital from April 2015 to March 2017 were randomly divided into the observation group and the control group. The patients in control group were treated with chemotherapy, while the observation group was treated by matrine injection based on the control group. Then the levels of T cell subsets, changes of serum CA125 and IL-6 levels before and after treatment, improvement of tumor lesion area, clinical efficacy and incidence of adverse reactions were observed and compared between two groups. **Results:** After treatment, the incidence of adverse reactions such as liver and kidney injury and gastrointestinal tract reaction, serum CA125 and IL-6 levels in the observation group were significantly lower than those of the control group, and the total effective rate (81.58%) was significantly higher than that in the control group ($P<0.05$), the levels of $CD3^+$, $CD4^+$ and $CD4/CD8^+$ in the observation group were significantly higher than those in the control group (50.00%), while the level of $CD8^+$ in the observation group was significantly lower than that in the control group ($P<0.05$). **Conclusion:** Matrine injection showed significant sensitization effect on the cervical cancer, which can effectively reduce the levels of serum CA125 and IL-6, and improve the immune function of T cells.

Key words: Matrine injection; Cervical cancer; Chemotherapy; T cell subsets; CA125; IL-6

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前言

宫颈癌是恶性肿瘤之一,其发病率较高,WHO 数据显示^[1]全球每年新增宫颈癌病例达 50 万左右,其中二分之一的患者

死亡,对女性的健康威胁极大。我国每年新发的宫颈癌患者大约 13 万,占全球新增例数的三分之一,且发病率逐年上升。宫颈癌早期并无典型的症状,经确诊时已是宫颈癌中晚期,进而给治疗带来较大难度^[2]。目前,临床较多使用化疗对其进行治

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疗,虽然化疗可以将患者生存周期延长,且提高患者的生存率,但是化疗使得患者的耐受性降低,甚至是中断治疗,从而影响患者的生存质量和疗效。研究显示^[4,5]化疗损伤了患者气血,导致肝肾脾胃等脏器功能失调,所以化疗时可辅助使用相应药物可对宫颈癌患者的气血及脏器功能进行调节。苦参有清热解毒的作用,且有效成分苦参碱承载多种生物活性,具有抗炎及抗病毒之功效。因此,研究重点探讨了苦参碱注射液对宫颈癌患者化疗增敏作用及对T细胞亚群、CA125、IL-6的影响。现报道如下。

1 资料与方法

1.1 一般资料

选择我院2015年4月至2017年3月治疗的76例宫颈癌患者,纳入标准^[6]:(1)经阴道镜检查及病理确诊为宫颈癌;(2)预估患者生存期>6个月;(3)之前为接受过放化疗治疗;(4)经患者及家属知情同意。排除标准^[7]:(1)患有其他恶性肿瘤病症者;(2)肝肾等功能不全者;(3)化疗禁忌者;(4)长期服用免疫抑制剂和免疫增强剂者;(5)处于妊娠期或哺乳期者。将所纳入的76例患者随机均分为观察组和对照组,每组38例,其中观察组患者年龄31-68岁,平均年龄(51.82±6.51)岁,鳞癌33例,腺癌5例,FIGO分期:IIb期9例,IIa期19例,IIb期10例,对照组患者年龄30-67岁,平均年龄(51.15±6.03)岁,鳞癌32例,腺癌6例,FIGO分期:IIb期11例,IIa期18例,IIb期9例,两组患者就以上指标进行比较,差异均无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

对照组给予化疗进行治疗,使用的药物有顺铂(山东齐鲁制药厂,国药准字H20073652),用量60 mg/m²,多西他赛(浙江海正药业股份有限公司,国药准字H20093092),用量70 mg/m²,4周一疗程,连续治疗3个疗程;观察组则在对照组化疗方案的基础上增加苦参碱注射液(辽宁玉皇药业有限公司,

国药准字H20083501)进行治疗,将20 mL苦参碱注射液溶于250 mL浓度为0.9%的氯化钠液进行静脉滴注,1次/d,用药至化疗结束后3 d,连续治疗3个疗程。

1.3 观察指标

1.3.1 患者治疗前后T淋巴细胞亚群、CA125及IL-6水平的检测 两组患者分别取治疗前后采集空腹肘静脉血3 mL,肝素抗凝,两组患者各取100 μL并加入单抗20 μL,均有混合后室温避光30 min,随后加入1.5 mL红细胞裂解液,在此室温避光10 min,以达到破坏红细胞的效果,使用离心机以2500 r/min的速度离心10 min,丢弃上层清液,每管加入2 mL PBS液,再次离心5 min,弃上清,2 h内利用II型流式细胞仪(美国BD公司生产)对T淋巴细胞亚群、CA125及IL-6水平进行检测。

1.3.2 临床疗效评定 参照WHO肿瘤近期疗效的评估标准对临床疗效进行评定,完全缓解(CR):肿块完全消失,疗效维持1个月以上;部分缓解(PR):肿瘤病灶最大垂直直径与最大直径之积减小50%以上,且疗效维持1个月以上;稳定(SD):肿瘤病灶最大垂直直径与最大直径之积减小25%以上,且无新的病灶出现;进展(PD):出现新的病灶或肿瘤病灶最大垂直直径与最大直径之积增大25%以上。总有效率等于CR与PR之和除以总例数*100%。

1.4 统计学分析

采用SPSS 19.0统计软件分析数据,计量资料均用均数±标准差($\bar{x} \pm s$)表示,组间比较采用t检验,计数资料均用[(n)%]表示,组间比较采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患者治疗前后血清CA125及IL-6水平变化的比较

两组患者治疗后血清CA125及IL-6水平较本组治疗前显著降低($P<0.05$),且观察组患者的血清CA125及IL-6水平均显著低于对照组($P<0.05$),具体见表1。

表1 两组患者治疗前后血清CA125及IL-6水平比较($\bar{x} \pm s$)

Table 1 Comparison of serum CA125 and IL-6 levels between the two groups before and after treatment ($\bar{x} \pm s$)

Groups	n	CA125(IU/mL)		P value	IL-6(pg/mL)		P value
		Before treatment	After treatment		Before treatment	After treatment	
Observation group	38	55.81±12.38	37.01±8.12* [#]	0.000	4.13±1.01	2.41±0.62* [#]	0.000
Control group	38	56.79±12.18	50.69±13.16*	0.039	4.02±0.93	3.21±0.73*	0.000
P value		0.729	0.000		0.623	0.000	

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

2.2 两组患者治疗前后T淋巴细胞亚群水平变化的比较

两组患者治疗后的CD3⁺、CD4⁺及CD4/CD8⁺水平显著高于本组治疗前,且观察组患者的CD3⁺、CD4⁺及CD4/CD8⁺水平明显高于对照组($P<0.05$);而两组患者治疗后的CD8⁺表达水平较本组治疗前相比显著降低,且观察组患者CD8⁺水平明显低于对照组($P<0.05$)。具体见表2。

2.3 两组患者不良反应发生情况的比较

治疗后,观察组患者的肝肾功能损伤、骨髓抑制剂胃肠道反应等不良反应率显著低于对照组,两组相比差异具有统计学意义($P<0.05$)。详见表3。

2.4 两组患者治疗后的疗效比较

治疗后,观察组的总有效率是81.58%,对照组的总有效率是50.00%,观察组显著高于对照组($P<0.05$)。详见表4。

3 讨论

宫颈癌是女性的生殖系统中较为常见的恶性肿瘤病症之一,发病率仅次于乳腺癌,我国每年新发宫颈癌患者例数占全球发病总数的30%左右,且一半患者因宫颈癌而死亡^[8,9]。由此可见,宫颈癌的发病率及致死率极高,呈逐年上升趋势,对女性的生命及健康有着严重的威胁,同时给自身家庭带来沉重的负

担^[10]。目前,临床上治疗宫颈癌的方法有手术治疗、放射性治疗、化疗等^[11],化疗能显著改善宫颈癌患者的生存率,但降低了患者的耐受性,往往因化疗药物的毒副作用被迫中断治疗,对

患者的生存治疗及临床疗效影响较大^[12,13]。因此,在保证化疗临床效果的情况下,如何降低药物毒副作用对患者耐受性的影响,进而提高患者生存质量成为了临床的研究重点及难题。

表 2 两组患者治疗前后 T 淋巴细胞亚群水平变化的比较($\bar{x} \pm s$)

Table 2 Comparison of the T lymphocyte subsets before and after treatment between two groups($\bar{x} \pm s$)

Groups	n	CD3 ⁺		P value	CD4 ⁺		P value
		Before treatment	After treatment		Before treatment	After treatment	
Observation group	38	47.34± 6.56	55.49± 7.61* [#]	0.000	31.12± 3.46	43.05± 3.56* [#]	0.000
Control group	38	47.81± 6.62	51.16± 7.15*	0.037	31.26± 4.18	36.12± 3.76*	0.000
P value		0.757	0.013		0.874	0.000	

Groups	n	CD8 ⁺		P value	CD4/CD8 ⁺		P value
		Before treatment	After treatment		Before treatment	After treatment	
Observation group	38	29.97± 3.32	26.62± 2.75* [#]	0.000	1.01± 0.25	1.62± 0.29* [#]	0.000
Control group	38	29.88± 3.42	28.18± 2.13*	0.011	1.02± 0.22	1.32± 0.19*	0.000
P value		0.908	0.007		0.854	0.000	

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

表 3 两组患者不良反应发生情况的比较[例(%)]

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

Adverse reactions	Observation group(n=38)					Control group(n=38)				
	0	I	II	III	IV	0	I	II	III	IV
Liver and kidney function damage	38	0	0	0	0	31	7	0	0	0
Bone marrow suppression	0	17	14	5	2	0	4	19	10	5
Gastrointestinal reactions	15	21	2	0	0	3	15	12	5	3

表 4 两组患者疗效比较[例(%)]

Table 4 Comparison of the curative effect between two groups [n(%)]

Groups	n	CR	PR	SD	PD	Total efficiency
Observation group	38	14(36.84)	17(44.74)	5(13.16)	2(5.26)	31(81.58)
Control group	38	4(10.53)	15(39.47)	11(28.95)	8(21.05)	19(50.00)
P value		P=0.004				P=0.004

相关研究表明^[14,15]临床上常用的中药材苦参不仅能清热解毒,而且还能燥湿杀虫,且《神农本草经》记载到“主治心腹结气,癥瘕积聚”,Ge L 等研究发现^[16]苦参中最主要的成分 - 苦参碱具有明显的抗肿瘤作用,可抑制肿瘤细胞的迁移及肿瘤浸润,直接影响端粒酶的活性,诱导肿瘤细胞分化及凋亡,同时灭杀肿瘤细胞,苦参碱对肿瘤细胞新生血管的生成具有抑制性作用^[17],且能阻止慢性炎症反应及致癌病毒诱发的恶性肿瘤。本研究结果显示苦参碱注射液辅助化疗治疗组的总有效率(81.58%)显著高于单一化疗治疗组的总有效率(50.00%),提示其具有化疗增敏作用。

国外研究显示^[18,19]肿瘤标志水平是诊断宫颈癌的重要依据。其中,CA125 是一种大分子糖蛋白,被发现于 1981 年,是由鼠抗人乳头状囊性卵巢上皮细胞系 OC125 制备出来,诊断敏感性较高,是女性生殖系统肿瘤中首选的肿瘤标志物,被广泛应用于宫颈癌的诊断治疗当中。IL-6 是一种分子量为 21KD 的糖蛋白,分别由一条分子量为 80 KD 的 α 链和一条分子量为

130 KD 的 β 链组成^[20-23],其发挥效应的方式主要是自分泌或旁分泌,对细胞免疫应答、造血调节中起着重要作用。T 淋巴细胞亚群在患者机体的肿瘤免疫系统中作用巨大^[24],其中 CD3⁺ 代表所有 T 细胞,CD4⁺ 属于辅助 / 诱导性 T 细胞,CD8⁺ 属于抑制 / 细胞毒 T 细胞,CD4⁺ 细胞对 B 细胞具有协助作用,同时对其他 T 细胞具有免疫应答之功效,CD8⁺ 是一种具有细胞毒活性效应细胞。有研究表明^[25,26]一旦患者机体出现恶性肿瘤,肿瘤会分泌因子将 CD3⁺、CD4⁺、CD8⁺ 的含量打乱,尤其是 CD4⁺/CD8⁺ 的含量,进而导致机体的免疫反应出现紊乱,且宫颈癌患者治疗后的 CD3⁺、CD4⁺ 及 CD4⁺/CD8⁺ 的表达水平会明显上升,进而患者的免疫功能也逐渐恢复,因 CD8⁺ 是抑制性 T 淋巴细胞,故治疗后的宫颈癌患者 CD8⁺ 会显著降低^[27,28]。本研究表明:苦参碱注射液辅助化疗治疗的患者 CD3⁺、CD4⁺ 及 CD4⁺/CD8⁺ 的表达水平显著高于单一化疗的患者,血清 CA125、IL-6 及 CD8⁺ 水平明显低于单一化疗者。此外,苦参碱注射液辅助化疗治疗组的肝肾功能损伤、骨髓抑制胃肠道反

应等不良反应发生率显著低于单一化疗组,提示苦参碱注射液不仅可以提高化疗的疗效,而且能降低化疗药物对正常细胞的毒副作用。

综上所述,苦参碱注射液辅助宫颈癌化疗的增敏效果显著,能有效降低患者 CA125 及 IL-6 水平,显著改善机体 T 细胞免疫功能。

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