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新辅助静脉化疗治疗中晚期宫颈癌患者的临床效果及机制分析*

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摘要 目的:探讨新辅助静脉化疗对中晚期宫颈癌患者的临床疗效及其可能作用机制。**方法:**收集于我院就诊或住院治疗的 60 例宫颈癌患者,根据治疗方案不同分为实验组和对照组,每组各 30 例。对照组患者采用放疗方案,实验组患者在对照组基础上应用新辅助静脉化疗方案,21 d 为一疗程,共 2 个疗程。治疗期间密切注意患者的生命体征,并对出现的并发症进行及时治疗。治疗结束后,对患者的血清肿瘤坏死因子- α (TNF- α)、血管内皮生长因子(VEGF)、患者副作用发生率以及临床疗效进行检测并比较。**结果:**与治疗前相比,两组患者治疗后的血清 TNF- α 、VEGF 水平均显著下降($P<0.05$);与对照组相比,实验组患者治疗后的血清 TNF- α 、VEGF 水平及副作用发生率较低($P<0.05$),临床治疗总有效率较高($P<0.05$)。**结论:**新辅助静脉化疗能够显著提高中晚期宫颈癌患者的临床疗效并减少化疗相关的不良反应,这可能与降低中晚期宫颈癌患者血清 TNF- α 、VEGF 水平有关。

关键词:新辅助静脉化疗;宫颈癌;肿瘤坏死因子- α ;血管内皮生长因子

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Clinical Effect of Neoadjuvant Chemotherapy on Patients with Advanced Cervical Cancer and Its Mechanisms*

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ABSTRACT Objective: To investigate the effect of neoadjuvant chemotherapy on patients with advanced cervical cancer and its possible mechanism. **Methods:** 60 cases of cervical cancer from our hospital were collected and divided into the experimental group and the control group with 30 cases in each group. Patients in the control group were treated with radiotherapy, based on the treatment of the control group, the new adjuvant intravenous chemotherapy were used on the patients in the experimental group for 2 courses, as 21d for one course. Pay close attention to the Patients' vital signs during the treatment, and apply timely treatment to complications. After the treatment, the serum levels of tumor necrosis factor- α (TNF- α), vascular endothelial growth factor (VEGF), the incidence of side effects and clinical efficacy were detected and compared. **Results:** Compared with before treatment, the serum TNF- α , VEGF levels were significantly decreased of the two groups of patients after treatment, ($P<0.05$); compared with the control group, serum TNF- α , VEGF levels and incidence of side effects of the experimental group are lower after treatment ($P<0.05$), the clinical total efficiency was higher ($P<0.05$). **Conclusion:** Neoadjuvant chemotherapy could enhance the clinical efficacy and reduce the side effects in the treatment of advanced cervical cancer, which might be related to the decrease of serum levels of TNF- α , VEGF.

Key words: Neoadjuvant chemotherapy; Cervical cancer; Tumor necrosis factor- α ; Vascular endothelial growth factor

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前言

宫颈癌(cervical carcinoma)是女性第二大常见恶性肿瘤。近年来,我国宫颈癌的发病率升高,且发病年龄呈年轻化^[2]。据统计,我国每年宫颈癌新发病例约 13 万例,占全世界新发病例总数的约 1/4,严重威胁当代女性的健康^[1]。临床通常采用手术的方法对宫颈癌进行治疗,研究表明宫颈癌根治术可以治愈大多数早期宫颈癌,但对于中晚期宫颈癌,手术的疗效欠佳,且患者术后的 5 年生存率较低。化疗在中晚期宫颈癌的治疗中也

具有较好的疗效^[3,4]。近年来,新辅助化疗(neoadjuvant chemotherapy, NACT)的方案受到广泛关注,其是指在手术或放疗前加用一个疗程化疗的治疗方案,这种化疗方案既可克服手术难度大、术后并发症多等缺点,又可避免放疗的方案对卵巢的损伤^[5]。因此,本研究主要探讨了新辅助静脉化疗治疗中晚期宫颈癌患者的临床疗效及安全性,并初步探讨了其可能机制,现报道如下。

1 资料与方法

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1.1 临床资料

收集 2013 年 1 月~2014 年 3 月于我院就诊或住院治疗的 60 例宫颈癌患者,根据治疗方案不同分为实验组和对照组,每组各 30 例。患者全部为女性,实验组患者平均年龄 (48.47±1.29)岁;对照组患者平均年龄(48.81±1.51)岁。所有患者均符合宫颈癌的临床诊断标准,患者年龄在 30-59 岁之间,均为女性;患者均已婚或未婚但有性生活女性;无其他宫颈以及妇科疾病;无肝肾功能不全,患者均无感染性疾病以及皮肤疾病,患者无转移性肿瘤,所有患者均无化疗禁忌症,实验前未接受过相关治疗。患者均同意进行实验。排除不符合纳入标准的患者,排除年龄在 30 岁以下以及 60 岁以下的患者;排除妊娠及哺乳期妇女;排除宫颈转移癌患者;排除宫颈不完整以及患有其他宫颈疾病的患者;排除肝肾功能不全的患者;排除患有其他妇科肿瘤的患者;排除有肿瘤全身性合并症的患者;排除有化疗禁忌症,不能接受化疗的患者;排除精神病患者。所有患者均符合国际妇科联合分期标准确诊为宫颈癌中晚期,并经细胞学、宫颈活组织检查确诊为宫颈癌,两组患者的一般资料相比无差异(P>0.05)。

1.2 方法

1.2.1 治疗方法 对照组患者采用放疗方案,放疗方案采用 10 mv X 线,前后对穿照射盆腔大野,DT:3000c Gy;盆腔四野,DT:2000c Gy,每周 1 次,共 3 次。腔内照射 42 Gy,A 点剂量 600 cGy 腔内照射时不做体外照射。实验组患者在对照组基础上应用顺铂 75 mg/m²+ 紫杉醇 175 mg/m²+ 氟尿嘧啶 1000 mg 进行静脉化疗,21 d 为一疗程,共 2 个疗程。治疗期间密切注意

患者的生命体征,并对出现的并发症进行及时治疗。

1.2.2 血清肿瘤坏死因子(TNF-α)水平检测 所有患者于治疗前后采集外周静脉血 2 mL,离心取上清,采用酶联免疫吸附法(ELISA),对患者的血清肿瘤坏死因子(TNF-α)水平进行检测。

1.2.3 血清血管内皮生长因子(VEGF)水平检测 所有患者治疗前后取外周静脉血 2 mL,离心取上清,采用酶联免疫吸附法(ELISA),检测患者的血清血管内皮生长因子(VEGF)水平。

1.2.4 患者副作用发生情况 治疗后,对患者恶心呕吐、口腔溃疡、腹泻、骨髓抑制、发热等副作用的发生情况进行统计。

1.2.5 临床疗效判定 患者治疗后经随访,根据按 WHO 制定的标准进行评价:完全缓解(CR):患者肿瘤消失并维持 4 周以上;部分缓解(PR):患者肿瘤体积缩小在 50%以上并维持超过 4 周为;稳定(SD):肿瘤体积缩小 25%~50%并维持 4 周以上;肿瘤体积增大甚至有新的病灶出现进展(PD)。治疗有效率=(完全缓解+部分缓解)/总患者数×100%。

1.3 统计学分析

采用 SPSS 19.0 统计软件,计量数据以均数±标准差($\bar{x} \pm s$)表示,采用 t 检验;计数资料以%表示,采用卡方检验,以 P<0.05 认为差异有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,实验组患者的治疗总有效率为 63.39%,与对照组相比较(46.67%,P<0.05),差异均具有统计学差异,具体见表1。

表 1 两组患者临床疗效的比较【例(%)】

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

	CR	PR	SD	PD	Total effective rate
Experimental group	12(40.0)	7(23.33)	10(33.33)	1(3.33)	19(63.33)*
Control group	8(26.67)	6(20.0)	13(43.33)	3(10.0)	14(46.67)

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

2.2 两组患者副作用发生情况比较

与对照组相比,实验组患者的副作用如恶心呕吐、口腔溃

疡、腹泻、骨髓抑制、发热的发生率较低(P<0.05),具体见表 2。

表 2 两组患者副作用发生情况的比较【例(%)】

Table 2 Comparison of the incidence of adverse reactions between two groups[n(%)]

	Nausea and vomiting	mouth ulcer	diarrhea	myelosuppression	fever	Adverse Effects Rate
Experimental group	3(10.0)	2(6.67)	3(10.0)	1(3.33)	3(10.0)	12(40.0)*
Control group	5(16.67)	2(6.67)	5(16.67)	2(6.67)	5(16.67)	19(63.33)

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

2.3 两组患者治疗前后血清肿瘤坏死因子(TNF-α)水平的比较

治疗后,两组患者的血清肿瘤坏死因子(TNF-α)水平与治疗前相比均下降(P<0.05),实验组患者 TNF-α 水平与对照组相比较低(P<0.05),具体见表 3。

2.4 两组患者治疗前后血清血管内皮生长因子(VEGF)水平的比较

治疗后,与治疗前相比,两组患者血清血管内皮生长因子(VEGF)水平均显著下降(P<0.05),实验组患者的 VEGF 水平与

对照组相比较低(P<0.05),具体见表 4。

3 讨论

手术治疗宫颈癌只适合早期患者,放疗治疗宫颈癌的效果较好,避免了手术的风险,且适用于各期的宫颈癌^[6]。但单纯放疗对病灶较大的患者,疗效并不理想。因此,探索新的治疗方式十分必要^[7]。近年来,新辅助化疗(Neoadjuvant chemotherapy, NACT) 被广泛关注并在过去的 20 年里在临床广泛应用,

NACT 应用的目的在于减少肿瘤的大小, 增加放疗的敏感性, 提高手术成功的几率, 增加手术的净切率, 减少复发, 为后来的治疗提供方便除, 同时, 对新辅助治疗的反应情况可以对患者的预后进行参考^[8,9]。

表 3 两组患者治疗前后血清 TNF- α 水平的比较(ng/mL, $\bar{x} \pm s$)

Table 3 Comparison of the serum TNF- α level between two groups before and after treatment(ng/mL, $\bar{x} \pm s$)

	Before treatment	After treatment
Experimental group	1.57 $\pm$ 0.41	0.92 $\pm$ 0.33
Control group	1.52 $\pm$ 0.55	1.17 $\pm$ 0.46

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

表 4 两组患者治疗前后血清 VEGF 水平的比较(μ g/L, $\bar{x} \pm s$)

Table 4 Comparison of the serum VEGF level between two groups before and after treatment(μ g/L, $\bar{x} \pm s$)

	Before treatment	After treatment
Experimental group	238.19 $\pm$ 62.14	145.27 $\pm$ 51.95
Control group	231.38 $\pm$ 71.31	177.21 $\pm$ 62.82

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

宫颈癌与其它肿瘤一样是血管依赖性生长肿瘤。血管生成(anigogenesis) 指从已存在的毛细血管床产生新生血管的过程^[10]。血管生成在多种疾病中起着十分重要的作用, 许多研究已经表明肿瘤的生长和转移依赖新生血管从宿主中获得营养, 并向宿主输送癌细胞, 使肿瘤发生转移^[11]。血管内皮生长因子(VEGF)是一种促血管生成因子, 是目前所知的广泛存在的最强的生长因子^[12], 能够特异性的作用于血管内皮细胞, 形成新生血管。大多数肿瘤细胞能够分泌 VEGF, 并作用于肿瘤细胞内, 促进内皮细胞增生, 介导淋巴微管及血管的生成^[13]。有研究证实许多恶性实体肿瘤如乳腺癌、前列腺癌中, 都呈现 VEGF 蛋白的高表达, 且与肿瘤的恶性程度、进展转移情况以及患者的预后关系密切^[14]。目前已有研究表明 VEGF 与宫颈癌发生关系密切, 能够增强肿瘤细胞的侵袭性以及抗凋亡的能力, 进而抑制肿瘤的生长和转移^[15]。本研究结果显示两组患者治疗后的 VEGF 水平均下降, 其中实验组患者的 VEGF 水平较低, 这与之前的研究相似^[20]。

肿瘤坏死因子(tumor necrosis factor, TNF)由巨噬细胞和单核细胞分泌, 具有是 α 和 β 两对, 但二者的生物活性相近^[16], 具有抗肿瘤活性, 能活化肿瘤血管, 诱导肿瘤细胞凋亡, 对许多细胞具有的杀伤作用, 在体外对多种肿瘤细胞系具有增值抑制作用^[17-19]。我们的实验结果显示实验组患者治疗后 TNF- α 水平较低, 表明本实验的治疗措施能够降低 TNF- α 水平, 对肿瘤细胞的生长产生抑制作用。

总之, 本研究表明新辅助静脉化疗能够显著提高中晚期宫颈癌患者的临床疗效并减少化疗相关的不良反应, 这可能与降低中晚期宫颈癌患者血清 TNF- α 、VEGF 水平有关。

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