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腹腔内贝伐珠单抗辅助卵巢癌术后化疗对患者血清 AFP、VEGF、TGF-β1、MIF 的影响

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摘要 目的:研究腹腔内贝伐珠单抗辅助卵巢癌术后化疗对患者血清甲胎蛋白(AFP)、血管内皮生长因子(VEGF)、转化生长因子(TGF-β1)、巨噬细胞移动抑制因子(MIF)的影响。**方法:**选取 2019 年 1 月至 2021 年 2 月的 210 例卵巢癌患者。按照随机数表法分为观察组(n=101)和对照组(n=109),对照组采用化疗治疗,观察组在对照组的基础上,采用腹腔内贝伐珠单抗辅助治疗。对比两组治疗效果,血清治疗前后 AFP、VEGF、TGF-β1、MIF 水平变化,不良反应,随访生存分析结果。**结果:**治疗后,观察组总有效率显著高于对照组 [89.11%(90/101)vs66.05%(72/109)](*P*<0.05); 血清 AFP、VEGF、TGF-β1、MIF 水平显著低于对照组 [(5.19± 1.37)ng/mLvs(10.21± 2.38)ng/mL,(22.61± 4.32)ng/Lvs(35.76± 6.34)ng/L,(168.03± 20.18)ng/Lvs(203.76± 28.69)ng/L,(4.81± 1.01)μg/Lvs(12.79± 2.50)μg/L](*P*<0.05);两组不良反应对比无显著差异(*P*>0.05);平均生存时间、2 年生存率显著高于对照组[(19.23± 1.36) 月 vs (19.23± 1.36) 月,79.21%(80/101)vs28.44%(31/109)](*P*<0.05), 局部复发与转移显著低于对照组[9.90%(10/101)vs13.76%(15/109)](*P*<0.05)。**结论:**腹腔内贝伐珠单抗辅助卵巢癌术后化疗可有效改善患者的临床症状,缓解疾病发展,降低血清 AFP、VEGF、TGF-β1、MIF 水平,提高患者生存预后。

关键词:腹腔灌注;贝伐珠单抗;卵巢癌;化疗;甲胎蛋白;血管内皮生长因子;转化生长因子;巨噬细胞移动抑制因子

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The Effect of Chemotherapy with Bevacizumab in the Treatment of Ovarian Cancer after Operation in Patients on Serum AFP, VEGF, TGF-β1 and MIF

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ABSTRACT Objective: To study the effect of chemotherapy with bevacizumab in the treatment of ovarian cancer after operation The influence on serum AFP, VEGF, TGF-β1 and MIF. **Methods:** 120 Ovarian cancer patients who received therapy from January 2019 to February 2020 in our hospital were selected as research objects. According to random number table, those patients were divided into the observation group (n=101) and the control group (n=109). The control group was treated with chemotherapy. The observation group was treated with bevacizumab on the basis of the control group. The results of the two groups were compared, AFP, VEGF and TGF be-fore and after serum treatment-β1. MIF level changes, adverse reactions, follow-up survival analysis results. **Results:** After treatment, The total effective rate of observation group was significantly higher than that of control group [89.11%(90/101)vs66.05%(72/109)](*P*< 0.05). Serum AFP, VEGF, TGF- β 1. MIF level was significantly lower than that of the control group [(5.19± 1.37)ng/mLvs (10.21± 2.38)ng/mL,(22.61± 4.32)ng/Lvs(35.76± 6.34)ng/L,(168.03± 20.18)ng/Lvs(203.76± 28.69)ng/L,(4.81± 1.01)μg/Lvs(12.79± 2.50)μg/L](*P*<0.05). There was no significant difference in adverse reactions between the two groups (*P*>0.05). The average survival time and 2-year survival rate of the treatment group were significantly higher than those of the control group [(19.23± 1.36)month vs (19.23± 1.36)month, 79.21%(80/101)vs28.44%(31/109)](*P*<0.05).Local recurrence and metastasis were significantly lower than those in the control group (*P*<0.05). **Conclusion:** Chemotherapy with bevacizumab in abdominal cavity can improve the clinical symptoms of patients with ovarian cancer after operation,alleviating disease development, the serum levels of AFP, VEGF, TGF-β1 and MIF were decreased, improve the survival and prognosis of patients.

Key words: Intraperitoneal perfusion; Bevacizumab; Ovarian cancer; Chemotherapy; Alpha fetoprotein; Vascular endothelial growth factor; Transforming growth factor; Macrophage migration inhibitory factor

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前言

卵巢癌是卵巢肿瘤的一种恶性肿瘤，生长在卵巢上，其中90%～95%为卵巢原发性的癌，由于卵巢癌早期无典型症状，筛查作用有限，早期有效的诊断较为困难，多数患者确诊时已是晚期，错过了最佳手术治疗时期[1]。目前临床上对于该病的发病因素尚不明确，但经研究及流行病学调查发现，环境、遗传、持续排卵等均是诱发该病的高危因素[2]。卵巢癌最初无症状，常在妇科检查时发现，患者可常感到下腹部不适，部分患者会出现月经失调或闭经，当发展到晚期的时候可出现乏力、消瘦、贫血等症状。目前临床上对于治疗卵巢癌的主要方案为手术联合化疗，具有一定的效果，但仍有部分患者可出现复发甚至疾病进展，还可能出现耐药情况[3,4]。贝伐珠单抗是一种单克隆抗体，可抑制血管内皮生长因子。近年来，靶向药物治疗恶性肿瘤已成为研究的热点[5]。本研究旨在探讨腹腔内贝伐珠单抗辅助卵巢癌术后化疗对患者血清甲胎蛋白（AFP）、血管内皮生长因子（VEGF）、转化生长因子（TGF-β1）、巨噬细胞移动抑制因子（MIF）的影响。

1 资料与方法

1.1 一般资料

选取2019年1月至2021年2月的210例卵巢癌患者，均经病理学诊断为卵巢癌。纳入标准[6]：符合国际妇产科联盟（FIGO）分期Ⅲ~Ⅳ期；未采用手术或放化疗治疗；生存期＞3个月；配合并同意本次研究者；排除标准：患有其他严重疾病；对本次治疗药物过敏者；妊娠期或哺乳期者；心肝肾严重异常者；患有凝血功能障碍；沟通障碍者。按照简单随机数表法分为观察组（n=101）和对照组（n=109），观察组年龄41～65岁，平均（53.26± 9.31）岁，Ⅲ期69例，Ⅳ期32例，病理类型：浆液型51例、黏液型32例、混合型18例；对照组年龄42～66岁，平均（53.98± 9.35）岁，Ⅲ期64例，Ⅳ期45例，病理类型：浆液型53例、黏液型36例、混合型20例。本研究经医学伦理会批准，患者均知情并签署知情同意书，两组一般资料均无显著差异（P＞0.05）。

1.2 方法

对照组在化疗前采用常规肝肾功能及血常规检查，将肿瘤热循环灌注机接入中心静脉导管，灌注45℃的生理盐水，然后快速滴注75 mg/m^{2}顺铂（生产厂家：齐鲁制药(海南)有限公司）和175 mg/m^{2}紫杉醇（生产厂家：北京双鹭药业股份有限公司）于腹腔内，进行腹腔局部热疗，每2周治疗一次。观察组在对照组的基础上，采用300 mg贝伐珠单抗（生产厂家：上海罗氏制药有限公司）治疗，方法同对照组。两组治疗21天为一个周期，均治疗3个周期。

1.3 观察指标

观察两组治疗效果，血清治疗前后甲胎蛋白（AFP）、血管内皮生长因子（VEGF）、转化生长因子（TGF-β1）、巨噬细胞移动抑制因子（MIF）水平变化，不良反应，随访生存分析结果。分别于两组治疗前1天及治疗30天后采集静脉血，离心分离血清后等待检查，采用酶联免疫吸附法检测血清TGF-β1、VEGF、MIF水平；采用化学发光法检测血清AFP水平。

1.4 疗效评定标准

病灶完全消失且维持4周以上无新病灶出现为完全缓解（CR）[7]。病灶直径缩小30%且维持4周以上无其他病变发生为部分缓解（PR）；病灶最大直径缩小超过50%或增大低于25%为稳定（SD）；病灶直径增大超过25%为进展（PD）。疾病控制率（%）=（CR+PR+SD）/ 总例数× 100%。

1.5 统计学分析

使用SPSS18.0统计软件进行统计，数据均符合正态分布，计数资料以[（例）%]表示，用x^2检验比较，计量资料以（$\bar{x}\pm s$）表示，采用t检验，组内比较使用配对样本t检验，采用P＜0.05为差异有统计学意义。

2 结果

2.1 两组治疗效果情况

观察组总有效率显著高于对照组（P<0.05），见表1。

表1 两组治疗效果情况[例(%)]

Table 1 Treatment effect of two groups[n(%)]

Group	n	CR	PR	SD	PD	ORR
Observation group	101	71	19	15	6	90(89.11)
Control group	109	55	17	19	18	72(66.05)

2.2 两组血清AFP、VEGF、TGF-β1、MIF水平情况变化

两组治疗前血清AFP、VEGF、TGF-β1、MIF水平均无显著差异（P>0.05），治疗后，两组血清AFP、VEGF、TGF-β1、MIF水平均较治疗前显著下降（P<0.05），两组治疗后血清AFP、VEGF、TGF-β1、MIF水平具有显著差异（P<0.05），见表2。

2.3 两组不良反应对比

两组不良反应对比无显著差异（P>0.05），见表3。

2.4 两组随访生存分析结果对比

观察组平均生存时间、2年生存率显著高于对照组，局部复发与转移显著低于对照组（P<0.05），见表4。

3 讨论

临床研究表明，卵巢癌的发病率低于宫颈癌和子宫内膜癌，但死亡率却位于妇科癌症首位，且预后较差，对患者的生命健康带来了严重的威胁[8]。放化疗和肿瘤细胞减灭术是治疗晚期卵巢癌的主要方法，临床发现[9,10]，部分患者经过放化疗和肿瘤细胞减灭术治疗后，肿瘤细胞仍会在淋巴系统和血液快速扩散，且复发率较高。

贝伐珠单抗与血管内皮生长因子（VEGF）具有良好的亲和性，能够有效抑制肿瘤细胞的转移[11]。临床研究表明[12]，抑制血

表 2 两组血清 AFP、VEGF、TGF-β1、MIF 水平情况变化($\bar{x}\pm s$)

Table 2 Serum AFP, VEGF, TGF-β1 and MIF in two groups changes of level($\bar{x}\pm s$)

Groups	time	AFP(ng/mL)	VEGF(ng/L)	TGF-β1(ng/L)	MIF(μg/L)
Observation group (n=101)	Before treatment	82.57± 10.36	53.29± 9.06	341.89± 35.21	46.80± 5.23
	After treatment	5.19± 1.37*	22.61± 4.32*	168.03± 20.18*	4.81± 1.01*
Control group(n=109)	Before treatment	81.98± 10.32	53.32± 9.08	342.03± 35.29	46.92± 5.30
	After treatment	10.21± 2.38*	35.76± 6.34*	203.76± 28.69*	12.79± 2.50*

Note: compare with pre treatment, *$P<0.05$.

表 3 两组不良反应对比($\bar{x}\pm s$)

Table 3 Comparison of adverse reactions between the two groups($\bar{x}\pm s$)

Groups	n	neurotoxicity	Myelosuppression	Gastrointestinal reaction	Liver and kidney function injury	Hair loss and numbness of fingertips	Total incidence
Observation group	101	1	1	3	3	2	10(9.90)
Control group	109	2	2	2	4	3	13(11.93)

表 4 两组随访生存分析结果对比($\bar{x}\pm s$)

Table 4 Comparison of follow-up survival analysis results between the two groups($\bar{x}\pm s$)

Groups	n	Mean survival time (month)	One year survival [n(%)]	2-year survival [n(%)]	Local recurrence and metastasis
Observation group	101	19.23± 1.36	89(88.11)	80(79.21)	10(9.90)
Control group	109	11.72± 1.05	52(47.70)	31(28.44)	15(13.76)

管内皮生长因子活性是贝伐珠单抗的主要治疗靶点。在[13]作者的研究中表明,VEGF 水平与上皮性卵巢癌患者预后存在密切的联系,若该因子及受体呈高表达,患者的预后可能会较差,而抑制该因子活性及表达可有利于促进治疗卵巢癌。VEGF 高表达会增加内皮细胞小孔,增加血管通透性,使血浆蛋白进入血管外,从而为微血管及肿瘤创造了生长环境[14]。微小肿瘤可通过血浆蛋白的被动扩散来获得足够的生长动力源,当肿瘤直径超过 2 mm 后,周围的环境会发生缺氧,而这种环境会进一步的对 VEGF 造成刺激,促进血管生成,导致恶性循环形成[15,16]。肿瘤生长对新血管生成具有一定的依耐性,但机体的正常组织不常生成新血管,因此临床认为[17],抗血管生成具有抗肿瘤作用。贝伐珠单抗的靶向抑制作用可对新血管进行直接抑制,还可促使肿瘤血管系统正常化,促进化疗药物渗透,提高治疗效果[18]。本研究显示,观察组平均生存时间、2 年生存率显著高于对照组,局部复发与转移显著低于对照组及治疗有效率显著优于对照组。说明了灌注化疗可有效降低卵巢癌细胞通透性,可针对性灭杀肿瘤细胞, 使药物能够能够更好的作用于血液循环,可对已经向外蔓延的肿瘤细胞进行抑制、消灭[19-21]。但观察组在加用贝伐珠单抗治疗后疗效更佳,这可能与贝伐珠单抗抑制 VEGF 的生物活性有关,从而促进肿瘤组织退化。且本研究对两组治疗期间观察发现, 两组不良反应发生率无显著差异。说明了贝伐珠单抗不会增加患者不良反应,安全可靠。

临床研究发现[22],卵巢癌患者血清 AFP、VEGF、TGF-β1、MIF 水平均显著高于正常人。AFP 是一种酸性糖蛋白,在正常人的含量中极低,若含量出现明显升高,可作为判断卵巢癌的诊断[23]。VEGF 是一种高度特异性的促血管内皮细胞生长因子,可促进血管通透性、细胞外基质变性、血管内皮细胞迁移、增殖和血管形成等[24,25]。TGF-β1 可促进细胞生长和分化,是 TGF-β 超家族的一员[26]。MIF 是一种前炎症因子和免疫活性物质,具有限制巨噬细胞吞噬不正常细胞的作用[27]。临床研究表明[28-30],TGF-β1、MIF 可反映卵巢癌肿瘤的侵袭转移能力。本研究显示, 观察组血清 AFP、VEGF、TGF-β1、MIF 水平均显著低于对照组。说明了腹腔内贝伐珠单抗辅助治疗能够在一定程度上阻止肿瘤复发和转移。

综上所述,腹腔内贝伐珠单抗辅助卵巢癌术后化疗可有效改善患者的临床症状, 缓解疾病发展, 降低血清 AFP、VEGF、TGF-β1、MIF 水平,提高患者生存预后。

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