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新辅助化疗联合肿瘤细胞减灭术对晚期卵巢癌患者的疗效及对血流动力学参数的影响*

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摘要 目的:探讨新辅助化疗联合肿瘤细胞减灭术对晚期卵巢癌患者的疗效及对血流参数的影响。**方法:**选取 2015 年 1 月 -2017 年 6 月我院诊治的 158 例晚期卵巢癌患者,按治疗方法分为对照组、观察组,各 79 例。对照组使用肿瘤细胞减灭术进行常规卵巢癌治疗,观察组在常规基础上联合新辅助化疗进行治疗。比较两组临床疗效、治疗前后血流动力学参数的变化及不良反应的发生情况。**结果:**治疗后,观察组化疗的表观缓解率(83.54 %)显著高于对照组(62.03 %)(P<0.05)。两组患者治疗前各血流动力学参数比较差异无统计学意义(P>0.05),观察组术后 1、4、12 w 颈动脉收缩期最大流速(peak systolic velocity,PSV)均显著低于对照组(P<0.05),血管阻力指数(resisitance index,RI)、搏动指数(pulsatility index,PI)均显著高于对照组(P<0.05)。两组患者在治疗期间出现的心脏毒性反应的发生率比较差异无统计学意义(P>0.05),对照组患者治疗期间骨髓抑制、恶心呕吐、肝脏损伤、肾脏损伤的不良反应程度显著低于观察组(P<0.05)。**结论:**新辅助化疗联合肿瘤细胞减灭术能够显著提高患者的临床疗效,改善卵巢的血流动力学参数。

关键词:卵巢癌;肿瘤细胞减灭术;新辅助化疗;血流参数

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Clinical Efficacy of Neoadjuvant Chemotherapy Combined with Cytoreductive Surgery in the Treatment of Patients with Advanced Ovarian Cancer and Its Influence on the Blood Flow Parameters*

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ABSTRACT Objective: To explore the clinical efficacy of neoadjuvant chemotherapy combined with cytoreductive surgery in the treatment of patients with advanced ovarian cancer and its influence on the blood flow parameters. **Methods:** 158 cases pof patients with advanced ovarian cancer admitted in our hospital from January 2015 to June 2017. All patients were divided into the control group and the observation group according to the treatment methods, 79 cases in each group. The control group was treated with cytoreductive surgery. The observation group was treated with neoadjuvant chemotherapy on a routine basis. The clinical efficacy, changes of blood flow parameters before and after treatment and incidence of adverse reactions were compared between two groups. **Results:** The apparent response rate (83.54%) of observation group was significantly higher than that in the control group (62.03%) (P<0.05). There was no significant difference in the blood flow parameters between the two groups before treatment(P>0.05). The PSV of observation group at 1, 4, and 12 weeks postoperation were significantly lower than those of the control group (P<0.05). The RI and PI of observation group were significantly higher than those of the control group (P<0.05). There was no significant difference in the incidence of cardiotoxicity between the two groups during treatment (P>0.05). In the control group, the degree of adverse reactions of myelosuppression, nausea and vomiting, liver injury and renal injury were significantly lower than those in the observation group during the treatment (P<0.05). **Conclusions:** Neoadjuvant chemotherapy combined with cytoreductive surgery can more effectively improve the clinical efficacy of patients and improve the ovarian blood flow parameters than cytoreductive surgery alone.

Key words: Ovarian carcinoma; Cytoreductive surgy; Neoadjuvant chemotherapy; Blood flow parameter

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前言

卵巢癌是女性生殖系统常见恶性肿瘤，发病率达 5 %,仅次于子宫颈癌、子宫体癌,5 年生存率仅 30 %,死亡率居于妇科肿瘤的首位,严重影响患者的身体健康、生命质量[1,2]。由于卵巢的胚胎发育、组织结构、内分泌功能等较复杂,卵巢癌发病早期症状不显著,70 %患者在确诊时常常已到中晚期 (III 期 -IV 期),恶性肿瘤已扩散至子宫、大网膜、双侧附件等部位,给临床

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治疗和患者预后带来较大难度[3,4]。

卵巢恶性肿瘤中上皮癌、恶性生殖细胞肿瘤是常见类型，临床中治疗卵巢癌以手术治疗为主，辅以放疗、化疗，即肿瘤减灭术联合术后化疗是目前临床中常见的治疗方法，手术的目的是尽可能的切除肿瘤灶，使残余肿瘤灶最大直径 <1 cm，实现满意肿瘤细胞减灭术。但受到肿瘤灶位置、大小、医师个人手术经验等的影响，满意肿瘤细胞减灭术的患者仅占 40 %左右，而未达到满意的患者的预后较差[5-7]，故临床中迫切需要一种新的治疗模式来改善以上的情况。本研究采用新辅助化疗联合肿瘤细胞减灭术治疗晚期卵巢癌的疗效较好，现报道如下。

1 材料与方法

1.1 一般资料

选取 2015 年 1 月 -2017 年 6 月我院诊治的 158 例晚期卵巢癌患者，按治疗方法分为对照组、观察组，各 79 例。两组基线资料比较无显著差异(P>0.05)，见表 1。本研究已通过我院伦理委员会审批。

表 1 两组基线资料比较(n, $\bar{x}\pm s$)

Table 1 Comparison of general information between two groups (n, $\bar{x}\pm s$)

Groups	Age(yesrs)	FIGO stage	Pathological type	Hostological grade
		IIIc stage/ IVstage	Serous carcinoma/clear cell carcinoma/mucinous carcinoma/ endometrioid carcinoma	Poorly differentiated/moderately differentiated/highly differentiated
Control group(n=79)	54.6± 7.5	54/25	52/12/9/6	18/38/23
Observation Group(n=79)	53.9± 8.1	57/22	53/12/7/7	16/41/22
t or x^2		0.261	0.373	0.268
P		0.610	0.933	0.874

1.2 纳入及排除标准

纳入标准：① 经病理学检查确诊为卵巢癌；② 病理分期为 IIIc 期或 IV 期；③ 预计生存期＞5 个化疗周期；④ 无化疗禁忌证；⑤ 无手术禁忌证；⑥ 已签知情同意书。排除标准：① 影像学显示有肺部、肝脏等转移；② 合并重大器官疾病及功能障碍；③ 合并神经系统、内分泌系统、血液系统疾病者；④ 合并其它恶性肿瘤者；⑤ 资料不全或中途退出研究者。

1.3 治疗方法

对照组使用肿瘤细胞减灭术进行常规卵巢癌治疗，手术范围包括全子宫、大网膜、双附件、盆腔淋巴结清扫、阑尾切除等，1 个月后行常规化疗方案：50-70 mg/m^2 顺铂腹腔滴注 135-175 mg/m^2 紫杉醇静脉滴注进行化疗，21 d 为 1 个疗程，共进行 3 个疗程。观察组在术前行新辅助化疗，用顺铂紫杉醇化疗，共 3 疗程，1 个月后行常规治疗，方法同对照组。

1.4 观察指标

(1)疗效[8]：完全缓解(complete remission，CR)，靶病灶全部消失，无新病灶出现，血清糖类抗原 125(CA125)≤ 35 U/ml；部分缓解 (partial remission，PR)，靶病灶最大直径之和减少≥ 30 %，维持 4 w，血清 CA125＞35 U/ml 或低于最初的 50 %以上；疾病稳定(stable disease，SD)，靶病灶最大直径之和未达部分缓解，或增大未达疾病进展，血清 CA125 未见明显升高；疾病进展(progressive disease，PD)，靶病灶最大直径之和至少增加 20 %，或出现新病灶，血清 CA125 显著升高。表观缓解率 =(完全缓解例数 部分缓解例数)/ 总例数× 100 %。(2)血流参数：于治疗前、术后 1、4、12 w 使用彩色多普勒超声诊断仪(Philips IU22)对患者的颈动脉收缩期最大流速 (peak systolic velocity，PSV)、血管阻力指数(resisitance index，RI)、搏动指数(pulsatility index，PI)进行检测。(3)不良反应[9]：观察并记录患者治疗期间出现的心脏毒性反应、骨髓移植、肝肾损伤等不良反应的发生情况。轻度、中度、严重反应分别以 Ⅰ、Ⅱ、Ⅲ级表示，功能丧失 / 威胁生命用Ⅳ级表示，发生相关死亡以 V 级表示。

1.5 统计学分析

用 SPSS 20.0 软件对数据进行分析，计量资料用($\bar{x}\pm s$)表示，组件比较采用 t 检验，计数资料以[n(%)]表示，组件比较次啊要 x^2 检验。以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后，观察组化疗的表观缓解率(83.54 %)显著高于对照组(62.03 %)(P<0.05)，见表 2。

表 2 两组患者临床疗效的比较[例(%)]

Table 2 Comparison of clinical efficacy between two groups[n(%)]

Groups	CR	PR	SD	PD	Apparent remission rate
Control group(n=79)	9(11.39)	40(50.63)	22(27.85)	8(10.13)	49(62.03)
Observation group (n=79)	18(22.78)	48(60.76)	11(13.92)	2(2.53)	66(83.54)
P					0.002

2.2 两组患者治疗前后血流动力学参数的比较

两组患者治疗前血流动力学参数比较差异无统计学意义(P>0.05)，观察组术后 1、4、12 w PSV 均显著低于对照组(P<0.05)，RI、PI 均显著高于对照组(P<0.05)，见表 3。

表 3 两组患者治疗前后血流动力学参数的比较($\bar{x}\pm s$)

Table 3 Comparison of the blood flow parameters between two groups before and after treatment($\bar{x}\pm s$)

Groups	PSV (cm/s)	RI	PI
Control group(n=79)			
Before treatment	26.12± 2.28	0.36± 0.03	0.62± 0.05
After operation 1 week	23.34± 2.05	0.41± 0.03	0.84± 0.06
After operation 4 weeks	20.37± 2.11	0.54± 0.04	1.01± 0.06
After operation 12 weeks	18.54± 2.08	0.63± 0.05	1.22± 0.09
Observation group(n=79)			
Before treatment	26.08± 2.67	0.35± 0.03	0.63± 0.06
After operation 1 week	21.04± 2.04*	0.61± 0.05*	1.12± 0.08*
After operation 4 weeks	17.58± 1.86*	0.73± 0.05*	1.41± 0.11*
After operation 12 weeks	14.85± 1.92*	0.82± 0.06*	1.62± 0.13*

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

2.3 两组患者不良反应的发生情况比较

两组患者在治疗期间出现的心脏毒性反应的发生率间无显著差异(P>0.05)，对照组患者治疗期间骨髓抑制、恶心呕吐、肝脏损伤、肾脏损伤的不良反应程度显著低于观察组(P<0.05)，见表 4。

表 4 两组患者不良反应的发生情况比较[例(%)]

Table 4 Comparison of occurrence of adverse reactions between two groups[n(%)]

Adverse reactions		Control group(n=79)	Observation group(n=79)	P
Heart toxic reactions	I stage and below I stage	75(94.94)	72(91.14)	0.348
	Ⅱ-Ⅲ stage	4(5.06)	7(8.86)	
Bone marrow supression	I stage and below I stage	66(83.54)	56(70.89)	0.028
	Ⅱ-Ⅲ stage	13(16.46)	23(29.11)	
Nausea and vomit	I stage and below I stage	71(89.87)	59(74.68)	0.005
	Ⅱ-Ⅲ stage	8(10.13)	20(25.32)	
Liver injury	I stage and below I stage	70(88.61)	61(77.22)	0.024
	Ⅱ-Ⅲ stage	9(11.39)	18(22.78)	
Kidney injury	I stage and below I stage	72(91.14)	64(81.01)	0.042
	Ⅱ-Ⅲ stage	7(8.86)	15(18.99)	

3 讨论

卵巢癌具有起病隐匿、早期症状不明显、早期诊断困难且易扩散的特点[10,11]，患者在确诊时已有 70-80 %处于中晚期阶段(III-IV 期)，错过了最佳的治疗时间，且该病治疗后复发率高达 70 %，因此卵巢癌死亡率居于妇科恶性肿瘤的首位[12-14]。2012 年，NCCN 诊疗指南推荐的标准治疗方案是肿瘤细胞减灭术联合术后基础化疗[15]，但效果不够理想。近些年，术前新辅助化疗已越来越多的应用于晚期卵巢癌的治疗中，即在肿瘤细胞减灭术前现接受一定次数化疗的治疗方案，有研究[16]显示新辅助化疗能够有效降低肿瘤负荷、提高手术成功率、改善患者预后。

本研究对观察组患者先进行新辅助化疗方案，结果显示与实施常规化疗方案的对照组相比，观察组化疗的缓解率(83.54 %)显著高于对照组(62.03 %)，提示新辅助化疗联合肿瘤细胞减灭术能够显著提高患者的临床治疗效果。分析原因可能与术前化疗存在以下优点有关：① 可有效消灭原发病灶和转移灶、减少肿瘤与周围组织的粘连，有助于减少术中出血、缩短手术时长、提高手术成功率[17,18]；② 可减少胸腔积液、腹水量，利于患者的围术期管理与全身状况改善，提高手术的安全性与患者耐受性[19,20]；③ 能够降低肿瘤细胞活性、侵袭力，减少手术操作引起的肿瘤转移等相关问题，降低术后复发[21,22]；④ 术后可在较短时间内开始化疗，利于治疗的连贯性，以达到有效控制肿瘤的目的[23,24]。Yang、Conrad 等[25,26]研究结果显示新辅助化疗联合肿瘤细胞减灭术可有效提高晚期卵巢癌患者的治疗总有效率，与本研

究结果一致。

此外，观察组术后 1、4、12 w PSV 均显著低于对照组，RI、PI 均显著高于对照组，体现了新辅助化疗对卵巢血流参数改善的积极影响，与其治疗效果密切相关，与 Philip 等[27]研究结果一致。本研究结果显示两组患者在治疗期间出现的心脏毒性反应的发生率间无显著差异，对照组患者治疗期间骨髓抑制、恶心呕吐、肝脏损伤、肾脏损伤的不良反应程度显著低于观察组，这可能与观察组患者在术前比对照组多实施了化疗治疗有关。观察组患者在术后化疗中，由于机体处于创伤后恢复阶段，身体素质较差，再次化疗则会对机体的损伤更严重[28-30]。本研究中仍存在样本量不够大、缺少围术期手术相关指标、治疗前后肿瘤标记物的检测等方面的不足，仍需再进一步深入研究。

综上所述，新辅助化疗联合肿瘤细胞减灭术能够显著提高患者的临床疗效，改善卵巢的血流动力学参数。

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