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新辅助化疗联合间隔肿瘤细胞减灭术治疗晚期卵巢癌的临床观察*

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摘要 目的:观察新辅助化疗与间隔肿瘤细胞减灭术联合治疗晚期卵巢癌的临床疗效。**方法:**选取我院收治的晚期卵巢癌患者 88 例,采取分层随机法分成两组,对照组采取间隔肿瘤细胞减灭术治疗,将全子宫、大网膜、双附件、肿瘤转移灶、阑尾切除,根据手术中的情况,切除腹主动脉旁、盆腔淋巴结及受累的脏器,观察组在对照组基础上采取新辅助化疗,行 2-3 次化疗后进行手术,采取 TP 方案进行新辅助化疗,150 mg/m² 紫杉醇,行静脉滴注,持续滴注 3 小时,每天 1 次;0.06 卡铂、200 mL 0.9%氯化钠注射液,行静脉滴注,每天 1-3 次;每个疗程间隔 3 周。比较两组的临床治疗总有效率、腹水量、术中出血量、病灶大小、手术时间、住院时间。**结果:**观察组的治疗总有效率(75.00%)显著高于对照组(54.55%)($P<0.05$),腹水量、术中出血量均明显少于对照组,病灶显著小于对照组($P<0.05$),手术时间、住院时间均明显短于对照组($P<0.05$)。**结论:**新辅助化疗联合间隔肿瘤细胞减灭术治疗晚期卵巢癌患者的临床效果明显优于单用间隔肿瘤细胞减灭术。

关键词:新辅助化疗;间隔肿瘤细胞减灭术;晚期卵巢癌;临床效果

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Clinical Observation on the Efficacy of Neoadjuvant Chemotherapy Combined with Interval Cytoreductive Surgery in the Treatment of Advanced Ovarian Cancer*

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ABSTRACT Objective: To observe the clinical efficacy of cell neoadjuvant chemotherapy combined with interval cytoreductive surgery in the treatment of advanced ovarian cancer. **Methods:** 88 cases of patients with advanced ovarian cancer in our hospital were selected and randomly divided into two groups. The control group was given interval cytoreductive surgery treatment. The uterus, omentum, salping, tumor metastasis and appendix were removed, according to the situation, the para aortic, pelvic lymph node and tired organs were given resection. While the observation group was given new adjuvant chemotherapy on the basis of control group, with surgery followed by 2-3 times chemotherapy. And TP regimen neoadjuvant chemotherapy was used: 150 mg/m² paclitaxel, intravenous infusion, continuous infusion for 3 hours, once a day; 0.06 carboplatinum (CBP), 200 ml sodium chloride injection (0.9%), intravenous drip, 1-3 times a day; each treatment interval of 3 weeks. Then, the total effective rate, ascitic volume, intraoperative bleeding, lesion size, operation time and hospital stay were respectively compared between two groups. **Results:** The total effective rate of observation group (75%) was significantly higher than that of the control group (54.55%)($P<0.05$). The ascitic volume and intraoperative bleeding of observation group were obviously lower than those of the control group. The lesion was also less than that of the control group ($P<0.05$). The operation time and the hospital stay were both shorter than those of the control group ($P<0.05$). **Conclusion:** The clinical efficacy of advanced ovarian cancer treated by cell neoadjuvant chemotherapy combined with interval cytoreductive surgery was significantly better than that of interval cytoreductive surgery alone.

Key words: Neoadjuvant chemotherapy; Interval cytoreductive surgery; Advanced ovarian cancer; Clinical effect

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前言

卵巢癌是与子宫颈癌、子宫体癌排在前三的女性生殖器官严重疾病,严重影响女性的生活质量和生命健康,是目前全世

界范围内导致妇女死亡最主要的生殖器官肿瘤之一^[1]。卵巢癌多发生于围绝经期的妇女群体,临床主要表现为腹胀、腹痛、不正常消瘦、月经不稳定等,目前其发病机制尚不完全明确,可能与致癌因子、免疫功能、内分泌、遗传以及饮食、生活习惯等

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有关^[9,10]。

目前,临床主要采用化疗治疗卵巢癌,主要治疗药物包括铂类抗肿瘤药物和紫杉醇等^[11]。卵巢癌中,上皮性肿瘤占恶性卵巢肿瘤的比例最高。尽管对卵巢癌治疗的研究不断有新进展,但多数晚期卵巢癌患者的预后仍然不佳。卵巢癌早期诊断困难,大部分患者发现时已经处于晚期^[1],此时部分患者的病情进展程度和身体条件已无法保证减灭手术的顺利进行,在该情况下进行的减灭手术效果可能大打折扣,甚至可能手术失败,而成功进行手术的患者也有很高的概率在术后短期内出现复发。

针对上述棘手情况,新辅助化疗作为一种过渡治疗手段被临床开发并应用。新辅助化疗的目的在于辅助手术的顺利进行,其可在术前一定程度的削减肿瘤细胞数量^[2],提高患者手术耐受,并且使肿瘤细胞增殖能力下降,对手术切除率有提高作用,并且可在一定程度上降低术后并发症的发生。本研究主要探讨了新辅助化疗联合间隔肿瘤细胞减灭术治疗晚期卵巢癌患者的临床效果,现将结果报道如下。

1 资料与方法

1.1 一般资料

选择2014年6月-2016年7月我院收治的晚期卵巢癌患者88例,采用分层随机法平均分为两组。观察组44例,平均年龄 (37.1 ± 3.4) 岁,平均体质量 (61.9 ± 5.7) kg;混合性囊腺癌6例,浆液性腺癌20例,透明细胞癌5例,粘液性腺癌13例;临床分期:III期患者16例,IV期患者28例;对照组44例,平均年龄 (36.3 ± 3.6) 岁,平均体质量 (58.9 ± 5.6) kg;混合性囊腺癌7例,浆液性腺癌19例,透明细胞癌6例,粘液性腺癌12例;临床分期:III期患者15例,IV期患者29例。观察组和对照组患

者一般资料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

1.2.1 对照组 对照组采取间隔肿瘤细胞减灭术治疗,将全子宫、大网膜、双附件、肿瘤转移灶、阑尾切除,根据手术中的情况,给予腹主动脉旁、盆腔淋巴结及受累的手累脏器进行切除。

1.2.2 观察组 观察组在对照组基础上,采取新辅助化疗,行2-3次化疗后,进行手术,采取TP方案进行新辅助化疗,150 mg/m² 紫杉醇,行静脉滴注,持续滴注3小时,每天1次;0.06 卡铂、200 mL 0.9%氯化钠注射液,行静脉滴注,每天1-3次;每个疗程间隔3周。

1.3 观察指标

评定两组患者临床疗效,分为完全缓解:治疗后病灶完全消失,持续观察4周,未发现新的病灶;部分缓解:治疗后病灶消失50%以上,持续观察4周,病灶未增大;稳定:治疗后病灶无明显改善,病灶缩小在50%以内,或者病灶增大25%以内;进展:治疗后病灶增大25%以上,持续观察4周,出现新的病灶^[9]。总有效率=完全缓解+部分缓解。观察两组患者腹水量、病灶大小、术中出血量、手术时间和住院时间。

1.4 统计学分析

采用统计软件SPSS 17.0完成统计学分析,计数资料用率(%)表示,组间比较采用卡方检验,计量资料以 $\bar{x} \pm s$ 表示,组间比较采用t检验,以 $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 两组晚期卵巢癌患者的临床疗效比较

观察组晚期卵巢癌患者的治疗总有效率(75.00%)显著高于对照组(54.55%),差异有统计学意义($P < 0.05$),详见表1

表1 两组患者临床疗效的对比[例(%)]

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

Groups	n	CR	PR	SD	PD	Total rate
Observation group	44	17(38.64)	16(36.36)	8(18.18)	3(6.82)	75.00
Control group	44	9(20.45)	15(34.09)	19(43.18)	1(2.27)	54.55
P						<0.05

2.2 两组晚期卵巢癌患者的手术效果比较

观察组晚期卵巢癌患者腹水量、术中出血量均明显少于对

照组,病灶显著小于对照组,差异均有统计学意义($P < 0.05$),详见表2。

表2 两组患者的手术效果对比 $[\bar{x} \pm s]$

Table 2 Comparison of the operative effects between two groups $[\bar{x} \pm s]$

Groups	n	Abdominal dropsy volume(mL)	Focus size(cm)	Blood loss(mL)
Observation group	44	128.2 $\pm$ 26.8	8.4 $\pm$ 1.6	508.2 $\pm$ 36.1
Control group	44	793.2 $\pm$ 31.7	15.5 $\pm$ 2.1	923.2 $\pm$ 29.6
P		<0.05	<0.05	<0.05

2.3 两组晚期卵巢癌患者的手术时间、住院时间比较

观察组晚期卵巢癌患者手术时间、住院时间均明显短于对照组($P < 0.05$),详见表3。

3 讨论

卵巢癌是一种较为常见的女性生殖系统恶性肿瘤^[4-8]。对妇女身心健康造成严重影响^[9-11],手术联合铂类药物化疗是其标准治疗方案。但多数卵巢癌患者在初诊时已属肿瘤晚期,失去了手术切除的机会,生存率较低^[1]。目前,卵巢癌的传统治疗方式为肿瘤细胞减灭术,术后结合紫杉醇类与铂类为主的联合药

物化疗综合治疗,但是其手术治疗和放化疗的疗效并不理想,易早期复发,导致卵巢癌的预后仍然较差^[2,3]。化疗是目前临床上应用较广的治疗方案,但在化疗过程中会出现脱发、恶心呕

吐等不良反应。此外,还有一些化疗药物具有极强的消化毒性,严重影响患者治疗效果和预后^[2,3]。因此,寻找一种毒性小、不良反应少的化疗药物已成为医学界的一大重点和难题。

表 3 两组晚期卵巢癌患者的手术时间、住院时间比较[$\bar{x} \pm s$]

Table 3 Comparison of the operation time and hospitalization between the two groups[$\bar{x} \pm s$]

Groups	n	Operation time(min)	Hospitalization(d)
Observation group	44	135.2 $\pm$ 11.8	11.6 $\pm$ 2.4
Control group	44	208.2 $\pm$ 15.5	15.1 $\pm$ 1.8
P		<0.05	<0.05

新辅助化疗指在术前进行的铂类药物为基础的联合化疗,可在术前对癌细胞起到杀伤作用,主要用于晚期卵巢癌并且无法在初始进行减灭手术的状态较差的患者^[13-16]。近年来,新辅助化疗逐渐作为一种过渡治疗被医师和患者所接受^[12],其作用主要是术前消灭部分癌细胞,减少瘤体体积,并且有减轻周围组织和病灶的粘连^[18-20]。但对于身体状况较差的卵巢癌晚期患者直接开展减灭手术的成功率令人堪忧,并且术后复发率较高,而新辅助化疗的开展可在术前稳定患者状态,提高手术耐受,一定程度上的降低了手术难度,理论上对患者有利。有研究表明^[17]新辅助化疗可有效提高手术的切除率,并可减少手术并发症,并且术前进行的新辅助化疗降低了肿瘤细胞活性,导致其侵袭能力以及增殖能力下降,因此手术刺激和血液流动等导致的肿瘤扩散、种植以及转移也因此而减少,对降低术后复发率具有积极作用^[21-25]。本研究结果显示观察组疗效优于对照组,并且术中各指标均更佳,说明了术前开展的新辅助化疗有效的提高了患者的手术耐受,降低了手术难度,使手术可更加顺利的进行。但需要注意的是,新辅助化疗周期以及减灭手术最佳时机目前仍然尚未有定论,一般可选择在进行 3-4 个疗程的化疗后进行手术。本研究并未对新辅助化疗最佳疗程数以及减灭手术时机进行探讨,存在一定的局限性,期待后续研究确定最佳化疗周期以及手术时机,使该治疗方案更好的运用于晚期卵巢癌患者的治疗中^[25-27]。

综上所述,晚期卵巢癌患者身体状况通常较差,部分患者耐受能力低下,粘连广泛,导致减灭手术难度大为提升,影响手术成功率和手术效果,为患者生存质量和生存期考虑,在减灭手术前合适的时机进行新辅助化疗是可行的过渡治疗方案,可减少癌细胞数量,减轻病灶和周围组织粘连,降低癌细胞活性,提高患者手术耐受能力,降低手术难度,其治疗晚期卵巢癌患者的临床效果明显优于单用间隔肿瘤细胞减灭术。

参考文献(References)

[1] You Q, Guo H, Xu D. Distinct prognostic values and potential drug targets of ALDH1. soenzymes in non-small-cell lung cancer I [J]. Drug Des Devel Ther, 2015, 9(2): 5087-5097

[2] Cardenas C, Alvero AB, Yun BS, et al. Redefining the origin and evolution of ovarian cancer: A hormonal connection[J]. Endocrine-related Cancer, 2016, 23(9): R411-422

[3] Lu L, Wang J, Wu Y, et al. Rap1A promotes ovarian cancer metastasis via activation of ERK/p38 and notch signaling[J]. Cancer Med, 2016, 5(12): 3544-3554

[4] Cui Y, She K, Tian D, et al. miR-146a Inhibits Proliferation and En-

hances Chemosensitivity in Epithelial Ovarian Cancer via Reduction of SOD2[J]. Oncol Res, 2016, 23(6): 275-282

[5] Salani R, O'Malley DM, Copeland LJ, et al. Feasibility of interval cytoreduction following neoadjuvant chemotherapy with carboplatin, weekly paclitaxel, and bevacizumab for advanced ovarian Cancer - A phase 1 study[J]. International journal of gynecological cancer, 2014, 24(4): 682-686

[6] Mallini P, Lennard T, Kirby J, et al. Epithelial-to-mesenchymal transition: what is the impact on breast cancer stem cells and drug resistance[J]. Cancer Treat Rev, 2014, 40(3): 341-348

[7] Nicoletto MO, Casarin A, Baldoni A, et al. Intraperitoneal Chemotherapy in Patients Pretreated for Ovarian Cancer Matched with Patients Treated with Parenteral Chemotherapy [J]. Anticancer Res, 2016, 36(12): 6541-6546

[8] Bepler G, Olaussen KA, Vataire AL, et al. ERCC1 and RRM1 in the international adjuvant lung trial by automated quantitative in situ analysis[J]. Am J Pathol, 2011, 17(8): 69-78

[9] Liu T, Liu Y, Gao H, et al. Clinical significance of yes-associated protein overexpression in cervical carcinoma: the differential effects based on histotypes[J]. Int J Gynecol Cancer, 2013, 23(4): 735-742

[10] Prat J. Staging classification for cancer of the ovary, fallopian tube, and peritoneum[J]. Int J Gynaecol Obstet, 2014, 124(1): 1-5

[11] Morelli MP, Overman MJ, Dasari A, et al. Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment[J]. Ann Oncol, 2015, 26(4): 731-736

[12] Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer [J]. N Engl J Med, 2015, 372(20): 1909-1919

[13] Li Q Q, Wang G, Liang H, et al. beta-Element promotes cisplatin-induced cell death in human bladder cancer and other carcinomas[J]. Anticancer Res, 2013, 33(4): 1421-1428

[14] Mrozik K M, Cheong C M, Hewett D, et al. Therapeutic targeting of N-cadherin is an effective treatment for multiple myeloma [J]. Br J Haematol, 2015, 171(3): 387-399

[15] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer [J]. New England Journal of Medicine, 2012, 366(15): 1382-1392

[16] Jayson G C, Kohn E C, Kitchener H C, et al. Ovarian cancer[J]. The Lancet, 2014, 384(9951): 1376-1388

[17] He C, Lu K, Liu D, et al. Nanoscale Metal-Organic Frameworks for the Co-Delivery of Cisplatin and Pooled siRNAs to Enhance Thera-

- peutic Efficacy in Drug-Resistant Ovarian Cancer Cells[J]. Journal of the American Chemical Society, 2014, 136(14): 5181-5184
- [18] Lesnock J L, Darcy K M, Tian C, et al. BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study[J]. British journal of cancer, 2013, 108(6): 1231-1237
- [19] Liu J, Liu Y, Li B, et al. Sophoridine suppresses inflammatory cytokine secretion by lipopolysaccharide-induced RAW264. 7 cells and its mechanism[J]. Chinese journal of cellular and molecular immunology, 2015, 31(5): 585-589
- [20] Zhao WJ, Deng BY, Wang XM, et al. XIAP Associated Factor 1 (XAF1) Represses Expression of X-linked Inhibitor of Apoptosis Protein (XIAP) and Regulates Invasion, Cell Cycle, Apoptosis, and Cisplatin Sensitivity of Ovarian Carcinoma Cells [J]. Asian Pac J Cancer Prev, 2015, 16(6): 2453-2458
- [21] Chang MC, Chen CA, Chen PJ, et al. Mesothelin enhances invasion of ovarian cancer by inducing MMP-7 through MAPK/ERK and JNK pathways[J]. Biochem J, 2012, 442(2): 293-302
- [22] Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy [J]. Science, 2015, 348(6230): 69-74
- [23] Esquivel J, Piso P, Verwaal V, et al. American Society of Peritoneal Surface Malignancies opinion statement on defining expectations from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer[J]. J Surg Oncol, 2014, 110(7): 777-778
- [24] Sloothak DA, Mirck B, Punt CJ, et al. Intraperitoneal chemotherapy as adjuvant treatment to prevent peritoneal carcinomatosis of colorectal cancer origin: a systematic review [J]. Br J Cancer, 2014, 111(6): 1112-1121
- [25] Womack AM, Hayes-Jordan A, Pratihari R, et al. Evaluation of ototoxicity in patients treated with hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin and sodium thiosulfate[J]. Ear Hear, 2014, 35(6): e243-247
- [26] Mehta AM, Van den Hoven JM, Rosing H, et al. Stability of oxaliplatin in chloride-containing carrier solutions used in hyperthermic intraperitoneal chemotherapy[J]. Int J Pharm, 2014, 479(1): 23-27
- [27] Dharmadhikari N, Shah R, Jagannath P. Initial experience with hyperthermic intra peritoneal chemotherapy and cytoreductive surgery [J]. Indian J Cancer, 2014, 51(2): 189-192
- [28] Tas F, Karabulut S, Serilmez M, et al. Clinical significance of serum epithelial cell adhesion molecule (EPCAM) and vascular cell adhesion molecule-1 (VCAM-1) levels in patients with epithelial ovarian cancer[J]. Tumour Biol, 2014, 35: 3095-3102
- [29] Siravegna G, Mussolin B, Buscarino M, et al. Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients [J]. Nat Med, 2015, 21(7): 827
- [30] Khan S, Taylor JL, Rinker-Schaeffer CW. Disrupting ovarian cancer metastatic colonization: insights from metastasis suppressor studies [J]. Journal of oncology, 2010, 2010: 286925

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- [24] 曹彬,郭仁维.microRNA 在早期诊断急性心肌梗死中的研究进展[J].中西医结合心脑血管病杂志, 2017, 15(1): 44-47
- Cao Bin, Guo Ren-wei. Research progress of microRNA in the early diagnosis of acute myocardial infarction [J]. Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease, 2017, 15(1): 44-47
- [25] 王颖. 微小 RNA 参与心肌缺血再灌注损伤的作用机制及研究进展[J].心血管病学进展, 2017, 38(4): 434-438
- Wang Ying. Mechanisms and Research Progress of MicroRNA in Myocardial Ischemia Reperfusion Injury [J]. Advances in Cardiovascular Diseases, 2017, 38(4): 434-438
- [26] Toldo S, Das A, Mezzaroma E, et al. Induction of microRNA-21 with exogenous hydrogen sulfide attenuates myocardial ischemic and inflammatory injury in mice [J]. Circ Cardiovasc Genet, 2014, 7(3): 311-320
- [27] Liu W, Chen X, Zhang Y, et al. Effects of microRNA-21 and microRNA-24 inhibitors on neuronal apoptosis in ischemic stroke [J]. Am J Transl Res, 2016, 8(7): 3179-3187
- [28] Prior DL, Stevens SR, Holly TA, et al. Regional left ventricular function does not predict survival in ischaemic cardiomyopathy after cardiac surgery[J]. Heart, 2017, 103(17): 1359-1367
- [29] Nagata Y, Konno T, Hayashi K, et al. Myocardial Tissue Characterization of Left Ventricular Reverse Remodeling in Ischemic Cardiomyopathy[J]. Circ J, 2016, 80(12): 2427-2428
- [30] 何喜民,姚震,马瑞莲,等.缺血性心脏病患者淋巴细胞 PPAR- α 与心室重构及心功能的相关性研究[J].海南医学院学报, 2014, 20(2): 184-187
- He Xi-min, Yao Zhen, Ma Rui-lian, et al. PPAR- α expression in lymphocytes of patients with ischemic cardiomyopathy and its correlation with cardiac functional [J]. Journal of Hainan Medical University, 2014, 20(2): 184-187