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PVB 与 PF 方案对局部晚期宫颈癌 PTEN、VEGF 和 CD105 表达的影响 *

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摘要 目的：比较 PVB 与 PF 方案对局部晚期宫颈癌患者 PTEN、VEGF 和 CD105 表达的影响。**方法：**选取我院妇科收治的局部晚期宫颈癌患者 150 例，随机分为两组，其中 PVB 组 75 例予顺铂、长春新碱、博来霉素化疗；PF 组 75 例予博来霉素、顺铂配合 5-氟尿嘧啶治疗。观察并对比治疗前后患者临床疗效及患者癌组织 PTEN、VEGF 表达阳性率、CD105 抗体标记的肿瘤 MVD 值等指标。**结果：**①治疗后两组 PTEN、VEGF 表达阳性率均有所改善，与 PVB 组（76.3 %）比较，PF 组 PTEN 表达阳性率（88.3 %）明显升高，差异有统计学意义（P＜0.05）；与 PVB 组（15.3 %）比较，PF 组 VEGF 表达阳性率（6.7 %）明显降低，差异有统计学意义（P＜0.05）；②治疗后两组 MVD 值均有所改善，与 PVB 组（38.93± 9.89）比较，PF 组 MVD 值（35.61± 10.33）明显降低，差异有统计学意义（P＜0.05）；③治疗后，与 PVB 组（76.67 %）比较，PF 组的有效率（86.67 %）明显较高，差异有统计学意义（P＜0.05）。**结论：**与 PVB 方案相比，PF 方案能够使局部晚期宫颈癌患者 PTEN 表达水平升高，降低 VEGF 和 CD105 表达水平，临床疗效更确切。

关键词：新化疗方案；晚期宫颈癌；PTEN；VEGF；CD105

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Comparison of PVB and PF on the Expressions of PTEN, VEGF and CD105 in Advanced Cervical Carcinoma*

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ABSTRACT Objective: To compare the effect of PVB and PF regimens on the expression of PTEN, VEGF and CD105 in locally advanced cervical cancer patients. **Methods:** 150 patients with locally advanced cervical cancer in our hospital were selected for gynecological patients, then they were randomly divided into two groups; 75 cases in group PVB, treated with cisplatin, vincristine, bleomycin chemotherapy; 75 cases in group PF, treated with bleomycin, cisplatin combined with 5- fluorouracil treatment. The curative effects and the positive expression rate of PTEN, VEGF and CD105 antibody labeled tumor MVD value index were compared before and after treatment between the two groups. **Results:** ① After treatment, the positive expression rate of PTEN and VEGF were improved in the two groups, and for the PF group, PTEN expression was obviously increased and VEGF expression was significantly decreased with statistical significance compared with that in the PVB group (P<0.05); ② after the treatment, the value of MVD of both groups was improved, and MVD was decreased more significantly in the PF group than in the PVB group (P<0.05); ③ in comparison of efficiency rate, it was significantly higher in the PF group than in the PVB group, and the difference was statistically significant (P<0.05). **Conclusions:** Compared with PVB scheme, PF scheme can increase PTEN expression level of the patients with locally advanced cervical cancer, as well as decrease VEGF and CD105 expression level, therefore, PF scheme has a more exact clinical curative effect.

Key words: New chemotherapy; Advanced cervical cancer; PTEN; VEGF; CD105

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前言

宫颈癌是宫颈部位细胞异常分化增生而引起的一种妇科最常见的恶性肿瘤性疾病，我国发病率已居世界第二位，并有逐年上升趋势，且向低龄化发展，其中 2/3 以上经诊断已属晚期[1]。宫颈癌早期临床表现不明显，病情发展可出现阴道异常出血、白色或血性阴道排液、脓性白带等，晚期继发尿频、尿急、肾盂积水、贫血、恶病质等危重症状[2-4]。

现代医学多采取宫颈癌根治术，对Ⅱ期宫颈癌的疗效确切，但对于局部晚期宫颈癌的疗效不理想，术后易复发[5]。最近研究发现，宫颈癌根治术前采用新辅助化疗，可以明显的提高手术成功率，防止局部病灶复发，减少向周围组织的转移，主要包括 PVB 方案和 PF 方案[6]。本研究通过观察比较 PVB 与 PF 方案对局部晚期宫颈癌患者 PTEN、VEGF 和 CD105 表达的影

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响,探讨适用于宫颈癌的有效化疗方案。

1 资料与方法

1.1 一般资料

选取 2011 年 1 月至 2014 年 1 月于我院以局部晚期宫颈癌为诊断而收入院患者 150 例，采用随机数字表分为 PVB 组和 PF 组。PVB 组 75 例,平均年龄(45.2± 4.5)岁;PF 组 75 例,平均年龄(44.8± 5.3)岁。两组患者的一般资料无统计学差异(P＞0.05),具有可比性。

1.2 选择标准

经病理学证实为晚期宫颈癌；依据 2009 年 FIGO 分期属于Ⅰb2-Ⅱa2 期[7];局部肿瘤直径在 4-10 cm 之间;患者之前均未经治疗;年龄在 30-55 岁;病历资料完整;患者自愿参与本实验,并签署知情同意书;治疗方案均获得伦理委员会批准。排除肝、胆严重疾病、其他恶性肿瘤、严重合并症、手术及化疗禁忌症以及其他原因不能完成实验者。

1.3 治疗方法

PVB 组:给予 50 mg/m² 顺铂,每日一次静滴;予 1 mg/m² 长春新碱,每日一次静滴;予 25 mg/m² 博来霉素,持续静滴 6 小时以上,每日 2 次;治疗 14 天为一个周期,一共治疗 2 个周期。PF 组:第 1 天予 30 mg 博来霉素;第 1-5 天予 20 mg/m² 顺铂,每日一次静滴,水化,予 200 mg/m² 5- 氟尿嘧啶,每日一次静滴,5 天为一个疗程,治疗两个疗程。用药期间禁食生冷辛辣等刺激性食物,戒烟酒,保持患者情绪稳定。根据药物治疗情况进行手术,取患者肿瘤组织进行病理检查。

1.4 观察指标及检测方法

观察化疗前后两组患者肿瘤组织中 PTEN 和 VEGF 表达阳性率、CD105 抗体标记的肿瘤 MVD 值指标。术中取出癌组织后常规制片，采用免疫组织化学染色法观察两组标本 PTEN、VEGF、CD105 表达的阳性率。依据 Weidner 的方法[9],将染色为棕黄色的区域作为血管,观察 200× 镜下三个视野内的血管数,MVD 为均值。

1.5 临床疗效判定

化疗开始前后,借助 B 超或盆腔 CT 评估肿瘤体积,根据 WHO 疗效评价标准:显效:肿瘤全部消失;有效:肿瘤缩小≥ 50 %;无效:肿瘤缩小＜50 %或无变化或增大。同时分别计算两组患者的总有效率。

1.6 统计学方法

采用统计学软件 SPSS19.0 进行分析，计量资料采用 t 检验,计数资料采用卡方检验处理,以 P＜0.05 为差异显著,有统计学意义。

2 结果

2.1 PTEN、VEGF 表达阳性率比较

治疗后两组 PTEN、VEGF 表达均较治疗前增强（见图 1,图 2),治疗后 PTEN 蛋白表达比较中,与 PVB 组(76.3 %)比较,PF 组 PTEN 表达阳性率(88.3 %)明显升高,差异有统计学意义(P＜0.05);与 PVB 组(15.3 %)比较,PF 组 VEGF 表达阳性率(6.7 %)明显降低,差异有统计学意义(P＜0.05),如表 1。

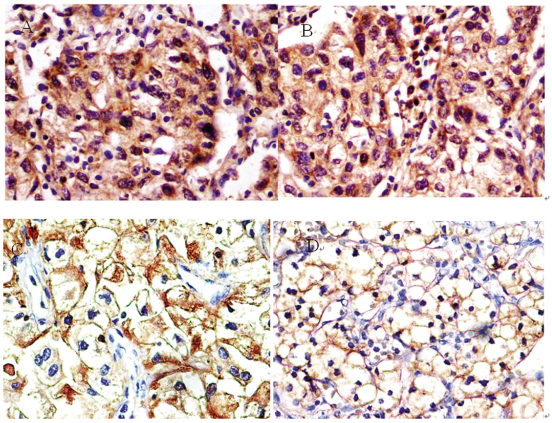

图 1 PTEN 的表达(× 400)

Fig.1 The expression of PTEN protein (× 400)

Note: A,B: PVB group; C,D: PF group; A,C: before treatment; B, D: after treatment.

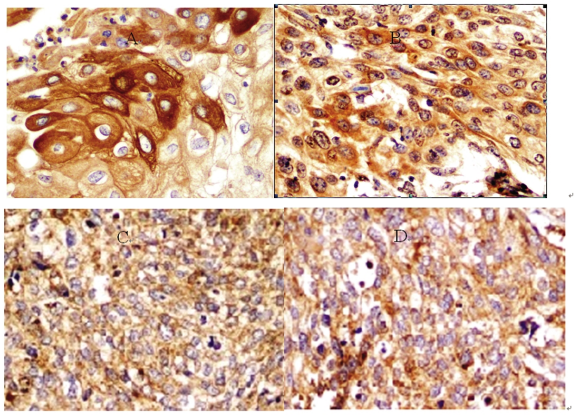

图 2 VEGF 的表达(× 400)

Fig.2 The expression of VEGF protein (× 400)

Note: A,B: PVB group; C,D: PF group; A,C: before treatment; B,D: after treatment.

表 1 治疗后两组患者 PTEN 和 VEGF 阳性表达率比较(%)

Table 1 Comparison of the positive rate of PTEN and VEGF expression(%)

Group		PTEN	VEGF
PVB group	Before treatment	67.1	16.4
	After treatment	76.3	15.3
PF group	Before treatment	66.9	17.8
	After treatment	88.3△	6.7△

Note: compared with PVB group after treatment, △P＜0.05.

2.2 CD105 抗体标记的肿瘤 MVD 值比较

两组治疗后 MVD 值表达均有所下降，与 PVB 组（38.93± 9.89）比较，PF 组 MVD 值（35.61± 10.33）明显降低，差异有统计学意义（P＜0.05），如表 2。

表 2 治疗后两组患者 CD105 抗体标记的肿瘤 MVD 值比较情况（$\bar{x}$± s）

Table 2 Comparison of MVD value of tumor labeled by CD105 antibody($\bar{x}$± s)

Group		MVD
PVB group	Before treatment	64.15± 11.04
	After treatment	38.93± 9.89
PF group	Before treatment	66.96± 10.04
	After treatment	35.61± 10.33△

Note: compared with PVB group after treatment, △P＜0.05.

2.3 临床疗效比较

治疗后，与 PVB 组（76.67 %）比较，PF 组的有效率（86.67 %）明显较高，差异有统计学意义（P＜0.05），如表 3。

表 3 治疗后两组患者临床疗效比较情况

Table 3 Comparison of the clinical efficacy between two groups

Group	N	Excellent(n)	Effective(n)	Invalid(n)	Efficiency rate(%)
PVB group	75	34	25	16	76.67
PF group	75	44	21	10	86.67△

Note: △P＜0.05, compared with PVB group.

3 讨论

宫颈癌在女性生殖器官恶性肿瘤中占首位，多因 HPV 病毒感染、早育、多产以及性生活不洁等原因导致，是危害女性生命的严重疾病，日益受到医学界的广泛重视[11]。目前，对于早期宫颈癌最有效的方法是根治性手术治疗，但大多数宫颈癌发现时已属晚期，尤其是局部晚期宫颈癌，由于手术难度大，容易发生转移，单纯手术效果并不理想[12]。

近年来，随着化疗药物药理研究的发展，学者发现术前化疗可以有效的控制肿瘤发展，防止转移与复发[13]。目前临床应用的化疗药物为顺铂、5- 氟尿嘧啶、博来霉素、紫杉醇等，根据药物的选择有不同的治疗方案，常用的为 PVB 方案、PF 方案，均以顺铂为主，PF 方案含有 5- 氟尿嘧啶，与顺铂有协同作用[14-16]，可以抑制肿瘤细胞 RNA 的复制，阻断细胞周期。有报道称[17]，PTEN 基因活性降低与恶性肿瘤的发生密切相关，其可以诱导细胞凋亡、降低端粒酶活性、防止细胞迁移、抑制肿瘤血管生成；VEGF 蛋白为血管内皮生成有关的因子，能够刺激血管的形成，同时提高血管壁的通透性，促进转移的发生[18]；PTEN 基因与 VEGF 的表达呈负相关。而 CD105 蛋白仅在肿瘤内部新生血管中有所表达，其含量直接显示肿瘤组织的活跃程度[19]。前期化疗方案可以通过影响 PTEN、VEGF、CD105 的表达来抑制肿瘤血管形成，防止肿瘤浸润转移，为根除手术做准备，提高其成功率[20]。

本研究结果显示，治疗后两组患者 PTEN、VEGF 表达阳性率均有所改善，与 PVB 组相比，PF 组 PTEN 表达阳性率明显升高，差异有统计学意义（P＜0.05）。结果说明，PF 方案提高 PTEN 表达水平，下调 VEGF 表达水平的作用更强。治疗后两组 MVD 值均有所改善，与 PVB 组相比，PF 组 MVD 值明显降低，差异有统计学意义（P＜0.05）。结果提示，PF 方案可以更好地抑制肿瘤血管生成。治疗后，与 PVB 组比较，PF 组的有效率更高，差异有统计学意义（P＜0.05）。结果表明，PF 方案的临床效用较 PVB 方案为强。

综上所述，PF 方案能够使局部晚期宫颈癌患者 PTEN 表达水平升高，VEGF 和 CD105 表达水平降低，临床疗效更确切，对临床具有指导意义，值得临床推广。

参 考 文 献（References）

[1] David J. Tumor and host factors that may limit efficacy of chemotherapy in non-small cell and small cell lung cancer [J]. Crit Rev Oncol Hematol, 2010, 75(3): 173-234

[2] Shen SN, Wang LF. Upregulation of microRNA-224 is associated with aggressive progression and poor prognosis in humancervical cancer [D]. Diagn Pathol, 2013, 7(8): 69

[3] Mariusz P. Pharmacogenetics research on?chemotherapy resistance in colorectal cancer over the last 20 years [J]. World J Gastroenterol, 2014, 20(29): 9775-9827

[4] Yang WT, Zheng PS. Promoter Hypermethylation of KLF4 Inactivates Its Tumor Suppressor Function in?CervicalCarcinogenesis [J]. PLoS One, 2014, 9(2): e88827

[5] Hao M, Zhang N. Neoadjuvant chemotherapy of cervical cancer with synchronous chemotherapy China [J]. Journal of Practical Gynecology and obstetrics, 2010, 21(03): 168-174

[6] Zvi G, Jing S, Sunil S. Chemotherapy Delivered After Viral Immunogene Therapy Augments Antitumor Efficacy Via Multiple Immune-mediated Mechanisms[J]. Mol Ther, 2010, 18(11): 1947-1959

（下转第 3172 页）

[44] Bredenoord AJ, Tutuian R, Smout AJ, et al. Technology review: esophageal impedance monitoring[J]. Am J Gastroenterol, 2007, 102 (1): 187-194

[45] Riddell RH. The biopsy diagnosis of gastroesophageal reflux disease, "carditis," and Barrett's esophagus, and sequelae of therapy[J]. Am J Surgical Pathol, 1996, 20(Suppl 1): S31-50

[46] Numans ME, Lau J, de Wit NJ, et al. Short-term treatment with PPIs as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics [J]. Ann Intern Med, 2004, 140 (7): 518-527

[47] Ayhan HC, Sedat B, Murat G, et al. Gastroesophageal reflux disease in chronic renal failure patients with upper GI symptoms: multivariate analysis of pathogenic factors [J]. Am J Gastroenterol, 2002, 97(6): 1352-1356

[48] Klauser AG, Schindlbeck NE, Mü ller-Lissner SA. Symptoms in gastro-oesophageal reflux disease[J]. Lancet, 1990, 335 (8683): 205-208

[49] Velanovich V, Vallance SR, Gusz JR, et al. Quality of life scale for gastroesophageal reflux disease[J]. J Am Coll Surg, 1996, 183(3):217-224

[50] Wong WM, Lam KF, Lai KC, et al. A validated symptoms questionnaire (Chinese GERDQ) for the diagnosis of gastro-oesophageal reflux disease in the Chinese population [J]. Aliment Pharmacol Ther, 2003, 17(11): 1407-1413

[51] Nilsson M, Johnsen R, Ye W, et al. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux[J]. Gut, 2004, 53 (7): 1730-1735

[52] Kopple JD, Feroze U. The effect of obesity on chronic kidney disease [J]. J Ren Nutr, 2011, 21(1): 66-71

[53] Mc Causland FR, Waikar SS, Brunelli SM. The relevance of dietary sodium in hemodialysis [J]. Nephrol Dial Transplant, 2013, 28 (4): 797-802

[54] Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease [J]. Am J Gastroenterol, 2013, 108(3): 308-328; quiz 329

[55] Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux[J]. Gut, 2004, 53(7): 1024-1031

[56] Donnellan C, Preston C, Moayyedi P, et al. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease[J]. Cochrane Database Syst Rev, 2005, 18(2): CD003245

（上接第 3102 页）

[7] Kenneth J, Nick J, Theresa AL. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer [M]. Cochrane Database Syst Rev, 2011, 11(11): CD005340

[8] Khadra G, Keith G. Adjuvant radiotherapy and/or?chemotherapy?after surgery for uterine carcinosarcoma[M]. Cochrane Database Syst Rev, 2011, 11(1): CD006812

[9] Takuji T, Hideki I. Metronomic?Chemotherapy: Possible Clinical Application in Advanced Hepatocellular Carcinoma[J]. Transl Oncol, 2013, 6(5): 511-519

[10] Zhu YS, Zhou YQ, Zhang W, et al. Cervical cancer and precancerous lesions and related risk factors of [J]. China maternal and child health research, 2008, 3(05): 425-428

[11] Ariosto SS, Robert AG. A theoretical quantitative model for evolution of cancer chemotherapy resistance [M]. Biol Direct, 2010, 13(5): 25

[12] Amos DM, Henry R. Mind the gaps: a qualitative study of perceptions of healthcare professionals on challenges and proposed remedies for cervical cancer help-seeking in post conflict northern Uganda[D]. BMC Fam Pract, 2013, 22(14): 193

[13] Alejandra C, Rebecca L, Jack C, et al. Cervical Screening at Age 50-64 Years and the Risk of Cervical Cancer at Age 65 Years and Older: Population-Based Case Control Study[J]. PLoS Med, 2014, 11 (1): e1001585

[14] Leslea P, Donna FL, Donna C, et al. Screening for cervical cancer: a systematic review and meta-analysis [J]. Syst Rev, 2013, 26(2): 35

[15] Xie H, Zhao YG, Stefano C. miR-205 Expression Promotes Cell Proliferation and Migration of Human?Cervical Cancer Cells [J]. PLoS One, 2012, 7(10): e46990

[16] Jonathan P. Interventions for encouraging sexual behaviours intended to prevent cervical cancer [J]. Cochrane Database Syst Rev, 2011, 11 (4): CD001035

[17] Haghshenas M, Golini MT, Rafiee A, et al. Prevalence and type distribution of high-risk human papillomavirus in patients with cervical cancer: a population-based study [J]. Infect Agent Cancer, 2013, 8(1): 20

[18] Li J, Kang LN, Qiao YL. Review of the cervical cancer disease burden in mainland China [J]. Asian Pac J Cancer prev, 2011, 12(5): 1149-1153

[19] Wani Y, Notohara K. Cervical adenocarcinomas concomitant with CIN or squamous cell carcinoma lack gastric phenotype[J]. Virchows Arch, 2010, 457(7): 214-218

[20] Siebers AG, Klinkhamer PJ, Grefte JM, et al. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial [J]. JAMA, 2009, 302(16): 1757-1764