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多西他赛或紫杉醇联合奈达铂在宫颈癌辅助化疗中的疗效及安全性分析

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摘要 目的:观察和比较多西他赛或紫杉醇联合奈达铂辅助化疗治疗宫颈癌患者的临床疗效及其安全性。**方法:**选择45例采用多西他赛联合奈达铂化疗的宫颈癌患者为观察组及45例同期采用紫杉醇联合奈达铂化疗的宫颈癌患者作为对照组，两组均行手术治疗,且术前接受辅助化疗。对比两组临床疗效、手术时间和术后病理状况及不良反应的发生情况。**结果:**化疗后,观察组临床有效率高于对照组(62.22 % vs. 55.56%),但组间比较差异无统计学意义(*P>0.05*)。化疗期间,观察组恶心、呕吐、腹痛、腹泻、白细胞、中性粒细胞减少、血红蛋白和血小板减少的发生率均低于对照组,但组间比较差异均无统计学意义(*P>0.05*);观察组神经毒性发生率明显低于对照组,组间比较差异有统计学意义(*P<0.05*)。化疗后,行手术治疗,观察组手术时间低于对照组,但组间比较差异无统计学意义(*P>0.05*);手术后,观察组盆腔淋巴结转移率和宫旁浸润率低于对照组,但组间比较差异无统计学意义(*P>0.05*)。**结论:**多西他赛联合奈达铂辅助化疗宫颈癌的疗效与紫杉醇联合奈达铂相当,且神经毒性、骨髓抑制方面的发生率明显降低,是临床低毒性且有效的宫颈癌术前新辅助化疗方案。

关键词:宫颈癌;辅助化疗;多西他赛;紫杉醇

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Analysis of the Efficacy and safety of Docetaxel or Paclitaxel combined with Nedaplatin in the Adjuvant Chemotherapy of Cervical Cancer

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ABSTRACT Objective: To observe and compare the clinical efficacy and safety of docetaxel and paclitaxel combined with nedaplatin in the treatment of cervical cancer. **Methods:** Forty-five patients with cervical cancer treated with docetaxel and nedaplatin were selected as the observation group and 45 patients with cervical cancer treated with paclitaxel and nedaplatin were selected as as the control group. The clinical efficacy, operative time, postoperative pathological conditions and incidence of adverse reactions were compared between the two groups. **Results:** After chemotherapy, the clinical efficiency of observation group was higher than that of the control group (62.22% vs. 55.56%), but there was no significant difference between the two groups (*P>0.05*). During chemotherapy, the incidence of nausea, vomiting, abdominal pain, diarrhea, leukopenia, neutropenia, hemoglobin and thrombocytopenia in the observation group were lower than those in the control group, but there was no significant difference between the two groups (*P>0.05*). During chemotherapy, the incidence of neurotoxicity, leukopenia and neutropenia in the observation group were significantly lower than those in the control group (*P<0.05*), the incidence of hemoglobin reduction and thrombocytopenia in the observation group was lower than that in the control group, but there was no significant difference between the two groups (*P>0.05*). There was no significant difference in the operation time between the two groups (*P>0.05*). After operation, the rate of pelvic lymph node metastasis and uterine infiltration in the observation group were lower than those in the control group (*P>0.05*). **Conclusion:** The efficacy of docetaxel combined with nedaplatin in the treatment of cervical cancer is similar to that of paclitaxel combined with nedaplatin, but the incidence of neurotoxicity and myelosuppression is significantly lower, which is a clinical low toxicity and effective neoadjuvant chemotherapy for cervical cancer.

Key words: Cervical cancer; Adjuvant chemotherapy; Docetaxel; Paclitaxel

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前言

宫颈癌是引起女性死亡的常见恶性肿瘤之一。近年来,我国宫颈癌的发病率逐渐上升[1]。传统的宫颈癌疗法是以放疗和手术为主,但对于有宫旁浸润或者直径大于 4 cm 宫颈癌患者,直接行手术治疗的难度较大,而采用放疗会危害女性阴道及卵巢功能[2,3]。新辅助化疗已成为目前治疗宫颈癌不可或缺的手段[4],但其方案多样且无统一标准,大部分效果欠佳,并伴有严重的毒副反应[5,6]。因此,寻找最佳的化疗方案仍是临床治疗宫颈癌迫切需要解决的难题。紫杉醇类药物联合铂类药物化疗是公认的治疗多种恶性肿瘤的有效方案[7,8]。因此,本研究观察和比较了多西他赛或紫杉醇联合奈达铂行术前辅助化疗治疗宫颈癌的疗效及安全性,结果报道如下。

1 资料与方法

1.1 一般资料

回顾性分析 2015 年 10 月至 2017 年 3 月我院收治的 IB 至 IIB 期宫颈癌患者的临床资料,以采用多西他赛联合奈达铂化疗的 45 例患者为观察组,以 45 例采用紫杉醇联合奈达铂化疗的患者作为对照组。对照组年龄 32~66 岁;鳞癌 43 例,腺癌 2 例;按照国际妇产科联盟(FIGO)宫颈癌分期:IB 期 2 例,IIA 期 11 例,IIB 期 32 例。观察组年龄 30~65 岁;鳞癌 41 例,腺癌 3 例,鳞腺癌 1 例;按照 FIGO 宫颈癌分期:IB2 期 3 例,IIA 期 9 例,IIB 期 33 例。两组受试者年龄、宫颈癌病理分期及类型比较差异均无统计学意义(*P>0.05*),具有可比性。本研究经患者本人及家属知情,且签署知情同意书,并获得医院伦理委员会批准。

1.2 纳入标准和排除标准

纳入标准:① 受试者均符合宫颈癌诊断标准;② 受试者均属于 FIGO 临床分期 IB-IIB 期范围患者;③ 受试者化疗后均行手术治疗;④ 受试者依从性良好。排除标准:① 受试者不耐受化疗;② 受试者伴有严重的脑、心血管、肝、肾及造血等疾病;③ 受试者三个月内未接受类似化疗;④ 多重癌。

1.3 化疗方案

1.3.1 化疗指征 所有受试者均满足:① 经活检病理确诊为宫颈癌;② 受试者宫颈癌病灶直径大于 4 cm;③ 受试者未患内科其它疾病;④ 受试者心电图无异常。

1.3.2 紫杉醇联合奈达铂化疗方案 对照组在化疗前 12 hr 和 6 hr,均口服 20 mg 地塞米松;化疗前 30 min,静脉滴注 400 mg 西咪替丁,预防过敏。化疗时,先给予 160 mg/m^2 紫杉醇(TAX)与 500 mL 9 %氯化钠混合液静脉滴注 3 小时; 间隔 4 小时,再给予 75 mg/m^2 奈达铂(NDP)与 500 mL 5 %葡萄糖混合液静脉滴注 4 小时。3 周为一周期,持续治疗 2 个周期。

1.3.3 多西他赛联合奈达铂化疗方案 观察组在化疗前连续 3 天口服 7.5 mg 地塞米松;化疗时,先给予 75 mg/m^2 多西他赛(DTX)与 500 mL 9 %氯化钠混合液静脉滴注 3 小时;间隔 1 小时,再给予 75 mg/m^2 奈达铂(NDP)与 500 mL 5%葡萄糖混合液静脉滴注 4 小时。3 周为一周期,持续治疗 2 个周期。

1.4 疗效评价

1.4.1 临床疗效 采用磁共振、妇科三合诊检测所有受试者化疗前后肿瘤大小和盆腔病情。依据 WHO 制定《实体瘤的疗效标准》评定为:受试者肿瘤持续 4 周完全消失则为完全缓解(CR);受试者肿瘤持续 4 周体积缩小 50 %以上为部分缓解(PR);受试者肿瘤持续 4 周体积缩小 50 %以下,或体积增大 25 %以内为稳定(SD);受试者肿瘤体积增大 25 %以上,或者有新病灶出现为进展(PD)。临床有效率 =(CR+PR)/ 总例数× 100 %。

1.4.2 化疗毒性反应 化疗前及化疗期间每三天,所有受试者行血常规、尿常规、心电图及肝肾功能等检查,严格记录受试者化疗期间的不良反应。依据 WHO 抗肿瘤药物毒性反应分级标准,将药物化疗毒副反应划分为 0~IV 度 5 个等级:受试者未出现毒副反应为 0 度;受试者出现轻度毒副反应为 I 度;受试者出现中度毒副反应为 II 度;受试者出现中度且无法耐受的毒副反应为 III 度;受试者伴有严重的并发症为 IV 度。

1.4.3 手术时间及术后病理状况 记录两组手术时间和术后盆腔淋巴结转移、宫旁浸润的发生情况。

1.5 统计学处理

所有数据均用软件 SPSS 20.0 进行分析, 计量资料以均数± 标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验,计数资料以率(%)表示,组间比较采用 x^2 检验,以 *P<0.05* 表示差异有统计学意义。

2 结果

2.1 两组的临床疗效比较

化疗后, 观察组完全缓解 4 例 (8.89 %), 部分缓解 24 例(53.33 %),稳定 15 例(33.33 %),进展 2 例(4.44 %)。与对照组相比,观察组临床有效率较高(62.22% vs. 55.56%),但差异无统计学意义(*P>0.05*),详见表 1。

表 1 两组患者的临床疗效比较[例(%)]

Table 1 Comparison of the Clinical efficacy between two groups[Cases (%)]

Groups	Cases	Complete Relief	Partial Relief	Stable	Progress	Clinical Efficiency	*P*
Control group	45	2(4.44)	23(51.11)	17(37.78)	3(6.67)	25(55.56)	0.52
Observation group	45	4(8.89)	24(53.33)	15(33.33)	2(4.44)	28(62.22)	

2.2 两组的不良反应发生情况比较

化疗期间,观察组恶心、呕吐、腹痛及腹泻发生率分别是 71.11 %、57.78 %、40.00 %和 8.89 %,对照组恶心、呕吐、腹痛及腹泻发生率分别是 73.33 %、73.33 %、53.33 %和 15.56 %,两组比较差异无统计学意义(*P>0.05*);观察组和对照组神经毒性发生率分别为 0.00 %和 8.89 %,观察组显著低于对照组(*P<0.05*);观察组白细胞减少和中性粒细胞减少发生率分别为 37.78 %和 22.22 %,血红蛋白减少和血小板减少发生率分别为 46.67 %和

4.44 %,均显著低于对照组(*P>0.05*),详见表 2。

表 2 两组患者的不良反应发生情况比较[例(%)]

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

Index		Groups	Toxicity classification (degrees)					Occurrence rate	*P*
			0	I	II	III	IV		
Gastrointestinal reaction	Nausea	Control group	12	4	6	23	0	33(73.33)	0.814
		Observation group	13	3	4	25	0	32(71.11)	
	Vomit	Control group	12	8	25	0	0	33(73.33)	0.12
		Observation group	19	3	23	0	0	26(57.78)	
	Stomach ache	Control group	21	17	7	0	0	24(53.33)	0.205
		Observation group	27	15	3	0	0	18(40.00)	
	Diarrhea	Control group	38	6	1	0	0	7(15.56)	0.334
		Observation group	41	4	0	0	0	4(8.89)	
	Neurotoxicity	Control group	41	4	0	0	0	4(8.89)	0.041
		Observation group	45	0	0	0	0	0(0.00)	
Myelosuppression	Leukopenia	Control group	14	10	15	6	0	31(68.89)	0.003
		Observation group	28	4	13	0	0	17(37.78)	
	Neutropenia	Control group	22	9	8	5	1	23(51.11)	0.004
		Observation group	35	2	6	2	0	10(22.22)	
	Hemoglobin decreased	Control group	17	21	7	0	0	28(62.22)	0.138
		Observation group	24	17	4	0	0	21(46.67)	
	Thrombocytopenia	Control group	40	3	2	0	0	5(11.11)	0.238
		Observation group	43	2	0	0	0	2(4.44)	

2.3 两组手术时间及术后病理状况的比较

化疗后,行手术治疗,观察组手术时间(209.56± 19.73)min 与对照组 (217.44± 18.32)min 相比差异无显著性 (*P>0.05*);术后,观察组盆腔淋巴结转移率和宫旁浸润率分别为 13.33 %和 6.67 %,均低于对照组(20.00 %和 8.89 %),但差异无统计学意义(*P>0.05*),详见表 3。

表 3 两组手术时间及术后病理状况的比较

Table 3 Comparison of the operation time and postoperative pathological conditions between two groups

Groups	Cases	Operation Time(min)	Pelvic lymph node metastasis	Infiltration of the palace side
Control group	45	217.44± 18.32	9(20.00)	4(8.89)
Observation group	45	209.56± 19.73	6(13.33)	3(6.67)
P		0.081	0.396	0.694

3 讨论

宫颈癌的发生多与 HPV 感染、性生活紊乱及早婚等因素相关[9,10]。早期宫颈癌患者常无明显临床体征,晚期宫颈癌患者常伴有阴道不规则出血,肿瘤块直径大,癌细胞浸润其他器官而引起继发性病症,严重危害女性健康[11,12]。近年来,新辅助化疗(NACT)已成为临床恶性肿瘤研究的热点[13,14],能有效缩小肿瘤体积,降低淋巴结转移发生率,抑制癌细胞的增殖活性,优化手术的临床疗效[15,16]。目前,NACT 主要是铂类药物联合化疗的方案。本研究主要探讨了多西他赛或紫杉醇联合奈达铂辅助化疗方案对宫颈癌患者的临床效果。

本研究结果显示多西他赛联合奈达铂方案的化疗效果及术后病理情况略优于紫杉醇联合奈达铂, 但差异无显著性,提示两种辅助化疗方案疗效相当。分析原因认为奈达铂是一种新型的铂类抗癌药物,能与核苷形成铂 - 核苷复合物,进而与癌细胞 DNA 链间和链内交联,阻碍其 DNA 复制,还可以特异性损伤癌细胞膜,引起癌细胞凋亡[17,18]。多西他赛又称多烯紫杉醇,与紫杉醇作用机制类似,均能与 β- 微管蛋白氨基端 31 及 217~231 氨基酸位点结合,推进微管聚合运动并稳定微管蛋白结构,阻止微管解聚,打破微管解聚和聚合的动态平衡,进而抑制纺锤体的形成,阻止染色体向细胞两极移动,致使快速分裂的癌细胞被停滞于有些分裂 G2 和 M 期,肿瘤细胞复制障碍而

引起凋亡[19,20]。另外，多西他赛是一种新型的紫杉烷类药物，与微管结合能力约为紫杉醇的 2 倍，对癌细胞的毒性更强[21,22]；同时，多西他赛在细胞内的聚集浓度高于紫杉醇，能更有效抑制肿瘤细胞的分裂，抑制肿瘤的生长和发展[23]。无论是紫杉醇联合奈达铂，还是多西他赛与奈达铂联用，二者联合用药的抗肿瘤靶点不同，可协同作用增强细胞毒性，且不会形成交叉耐药[24,25]，在辅助化疗宫颈癌的临床效果相当。

紫杉醇类化疗药物易引起消化道反应、神经毒性及骨髓抑制，多为轻、中度，大部分能通过辅助用药后缓解；但仍会影响影响患者用药的耐受性[26]。在联合用药消化道反应方面，本研究结果显示两组化疗期间均有部分患者出现呕吐、腹泻、腹痛的症状，均在毒副反应 II 度及以下，未出现比较严重的病例，说明这些化疗毒性反应是患者可耐受的，且能通过辅助用药和临床处理得以缓解，与既往研究结果相符[26]。在联合用药神经毒性反应方面，本研究结果显示观察组化疗期间 0 例神经毒性反应，对照组出现 4 例 I 度毒性反应，主要表现在患者肢体及指端感觉麻木。轻中度神经毒性反应可通过降低化疗用药剂量和辅助药物缓解，但神经毒性反应有可能会随着紫杉醇联合奈达铂化疗方案用药剂量的增加而加重，影响患者生活质量[27,28]。在联合用药骨髓抑制方面，本研究结果显示紫杉醇联合奈达铂组患者化疗期间骨髓抑制比多西他赛联合奈达铂组严重，分析原因认为化疗极易引起患者骨髓抑制，导致白细胞大量减少，免疫力下降，出现发热、贫血及出血等体征。对于轻中度骨髓抑制的患者，需要降低临床化疗剂量，同时口服提升血小板、白细胞类药，即可缓解症状。但本研究中，对照组甚至出现 IV 度中性粒细胞减少及 III 度白细胞减少，出现严重的骨髓抑制；可能需要暂停或中断治疗，严重影响患者化疗效果[29-31]。

综上所述，多西他赛与紫杉醇联合奈达铂在辅助化疗宫颈癌的临床疗效相当，但多西他赛毒副反应较轻，尤其是在神经毒性和骨髓抑制方面。多西他赛联合奈达铂在辅助化疗宫颈癌方面可能更具有优越性。

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