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吉西他滨联合化疗方案治疗复发转移性乳腺癌的临床疗效观察

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摘要 目的:观察吉西他滨与顺铂联合以及吉西他滨与紫杉醇联合治疗复发转移性乳腺癌的疗效和不良反应。**方法**:本研究收集65例女性乳腺癌术后复发转移的患者作为研究对象。随机分成两组,分别应用吉西他滨与顺铂(GP方案组)、吉西他滨与紫杉醇(GT方案组)联合进行治疗。GP方案组患者有30例,第1天、第8天用吉西他滨800mg~1000mg/m^{2}溶于0.9%的100mL生理盐水中静脉滴注; 第1天~第3天,21天重复用顺铂30mg/m^{2}溶于0.9%的250mL生理盐水中静脉滴注;GT方案组患者有35例,吉西他滨的使用方法与GP方案组相同,第2天,21重复用紫杉醇135mg/m^{2}溶于0.9%的500mL生理盐水中静脉滴注。对化疗时产生的不良反应进行对症处理。**结果**:GP方案组化疗有效率为46.67%,疾病控制率为70.00%;GT方案组化疗有效率为42.86%,疾病控制率为68.57%,两组比较差异均无统计学意义(P>0.05)。GT组脱发的发生率为62.86%,明显高于GP组的10.00%(P<0.001),其他不良反应在两组之间差异无统计学意义(P>0.05)。**结论**:GP方案和GT方案在治疗复发转移性乳腺癌有较好的疗效,不良反应较轻,可作为复方转移性乳腺的一种化疗方案。

关键词:吉西他滨;复发转移;乳腺癌

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Clinical Observation of Chemotherapy Regimen Based on Gemcitabine in the Treatment of Metastasis Breast Cancer

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ABSTRACT Objective: To compare the efficacy and side effects of GP and GT regimen in the treatment of metastasis breast cancer. **Methods:** We collected 65 cases of female patients with metastasis breast cancer as research subjects, which were randomly divided into two groups and jointly treated with GP regimen or GT regimen.There were 30 cases of patients in GP regimen group which were injected with Gemcitabine 800mg ~ 1000mg/m^2 dissolved in 0.9% saline infusion 100ml in day 1 and day 8, with Cisplatin 30mg/m^2 dissolved in 0.9% saline infusion 250 mL in other days; There were 35 cases of patients in GT regimen group which were injected with Gemcitabine 800mg ~ 1000mg/m^2 dissolved in 0.9% saline infusion 100ml in day 1 and day 8, with taxol 135mg/m^2 dissolved in 0.9% saline infusion 500ml in other days. Take expectant treatment when patients have side effects. **Results:** The efficiency of chemotherapy in GP regimen group was 46.67% and 42.86% in GT regimen group,the disease control rate in GP regimen group was 70.00% and 68.57% in GT regimen group, the difference was all not statistically significant(P>0.05). The incidence of alopecia in GT regimen group was 62.86%, significantly higher than 10.00% in GP regimen group (P<0.001), Other side effects between the two groups showed no significant difference (P>0.05). **Conclusion:** GP and GT regimen are both effective in the treatment of metastasis breast cancer, and also, they both have mild side effects.

Key words: Gemcitabine; Metastasis; Breast cancer

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前言

乳腺癌是影响到我国女性健康的十大肿瘤之一。近年来,发病率逐年升高,成为导致妇女死亡的主要恶性肿瘤[1,2]。而在我国,乳腺癌的发病率快速增长,远高于世界的平均水平[3,4]。目前对乳腺癌的临床治疗,主要是通过手术、化疗、放疗、靶向治疗等方法,化学药物治疗主要是应用蒽环类药物、紫杉类药物、氟尿嘧啶类药物, 使得患者在临床化疗中得到较好的疗效[5,6]。但是对上述药物治疗后乳腺癌发生复发、转移,临床并未有公认的治疗方案。研究表明,吉西他滨对乳腺癌有明显的治疗效果[7,8]。本研究选用吉西他滨与顺铂联合(简称GP方案)或者吉西他滨与紫杉醇联合(简称GT方案)治疗复发转移性乳腺癌,探讨其临床疗效,以期为复发转移性乳腺癌提供新的化疗方案。

1 资料与方法

1.1 一般资料

本研究收集65例女性乳腺癌术后复发转移的患者, 经术后病理分析证实为乳腺浸润性导管癌,年龄为36~67岁,平均为44.2岁。随机分成两组,GP方案组30例,GT方案组35例,分别应用吉西他滨与顺铂联合、吉西他滨与紫杉醇联合进行治

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疗。原发病灶均进行过乳腺癌根治术,术后给与蒽环类、紫杉醇类药物治疗,患者 KPS 评分均在 60 分以上,并且行其他常规检查均显示正常,无化疗禁忌,见表 1。

表 1 两组患者一般情况比较(n)

Table 1 Comparison of general situations between the two groups

项目 Items		总例数 Total cases	GP 方案组 GP regimen group	GT 方案组 GT regimen group
年龄 Age	<50 years	48	22	26
	≥ 50 years	17	8	9
月经状态 Menstrual status	绝经前 Premenopausal	31	15	16
	绝经后 Postmenopausal	34	15	19
既往治疗 Previous treatment	单用蒽环类 Anthracyclinealone	25	12	13
	蒽环类联合紫杉类 Anthracyclineal combine with Taxane	40	18	22
骨转移 Bone metastases	Yes	40	17	23
	No	25	13	12
内脏转移 Visceral metastases	Yes	31	16	15
	No	34	14	20
转移灶 Metastases	<2	28	12	16
	≥ 2	37	18	19

1.2 治疗方案

GP 方案组患者有 30 例,第 1 天、第 8 天用吉西他滨 800 mg~1000 mg/m^2 溶于 0.9%的 100 mL 生理盐水中静脉滴注;第 1 天~第 3 天,21 天重复用顺铂 30 mg/m^2 溶于 0.9%的 250 mL 生理盐水中静脉滴注;GT 方案组患者有 35 例,吉西他滨的使用方法与 GP 方案组相同,第 2 天,21 重复用紫杉醇 135 mg/m^2 溶于 0.9%的 500 mL生理盐水中静脉滴注。对化疗时产生的不良反应进行对症处理。

1.3 疗效评价

参照 WHO 在 1981 年制定的评价标准分为完全缓解、部分缓解、无变化和进展,分别用 CR、PR、NC、PD 表示。毒性作用分为无(0)、轻度(I)、中度(II)、重度(III)、威胁生命(IV)五个等级。化疗有效率用 (CR+PR)/ 病例总数表示,疾病控制率用 (CR+PR+NC)/ 病例总数表示。

1.4 统计学方法

采用 SPSS11.0 统计学软件进行统计,疗效和不良反应应用卡方检验,P<0.05 为差异有统计学意义。

2 结果

2.1 化疗效果

GP 方案组 30 例患者中 CR 有 13.33%(4/30)、PR 有 33.33%(10/30)、NC 有 23.33%(7/30)、PD 有 30%(9/30),总有效率为 46.67%,疾病控制率为 70%。完全缓解的病例中淋巴结转移的有 2 例,胸壁转移的有 1 例,肺转移的也有 1 例。而 GT 方案组 35 例患者中,CR 有 11.43%(4/35)、PR 有 31.43%(11/35)、NC 有 25.71%(9/35)、PD 有 31.43%(11/35),总有效率为 42.86%,疾病控制率为 68.57%。其中淋巴结转移的有 2 例,胸壁转移和肝转移各 1 例。两组化疗效果比较差异无统计学意义(x^2=0.095,P=0.758),两组疾病控制比较差异无统计学意义(x^2=0.016,P=0.901),见表 2。

表 2 两组的化疗效果比较

Table 2 Comprison of the effect of chemotherapy between the two groups

组别 GroupsGP	病例数 Cases	CR	PR	NC	PD	化疗有效率(%) Efficiency of chemotherapy(%)	疾病控制率(%) Disease control rate(%)
GP 方案组 GP regimen group	30	4	10	7	9	46.67	70.00
GT 方案组 GP regimen group	35	4	11	9	11	42.86	68.57

2.2 不良反应

患者在进行化疗后都会发生一些不良反应,如脱发、胃肠道反应、骨髓移植等,GP 方案和 GT 方案执行后不良反应大多数是 I 度和 II 度。GP 方案组发生 III~IV 度中发生白细胞减少的概率为 13.33%,血小板减少发生的概率为 6.67%,贫血发生率为 13.33%,脱发发生率为 10%,恶心呕吐发生率为 23.33%;GT 方案组发生 III~IV 度中发生白细胞减少的概率为 14.29%,血小板减少发生的概率为 11.43%,贫血发生率为 17.14%,脱发发生率为 62.86%,恶心呕吐发生率为 17.14%。经统计学分析,两组之间脱发的发生率差异有统计学意义 (P<0.001)GT 组明

表 3 两组的不良反应比较[n(%)]

Table 3 Comprison of the adverse reaction between two groups[n(%)]

组别 Groups	例数 Cases	白细胞减少 Leukocy tereduction	血小板减少 Blood platelet reduction	贫血 Anemia	脱发 Alopecia	恶心呕吐 Nausea and vomiting
GP 方案组 GP regimen group	30	4(13.33)	2(6.67)	4(13.33)	3(10.00)	7(23.33)
GT 方案组 GP regimen group	35	5(14.29)	3(8.57)	6(17.14)	22(62.86)	6(17.14)
X^2		0.012	0.083	0.180	19.068	0.387
P		0.912	0.774	0.671	<0.001	0.534

显高于 GP 组，其他不良反应在两组之间差异无统计学意义(P>0.05)见表 3。

3 讨论

目前,对乳腺癌的初次治疗大多是采用蒽环类药物或者紫杉类药物,在临床上应用广泛且取得了良好的治疗效果[9-10]。但是对于复发转移性的乳腺癌采用何种治疗方案由于各种药物都未有达到较好的疗效在临床一直未有统一意见[11-12]。

吉西他滨是一种作用于细胞周期的代谢类药物,主要作用于 S 期细胞,即处于 DNA 合成器的肿瘤细胞[13],它可以通过核苷酸激酶的作用,抑制 DNA 合成、脱氧胞嘧啶脱氨酶,同时减少细胞内代谢物的降解[14,15]。在采用吉西他滨的情况下,可以有效的阻止 G1 期向 S 期进展,这已经在胰腺癌、非小细胞型肺癌中得到了验证[16]。近年来,逐渐广泛应用于乳腺癌。

顺铂作用的靶点是 DNA,其可以与 DNA 之间形成链间和链内的交链，干扰 DNA 复制以及与核蛋白、胞浆蛋白的结合[17]。已证实对乳腺癌、肺癌的多种肿瘤有效果[18]。紫杉醇是植物中的一种代谢产物,其可以结合到聚合的微管上,而不与聚合的微管蛋白二聚体反应,从而干扰细胞的各种功能,阻断细胞的正常有丝分裂,在卵巢癌、乳腺癌、肺癌等也有效果[19-20]。

本研究选用吉西他滨与顺铂联合或者吉西他滨与紫杉醇联合治疗复发转移性乳腺癌并探讨其临床疗效,发现两组化疗效果比较差异无统计学意义(P>0.05)。两组化疗方案的不良反应大多数都是 I 度到 II 度,在脱发、胃肠道反应、骨髓移植等不良反应中,脱发的发生率差异有统计学意义(P<0.001),GT 组显著高于 GP 组,其他不良反应在两组之间差异无统计学意义(P>0.05)。大多数的患者虽出现不同程度的恶心呕吐、厌食、贫血等不良反应,但是在对症处理后,均能继续进行化疗,未发生出现严重不良反应而终止治疗的患者。

通过本研究的比较和分析,我们发现选用吉西他滨与顺铂联合或者吉西他滨与紫杉醇联合治疗复发转移性乳腺癌均可以产生确定的疗效,主要的不良反应为胃肠道反应、血液学毒性和脱发等,但是只要进行对症处理,患者均能有效的完成化疗方案,采用这两种化疗方案治疗复发转移性赴乳腺癌可根据不同的患者进行选择,是一种较好的化疗方案。

参考文献(References)

[1] 卫旭彪, 韩铖琛, 白辰光, 等. 上海部分地区 30 年女性乳腺癌发生的临床病理学差异比较 [J]. 临床与实验病理学杂志, 2010, 26(5): 528-531
Wei Xu-biao, Han Cheng-chen, Bai Chen-guang, et al. Comparison of clinicopathological difference between incidences of female breast cancer during the latest 30 years in partial area of Shanghai [J]. Chinese Journal of Clinical and Experimental Pathology, 2010, 26(5):528-531

[2] 钱云, 张敬平, 董静, 等. X 线修复交叉互补基因 194 和 399 两位点多态性与乳腺癌易感性[J]. 中华预防医学杂志, 2010, 44(3):242-246
Qian Yun, Zhang Jing-ping, Dong Jing, et al. Relationship betweenpolymorphisms of X-ray repair cross-complementing group 1 gene Arg194-Trp, Arg399Gln and susceptibility of breast cancer[J]. Chinese Journal of Preventive Medicine, 2010, 44(3):242-246

[3] 姚雪英, 倪姗姗, 周俊, 等. 浙江地区女性乳腺癌危险因素的病例对照研究[J]. 浙江大学学报(医学版), 2012, 41(5):512-518
Yao Xue-ying, Ni Shan-shan, Zhou Jun, et al. A case-control study on risk factors of female breast cancer in Zhejiang province [J].Journal of Zhejiang University(Medical Sciences), 2012, 41(5):512-518

[4] 王书昌, 杨学伟, 张玉玲, 等. 乳腺癌中 Survivin 和 VEGF 的表达[J]. 现代生物医学进展, 2011, 11(21):4159-4162
Wang Shu-chang, Yang Xue-wei, Zhang Yu-ling, et al. Survivin and VEGF Expressions in Breast Cancer and their Relations[J].Progress in Modern Biomedicine, 2011, 11(21):4159-4162

[5] 周莉莉, 李志革. 乳腺癌中 BRCA-1 和 IGF-1R 的研究进展[J].临床肿瘤学杂志, 2009, 14(1):84-88
Zhou Li-li, Li Zhi-ge. Progression of BRCA-1 and IGF-1R in breast neoplasms[J]. Chinese Clinical Oncology, 2009, 14(1):84-88

[6] Alwaili K, Alrasadi K, Awan Z, et al. Approach to the diagnosis and management of lipoprotein disorders [J]. Curr Opin Endocrinol Diabetes Obes, 2009, 16(2):132-140

[7] Therond P. Catab olism of lipoproteins and metabolic syndrome [J]. Curr Opin Endocrinol Diabetes obes, 2009,12(4):366-371

[8] Willemsen AE, van Herpen CM, Wesseling P, et al. Fatal thrombotic microangiopathy after a single dose of gemcitabine as fourth-line palliative treatment for metastasized ductal breast carcinoma [J]. Acta oncol, 2011, 50(3):462-465

[9] 杜跃耀. DNA 拓扑异构酶Ⅱα(topo Ⅱα)与乳腺癌蒽环类药物化疗敏感性的研究进展[J]. 复旦学报(医学版), 2012, 39(2):203-206
Du Yue-yao. The research progress of the association between DNA topoisomerase Ⅱα (topo Ⅱα) and sensitivity to chemotherapy for breast cancer [J]. Fudan University Journal of Medical Sciences, 2012, 39(2):203-206

[10] 赵永宏, 郑晓库, 哈敏文, 等. 乳腺癌组织中 Ki-67、ER 表达变化及其与蒽环类化疗药物敏感性的关系 [J]. 山东医药, 2010, 50(2):

24-26
Zhao Yong-hong, Zheng Xiao-ku, Ha Min-wen, et al. Correlation between the expression of Ki-67、ER and sensitivity of adjuvant anthracycline-based chemotherapy in breast cancer patients [J]. Shandong Medical Journal, 2010, 50(2):24-26

[11] 黄红艳, 王涛, 江泽飞, 等. AVASTIN 联合泰索帝治疗 HER-2 阳性晚期乳腺癌 2 例及文献回顾 [J]. 现代生物医学进展, 2009, 9(18): 3464-3466
Huang Hong-yan, Wang Tao, Jiang Ze-fei, et al. The clinical Report and Literature Review of Taxotere Combination with Bevacizumab in Treatment of Two HER-2 Positive Matastatic Breast Cancer Patients[J]. Progress in Modern Biomedicine, 2009, 9(18):3464-3466

[12] Duraker N, Demir D, Bati B, et al. Survival benefit of post-mastectomy radiotherapy in breast carcinoma patients with T1-2 tumor and 1-3 axillary lymph node(s) metastasis[J]. Jpn J Clin Oncol, 2012, 42 (7):601-608

[13] Xu Q, Xu N, Fang W, et al. Complete remission of platinum-refractory primary Fallopian tube carcinoma with third-line gemcitabine plus cisplatin: A case report and review of the literature [J]. Oncol Lett, 2013, 5(5):1601-1604

[14] Leonardi V, Palmisano V, Pepe A, et al. Docetaxel and gemcitabine in the treatment of metastatic breast carcinoma: a dose finding study [J]. Tumori, 2009, 95(4):427-431

[15] Estephan F, Valero V, Esteva FJ, et al. Phase I study of prolonged-infusion gemcitabine combined with cyclophosphamide in patients with metastatic carcinoma of the breast: tolerability of an optimal dose schedule [J]. Oncology, 2009, 77(1):63-70

[16] 郑青平, 罗展雄, 李旌, 等. 血管内皮抑素联合 GP 方案治疗Ⅳ期非小细胞肺癌的临床观察[J]. 广西医学, 2011, 33(5):564-565
Zheng Qing-ping, Luo Zhan-xiong, Li-jing, et al. Observation of Endostatin Plus Gemcitabine and Cisplatin Regimen for Stage Ⅳ Non-small Cell Lung Cancer [J]. Guangxi Medical Journal, 2011, 33(5): 564-565

[17] Funakoshi S, Hashiguchi A, Teramoto K, et al. Second-line chemotherapy for refractory small cell neuroendocrine carcinoma of the esophagus that relapsed after complete remission with irinotecan plus cisplatin therapy: Case report and review of the literature [J]. Oncol Lett, 2013,5(1):117-122

[18] Proverbs-Singh T, Chiu SK, Liu Z, et al. Arterial thromboembolism in cancer patients treated with cisplatin: a systematic review and meta-analysis[J]. J Natl Cancer Inst, 2012,104(23):1837-1840

[19] Pham AQ, Berz D, Karwan P, et al. Cremophor-induced lupus erythematosus-like reaction with taxol administration: a case report and review of the literature[J]. Case Rep Oncol, 2011, 4(3):526-530

[20] 张嵩, 王新安, 张群成, 等. 曲古抑菌素 A 和紫杉醇对肺腺癌细胞增殖和凋亡的影响[J].中华肿瘤杂志, 2012, 34(7):492-496
Zhang Song, Wang Xin-an, Zhang Qun-cheng, et al. Effect of trichostatin A and paclitaxel on the growth and apoptosis of lung adenocarcinoma cell lines[J]. Chinese Journal of Oncology, 2012, 34(7):492-496

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[12] 黄国威, 鲁培荣, 宿茂伟. 内镜下治疗胆总管结石 82 例的临床分析[J]. 医学理论与实践, 2012, 25, (13):1595-1596
Huang Guo-wei, Lu Pei-rong, Su Mao-wei. Clinical analysis on choledochoscope for choledocholithiasis of 82 cases [J]. J Med Theory and Practice, 2012, 25, (13):1595-1596

[13] 吴基洲 , 刁占琳. 内镜治疗胆总管结石的临床体会[J]. 临床和实验医学杂志, 2012, 11(06):455-456
Wu Ji-zhou, Diao Zhan-lin. Clinical comprehend Endoscopic treatment of choledocholithiasis [J]. Journal of Clinical and Experimental Medicine, 2012,11(06):455-456

[14] 叶丽萍,张玉, 林敏华, 等. 内镜治疗肝硬化合并胆总管结石的临床研究[J].中华消化内镜杂志, 2011, 28(12): 671-674
Ye Li-ping, Zhang Yu, Lin Min-hua, et al. Endoscopic treatment of choledocholithiasis in patients with decomipensated cirrhosis[J]. Chin J Dig Endocc, 2011, 28(12): 671-674

[15] 周建波, 宋奇峰, 吴伟萍, 等. 内镜治疗胆总管下段相对狭窄合并胆总管结石[J]. 中华消化内镜杂志, 2011, 28(06):345-347
Zhou Jian-bo, Song Qi-feng, Wu Wei-ping, et al. Choledochoscope for common bile duct inferior segment stricture and choledocholithiasis [J]. Chin J Dig Endocc, 2011, 28(06):345-347

[16] 丁庆英, 刘培喜, 孙文生. 内镜治疗老年胆石病 500 例临床分析[J]. 山东医药, 2010, 50(49):103
Ding Qin-ying , Liu Pei-xi, Sun Wen-sheng. Clinical analysis on choledochoscope for choledocholithiasis of 500 cases for old age [J]. Shan Dong Medicine, 2010, 50(49):103

[17] Cheon YK, Cho YD, Moon JH, et a1. Evaluation of long-term results and recurrent factors after operative and nonoperative treatment for hepatolithiasis[J]. Surgery, 2009, 146:843-853

[18] 吴国栋, 张丰深, 孙海, 等. 胆总管结石内镜治疗与开腹手术的临床对比观察[J]. 中华消化内镜杂志, 2011, 28(6):342-343
Wu Guo-dong, Zhang Feng-shen, Sun Hai, et al. Compa-rison observation of open choledocholithotomy with endoscopic sphincterotomy[J]. Chin J Dig Endocc, 2011, 28(6):342-343

[19] 方兰, 黎朝良, 王斌, 等. 胆总管结石内镜下取石与开腹取石对机体炎症反应和免疫功能的影响 [J]. 中华消化内镜杂志, 2012, 29 (10):577-580
Fang Lan, Li Chao-liang, Wang Bin, et al. Impact of endoscopic sphincterotomy and bile duct exploration with open surgery on inflammatory response and immune function[J]. Chin J Dig Endosc, 2012, 29 (10):577-580

[20] Robison LS, Varadarajulu S, Wilcox CM.Safety and success of precut biliary sphincterotomy:Is it linked to experience or expertise [J]. World J Gastroenterol, 2007, 13:2183-2186

[21] 徐宏伟, 吴坚芳, 陆喜荣, 等. 双镜联合微创手术与开腹手术治疗胆囊结石合 胆总管结石的对比研究[J].中华消化内镜杂志,2011, 28(6):332-333
Xu Hong-wei, Wu Jian-fang, Lu Xi-rong, et al. Compared study about Bimirror combine Minimally invasive and open surgery for cholecystolithiasis and choledocholithiasis[J]. Chin J Dig Endosc, 2011, 28 (6):332-333