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复方苦参注射液联合紫杉醇和替吉奥治疗晚期胃癌的临床疗效观察*

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[摘 要]目的:观察复方苦参注射液联合紫杉醇(PTX)和替吉奥(S-1)治疗晚期胃癌的短期疗效和毒副反应。方法:选择晚期胃癌患者50例,随机分为观察组和对照组,每组25例。观察组:紫杉醇135 mg/m²,静脉滴注,第1天;替吉奥胶囊每日80 mg,口服,每日2次,1~14天,停药1周;复方苦参注射液12 mL,加入200 mL0.9%氯化钠注射液稀释,静脉滴注,1~14天,停药1周。对照组:紫杉醇135 mg/m²,静脉滴注,第1天;替吉奥胶囊每日80 mg,口服,每日2次,1~14天,停药1周。21天为1个周期,每例至少完成4个治疗周期。两组疗效评价参照WHO近期疗效评价标准;不良反应评价参照抗癌药物毒副反应的分度标准。结果:观察组有效率为56.0%(14/25),临床受益率为84.0%(21/25);对照组有效率为44.0%(11/25),临床受益率为72.0%(18/25)。两组间有效率及临床受益率比较,差异均无统计学意义($P>0.05$)。两组患者化疗后各种不良反应发生率比较,差异均无统计学意义($P>0.05$)。结论:复方苦参注射液联合紫杉醇和替吉奥治疗晚期胃癌具有良好的临床疗效,且不增加化疗药物不良反应。

[关键词]晚期胃癌;紫杉醇;替吉奥;复方苦参注射液;临床疗效
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Observation on Clinical Effects of Compound *Kushen* Injection Combined with Paclitaxel and Tegafur Gimeracil Oteracil Potassium Capsules in the Treatment for Advanced Gastric Cancer

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Abstract Objective: To observe short-term effects and toxic reaction of compound *Kushen* injection combined with paclitaxel (PTX) and tegafur gimeracil oteracil potassium capsules (S-1) in the treatment for advanced gastric cancer. Methods: Fifty patients were randomized into the observation group and the control group, 25 cases each group. The observation group: PTX, 135 mg/m², intravenous dripping, at the first day; S-1 80 mg/d, oral administration, bid, 1~14 days, drug withdrawal for one week; compound *Kushen* injection, 12 mL, adding 200 mL, 0.9% sodium chloride injection to dilute, intravenous dripping, 1~14 days, drug withdrawal for one week. The control group: PTX, 135 mg/m², intravenous dripping, at the first day; S-1 80 mg/d, oral administration, bid, 1~14 days, drug withdrawal for one week. 21 days were one course, each case must finish four therapeutic cycles at least. Clinical effects were assessed in light of evaluation criteria for short-term efficacy of WHO; toxic reactions were assessed according to classification criteria for toxic reaction of anti-cancer drugs (WHO). Results: The effective rate of the observation group was 56.0%(14/25), clinical benefit rate was 84.0%(21/25); the effective rate of the control group was 44.0%(11/25), clinical benefit rate was 72.0%(18/25). The difference had no statistical meaning in the comparisons of the effective rate and clinical benefit rate between both groups. The difference had no statistical meaning in the comparisons of the incidences of adverse reaction after chemotherapy between both groups ($P>0.05$). Conclusion: Compound *Kushen* injection combined with PTX and S-1 could gain better effects in the treatment for advanced gastric cancer, and it would not arouse adverse reaction of chemotherapeutic agents.

Keywords advanced gastric cancer; PTX; S-1; compound *KuShen* injection; clinical effects

胃癌是人类最常见的恶性肿瘤之一[1]。手术是胃癌的首选治疗方法，但由于胃癌早期诊断率较低，很多进展期患者无法进行根治切除术[2-3]。这类患者，若给予单纯支持治疗，其最好的中位生存期最多3～5个月[4]。化疗在胃癌综合治疗中的重要性越来越重要[5]。相关临床研究报告已经揭示替吉奥(S-1)联合紫杉醇(PTX)在进展期胃癌患者治疗中的有效性和安全性比铂类高[6]。苦参碱具有抗癌活性，对肿瘤细胞有显著的抑制作用，其中药制剂复方苦参注射液(岩舒注射液)具有止血、镇痛、抑制癌细胞分散等功能，还能改善造血功能、增强人体免疫力[7]。本研究通过对晚期胃癌患者给予复方苦参注射液联合PTX和S-1治疗，观察其临床治疗效果，为晚期胃癌患者在今后临床治疗方案的优化选择提供参考。

资料与方法

1.1　临床资料　筛选2015年1月至2018年12月在甘肃省人民医院就诊，并给予复方苦参注射液联合PTX+S-1化疗或只给予PTX+S-1化疗的晚期胃癌患者各25例，分别作为观察组和对照组。两组患者一般资料比较，差异无统计学意义($P>0.05$)，具有可比性。见表1。

表1　两组患者一般资料比较

性别	类别	观察组(例)	对照组(例)	合计(例)	*RR*(95%*CI*)	*P*
总人数	50	25	25	50	1.00(0.93,1.08)	1.00
性别	男	14	15	29	0.93(0.58,1.50)	0.77
	女	11	10	21	1.10(0.57,2.11)	0.77
年龄	＜60	13	12	25	1.08(0.62,1.89)	0.78
	≥60	12	13	25	0.92(0.53,1.61)	0.78
ECOG评分/分	0	8	9	17	0.89(0.41,1.93)	0.77
	1	11	11	22	1.00(0.54,1.87)	1.00
	2	6	5	11	1.20(0.42,3.43)	0.73
体表面积/m^2	＜1.25	5	6	11	0.83(0.29,2.38)	0.73
	1.25-2.50	15	14	29	1.07(0.67,1.72)	0.77
	＞2.5	5	5	10	1.00(0.33,3.03)	1.00
分化程度	低分化腺癌	9	8	17	1.13(0.52,2.44)	0.77
	中分化腺癌	12	14	26	0.86(0.50,1.46)	0.56
	印戒细胞癌及其他	4	3	7	1.33(0.33,5.36)	0.69
既往化疗史	有	14	13	27	1.08(0.65,1.80)	0.78
	无	11	12	23	0.92(0.50,1.67)	0.78
疾病状态	无法切除	16	14	30	1.14(0.72,1.80)	0.57
	术后复发	9	11	20	0.82(0.41,1.62)	0.57
转移部位	肝	2	1	3	2.00(0.19,20.67)	0.56
	肺	1	2	3	0.50(0.05,5.17)	0.56
	骨	1	1	2	1.00(0.07,15.12)	1.00
	腹腔及腹膜后淋巴结	3	2	5	1.50(0.27,8.22)	0.64
	左锁骨上淋巴结	2	1	3	2.00(0.19,20.67)	0.56

1.2　治疗方法　观察组：紫杉醇注射液(成都曼斯特生物科技有限公司，批号：A01774397，规格：60 mg/支)135 mg/m^2，静脉滴注，第1天；替吉奥胶囊(齐鲁制药有限公司，国药准字20100150，规格：20 mg/粒)每日80 mg，口服，每日2次，1～14天，停药1周；复方苦参注射液(山西振东制药股份有限公司，批号：2174521，规格：5 mL/支)12 mL，加入200 mL氯化钠注射液稀释，静脉滴注，1～14天，停药1周。对照组：紫杉醇135 mg/m^2，静脉滴注，第1天；替吉奥胶囊每日80 mg，口服，每日2次，1～14天，停药1周。21天为1个周期，每例至少完成4个治疗周期。

在计划每次化疗前患者应先完善常规化验及检查(腹部超声、胸片、心电图、血常规、生化全套、

凝血全套),各项检查结果无明显异常时可继续按计划化疗;如检查结果严重异常,可给予对症处理,好转后可继续按计划化疗,无好转则终止此次计划。紫杉醇给药时应常规给予止吐、补液等对症治疗,并行心电监护,必要时给予吸氧,用药第2天及1周后再次复查血常规、生化全项。用药期间如患者发生严重的化疗不良反应,应终止计划。

1.3 观察指标 疗效评价参照WHO近期疗效评价标准。首次化疗前行颈、胸、腹及盆腔增强CT检查,记录病灶部位、大小及数目。4个治疗周期后再次行颈、胸、腹及盆腔增强CT检查,对比病灶部位、大小及数目。1)化疗疗效。完全缓解(CR):指所有的瘤块以及肿瘤的临床表现完全消失且持续至少1个月;部分缓解(PR):指可测量的肿瘤垂直两直径的和较基线缩小50%并持续至少1个月,无新病灶出现,无任何病灶的增长恶化;稳定(SD):指肿块缩小不到50%或增大未超过25%,无新病灶出现;进展(PD):至少有一个病灶,双径乘积或单径增大25%以下,或出现新病灶。有效率为CR+PR,临床受益率为CR+PR+SD。2)化疗不良反应参考WHO抗癌药物毒副反应的分度标准,分为:0级、1级、2级、3级和4级。

1.4 统计学方法 数据采用Stata 12.0 软件进行统计分析。二分类变量采用RR为疗效量,各效应量均采用区间估计和假设检验,区间估计采用95%CI,假设检验用Q检验。$P<0.05$为差异有统计学意义。

2 结果

2.1 化疗周期 观察组25例共完成121周期化疗,对照组25例共完成117周期化疗,差异无统计学意义($P>0.05$)。

2.2 临床疗效 两组有效率及临床受益率比较,差异均无统计学意义($P>0.05$)。见表2。

2.3 化疗不良反应 两组方案主要的化疗不良反应为疲劳、关节肌肉疼痛、恶心呕吐、腹泻和白细胞减少等,两组各种不良反应差异无统计学意义($P>0.05$)。见表3—4。

表2 两组临床疗效比较

组别	例数	CR	PR	SD	PD	有效率(%)	受益率(%)
观察组	25	1	13	7	4	56.0	84.0
对照组	25	0	11	7	7	44.0*	72.0*
RR(95%*CI*)		3.00(0.13,70.30)	1.38(0.45,4.20)	1.00(0.29,3.44)	0.49(0.12,1.95)		
P		0.49	0.57	1.00	0.31		

注:*表示与对照组比较,$P>0.05$

表3 两组不良反应比较

不良反应	观察组					对照组					*RR*(95%*CI*)	*P*
	1级	2级	3级	4级	发生率(%)	1级	2级	3级	4级	发生率(%)		
白细胞减少	1	1	1	0	12	1	2	2	1	24	0.43(0.09,1.97)	0.28
中性粒细胞减少	0	1	0	1	8	1	0	1	1	12	0.64(0.10,4.19)	0.64
贫血	1	0	1	0	8	1	1	1	1	16	0.46(0.08,2.75)	0.39
血小板减少	1	1	0	0	8	1	1	2	1	20	0.35(0.06,1.99)	0.24
周围神经毒性	1	0	1	0	8	1	0	1	0	8	1.00(0.13,7.72)	1.00
恶心呕吐	2	1	1	1	20	2	2	1	1	24	0.79(0.21,3.03)	0.73
腹泻	1	1	0	1	12	1	2	1	1	20	0.55(0.12,2.58)	0.44
口腔黏膜炎	0	0	1	1	8	1	0	1	1	12	0.64(0.10,4.19)	0.64
肝肾功能损伤	1	1	0	0	8	1	1	1	0	12	0.64(0.10,4.19)	0.64
肌肉关节疼痛	2	0	1	1	16	2	1	1	1	20	0.76(0.18,3.25)	0.71
疲劳	4	2	1	1	32	4	3	2	3	48	0.51(0.16,1.61)	0.25

表4　两组化疗不良反应率比较

不良反应	观察组		对照组		RR(95%CI)	P
	例数	率(%)	例数	率(%)		
白细胞减少	1	4	3	12	0.31(0.03,3.16)	0.32
中性粒细胞减少	1	4	2	8	0.48(0.04,5.65)	0.56
周围神经毒性	1	4	1	4	1.00(0.06,16.93)	1.00
恶心呕吐	2	8	2	8	1.00(0.13,7.72)	1.00
口腔黏膜炎	2	8	2	8	1.00(0.13,7.72)	1.00
肌肉关节疼痛	2	8	2	8	1.00(0.13,7.72)	1.00
疲劳	2	8	5	20	0.35(0.06,1.99)	0.24

3　讨论

胃癌是消化道常见的恶性肿瘤之一[8]。晚期胃癌预后较差,化疗是主要治疗手段[4]。PTX能够通过诱导微管蛋白聚合、抑制其解聚,使细胞周期停止于G_2～M期,抑制肿瘤细胞的有丝分裂,发挥抗肿瘤作用[9]。S-1是一种氟尿嘧啶衍生物的口服制剂,与5-氟尿嘧啶相比有作用时间长、毒副反应小的特点[10]。PTX联合S-1治疗晚期胃癌的方案[11],备受关注。晚期胃癌患者经过PTX联合S-1方案化疗后,与单纯支持治疗相比其生存期明显增长[12-14]。

复方苦参注射液,是由苦参、白茯苓等组成,辅料为聚山梨酯80、氢氧化钠、冰醋酸[15]。本方可治湿热内结、热迫血行所造成的多种癌性疼痛及出血[16]。方中苦参清热燥湿为君药;白茯苓清热利湿,解毒消肿为臣药。诸药相伍,共奏清热燥湿、解热毒、散郁结、通畅血行及镇痛之功[17]。苦参是复方苦参注射液的主要组成成分,有很好的抗癌效果[18]。苦参碱具有抗癌活性,对肿瘤细胞有显著的抑制效果。通过对小鼠进行实验,苦参碱对慢性粒细胞白血病外周多向造血祖细胞集落出现率有显著的抑制作用,抑制率达0.76[19]。此外,苦参还有升高白细胞的作用,实验证实氧化苦参碱可阻止小鼠因丝裂寄素(MMC)、环磷酰胺所造成的白细胞降低症,静脉注射或肌肉注射30 mg/kg苦参总碱以及100 mg/kg氧化苦参碱对正常家兔外周血白细胞数有显著的升高效果[20]。有研究指出,复方苦参注射液能够抑制肿瘤细胞侵袭及转移[21-22],并且能抑制肿瘤细胞增殖,促进其凋亡[23-25]。

本研究以复方苦参注射液联合PTX和S-1治疗晚期胃癌。结果显示两组有效率及临床受益率比较差异均无统计学意义。表明复方苦参注射液联合PTX和S-1治疗晚期胃癌有较好的有效率和临床受益率。两组不良反应大多出现在化疗当天至化疗第1周内,多可自行缓解。两组各种不良反应比较差异无统计学意义。表明复方苦参注射液联合PTX和S-1治疗晚期胃癌时患者不良反应并未增多。两组完成化疗同期情况比较差异无统计学意义,提示观察组与对照组接受治疗的依从性相当。

综上所述,复方苦参注射液联合PTX和S-1治疗晚期胃癌具有良好的临床疗效,且不增加化疗药物的不良反应。

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