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益气活血汤联合化疗灌注治疗中晚期膀胱癌的临床疗效

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摘要 目的: 探讨益气活血汤联合化疗灌注治疗中晚期膀胱癌的临床疗效及其对患者免疫功能及生活质量的影响。**方法:** 选择2011年6月至2016年12月在我院进行手术治疗的中晚期膀胱癌患者86例,随机分为两组。对照组31例患者术后接受化疗灌注治疗,观察组55例患者在对照组基础上服用益气活血汤。比较两组患者治疗后的临床疗效、治疗前后 $CD4^+$ 含量、$CD4^+/CD8^+$ 及NK细胞活性、生活质量评分的变化及治疗期间不良反应的发生情况。**结果:** 治疗后,观察组的总缓解率显著高于对照组($P<0.05$);两组患者 $CD4^+$ 含量及NK细胞活性均较治疗前显著升高($P<0.05$),$CD8^+$ 细胞含量均较治疗前显著降低($P<0.05$),且观察组患者的 $CD4^+$ 数量、NK细胞活性、$CD4^+/CD8^+$ 比例均显著高于对照组($P<0.05$);两组患者的生活质量评分均较治疗前明显升高,且观察组的生活质量评分显著高于对照组($P<0.05$);观察组胃肠不适、骨髓抑制的发生率均显著低于对照组($P<0.05$),两组患者肝损伤、发热的发生率比较差异无统计学意义($P>0.05$)。**结论:** 益气活血汤辅助灌注化疗可显著提高中晚期膀胱癌术后患者的临床疗效,改善患者的免疫功能及生活质量,并降低化疗所致不良反应的发生率。

关键词: 中晚期膀胱癌;益气活血汤;化疗灌注;免疫功能;生活质量;疗效

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Clinical Curative Effect of Yiqihuoxue Decoction Combined with Chemotherapy on the Patients with Advanced Bladder Cancer

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ABSTRACT Objective: To explore the clinical efficacy of yiqihuoxue decoction combined with chemotherapy on the patients with advanced bladder cancer and influence on the immune function and quality of life. **Methods:** 86 cases of patients with advanced bladder cancer were enrolled in our hospital from June 2011 to December 2016 and randomly divided into two groups. The control group (n=31) was given infusion chemotherapy treatment, and the study group (n=55) adopted yiqihuoxue decoction based on the patients of control group. The curative effect, changes of immune cells and quality of life score before and after treatment as well as the incidence of adverse reactions were compared between two groups. **Results:** The total remission rate of study group was significantly higher than that of the control group ($P<0.05$). After treatment, the $CD4^+$, number, NK cell activity and quality of life scores of both groups were remarkably increased compared with those before treatment ($P<0.05$), and $CD8^+$ number were significantly decreased ($P<0.05$), and $CD4^+$ number, NK cell activity, $CD4^+/CD8^+$ and quality of life score of study group were higher than those of the control group ($P<0.05$); the incidence of gastrointestinal discomfort, bone marrow suppression of patients in the study group were lower than those of the control group ($P<0.05$), and no significant difference was found in the liver injury and fever between two groups ($P>0.05$). **Conclusions:** Yiqihuoxue decoction combined with infusion chemotherapy could not only increase the curative effect, improve the immune function and quality of life for the patients with advanced bladder cancer, but also decrease the incidence of chemotherapy-induced adverse reactions.

Key words: Advanced bladder cancer; Yiqihuoxue decoction; Infusion chemotherapy; Immune function; Quality of life; Curative effect

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前言

膀胱癌是临床常见的泌尿系统肿瘤之一,近几年其发病率呈现明显上升的趋势[1]。膀胱癌患者临床主要表现为无痛性血尿、消瘦、下腹部疼痛等现象,目前临床治疗该疾病以手术治疗为首选方案,然而临床研究表明患者术后3-5年复发率较高,因此术后常规放化疗成为临床控制患者术后复发以及延长患者生存期的关键[2-4]。近几年,随着现代医学技术的飞速发展,灌注化疗在中晚期膀胱癌的应用中愈加广泛[5]。虽然化疗用于膀胱癌治疗的临床疗效显著,但是化疗副作用一直是困扰患者及医务人员的难题之一,比如化疗后化学性膀胱炎、膀胱痉挛、骨

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髓抑制、食欲不振等均影响患者的生存质量[6,7]。有研究表明肿瘤患者化疗期间免疫功能受到一定程度的影响,而其免疫功能与患者化疗期间的毒副不良反应密切相关[8,9]。

中医认为膀胱癌属于癃闭、尿血、血淋范畴,患者表现为机体虚弱、正气不足、气郁血瘀,因此益气活血对于膀胱癌的疗效显著[10],本研究以在本院进行治疗的中晚期膀胱癌患者为研究对象,探讨益气活血汤联合化疗灌注治疗对中晚期膀胱癌患者免疫功能的影响,从而分析该疗法的临床疗效及其对患者生活质量的影响,现将研究结果报道如下:

1 资料和方法

1.1 临床资料

选择 2011 年 6 月至 2016 年 12 月在我院进行手术治疗(膀胱部分切除术,经尿道膀胱肿瘤切除术)的中晚期膀胱癌患者 86 例, 所有患者经诊断均符合国际抗癌协会与美国癌症分期委员会制定的关于中晚期膀胱癌的诊断标准[11]。排除标准:生存期不足 3 月患者;有放化疗治疗史患者;膀胱癌复发患者;合并其他肿瘤患者;合并严重心肝肾功能疾病患者;患有自身免疫疾病患者。所有患者均对本研究知情同意,且经过医院伦理委员会同意。两组患者的基本情况见表 1,经分析两组患者的性别、年龄、病程及肿瘤转移情况等差异均无统计学意义(P<0.05),具有可比性。

表 1 两组患者一般临床资料的比较

Table 1 The comparison of general clinical conditions of patients between two groups

Group	Number	Gender (F/M)	Age (year)	Course of disease (year)	Metastasis		
					Liver metastasis	Lung metastasis	Bone metastasis
Control Group	31	19/12	45.23± 3.1	3.11± 0.29	3	2	2
Study Group	55	36/19	44.76± 2.9	3.06± 0.31	7	4	3

1.2 治疗方法

所有患者手术治疗后经临床诊断需要进行放化疗。对照组患者接受双侧髂内动脉化疗灌注:将 50 mg 丝裂霉素(江苏恒瑞医药股份有限公司生产,国药准字 H20023846)溶于 500 mL 生理盐水配制化疗药物。所有患者采取平卧位,全身麻醉,由右侧股动脉穿刺,将三腔导尿管由尿道插入,排空膀胱尿液,将三腔导尿管的入水端和出水端连接体腔热灌注治疗仪,化疗药物由治疗仪的灌注管进入患者膀胱,再由治疗仪引流管引出尽量形成循环灌注。每次治疗 40 min,每 3 天 1 次,总共治疗 4 次。观察组在对照组基础上服用益气活血汤:汤药配方:人参、黄芪、麦冬门各 15 g,茯苓、党参及薏苡仁各 10 g,桑寄生、大黄及牡丹皮各 6 个,水煎服用,每天 1 剂,连续服用 12 天。

1.3 观察指标及评价标准

比较两组患者治疗后的临床疗效, 评价标准:完全缓解(CR):病灶全部消失,临床症状全部缓解;部分缓解(PR):病灶长径缩短 30%以上,临床症状部分缓解;疾病稳定(NC):治疗前后病灶及临床症状无明显变化;疾病进展(PD):病灶大小增加 20%以上或出现新的病灶。比较两组患者治疗前后的免疫功能:采用细胞流式法分别检测两组患者治疗前后 $CD4^+$ 以及 $CD8^+$ 的细胞含量并计算 $CD4^+/CD8^+$,NK 细胞活性采用 126I 释放法检测。采用健康状况调查(SF-36)量表评价两组患者治疗后 1 个月的生活质量;记录并分析两组患者治疗期间不良反应的发生情况。

1.4 统计学处理方法

采用 SPSS19.0 分析软件进行统计学分析。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,计数资料采用 x^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

由表 2 可见,观察组治疗后的总缓解率为 50.9%,显著高于对照组(P<0.05)。

表 2 两组患者治疗后临床疗效的比较[例(%)]

Table 2 The comparison of clinical curative effect of patients after treatment between two groups [n (%)]

Groups	Number	CR	PR	NC	PD	Total remission rate
Control group	31	2(6.5)	7 (22.6)	14 (45.2)	8 (25.8)	9 (29.0)
Study group	55	6 (10.9)	22 (40.0)	18 (32.7)	9 (16.4)	28 (50.9)*

Note: *P<0.05: compared with the control group.

2.2 两组治疗前后免疫功能的比较

由表 3 可见, 两组患者治疗后的 $CD4^+$ 含量及 NK 细胞活性均较治疗前显著升高 (P<0.05),$CD8^+$ 细胞含量均显著降低(P<0.05), 且观察组患者的 $CD4^+$ 含量、$CD4^+/CD8^+$ 及 NK 细胞活性均显著高于对照组(P<0.05)。

2.3 两组治疗前后生活质量评分的比较

由表 4 可见,两组患者治疗后的生活质量评分均较治疗前显著升高,且观察组的生活质量评分显著高于对照组(P<0.05)。

2.4 两组不良反应发生情况的比较

由表 5 可见,观察组胃肠不适、骨髓抑制的发生率均显著低于对照组(P<0.05),两组患者肝损伤、发热的发生率比较差异均无统计学意义(P>0.05)。

3 讨论

表 3 两组患者治疗前后免疫细胞含量或活性的比较($\bar{x}\pm s$)

Table 3 The comparison of immune cell content or activity before and after treatment between two groups ($\bar{x}\pm s$)

	Control Group (n=31)		Study Group (n=55)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
CD4+ (%)	30.24± 5.63	34.25± 6.02*	31.06± 6.31	38.06± 5.93*#
CD8+(%)	18.36± 3.62	15.01± 2.63*	17.84± 3.21	13.52± 3.03*#
CD4+/CD8+	1.34± 0.38	1.27± 0.31	1.38± 0.41	1.53± 0.24*#
NK cell (mmol/L)	21.03± 2.87	22.14± 4.06*	20.75± 3.01	28.54± 5.31*#

Note: *P<0.05: compared with pre-treatment, #P<0.05: compared with the control group.

表 4 两组患者治疗前后的生活质量评分比较($\bar{x}\pm s$)

Table 4 The comparison of the quality of life score before and after treatment between two groups ($\bar{x}\pm s$)

	Control Group (n=31)		Study Group (n=55)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
PF	47.63± 7.23	61.52± 8.69*	48.67± 8.56	67.68± 9.86*#
RP	37.86± 5.79	51.26± 7.12*	38.17± 6.31	58.37± 6.82*#
BP	65.73± 6.31	73.58± 6.16*	66.34± 5.87	84.63± 9.32*#
GH	36.23± 5.34	49.67± 6.31*	36.57± 5.62	66.34± 7.57*#
VT	37.87± 6.35	61.57± 10.36*	38.14± 7.06	66.37± 11.43*#
SF	38.76± 5.87	58.62± 8.96*	39.57± 6.34	67.57± 11.36*#
RE	36.57± 6.31	59.31± 10.63*	37.16± 7.21	65.23± 13.05*#
MH	38.62± 5.31	58.23± 9.54*	39.03± 4.87	62.72± 10.15*#
Total score	343.58± 21.32	468.56± 32.54*	345.65± 23.67	503.91± 37.52*#

Note: *P<0.05: compared with pre-treatment, #P<0.05: compared with the control group.

表 5 两组患者治疗期间不良反应发生情况的比较[例(%)]

Table 5 The comparison of incidence of adverse reactions between two groups [n (%)]

Group	Number	Gastrointestinal discomfort	Myelosuppression	Hepatorenal dysfunction	Fever
Control Group	31	17 (54.8)	14 (45.2)	18 (58.1)	9 (29.0)
Study Group	55	18 (32.7)*	13 (23.6)*	20 (36.4)	13 (23.6)

Note: *P<0.05: compared with the control group.

膀胱癌属于泌尿系统常见的恶性肿瘤之一,临床表现出血尿患者中 50%均由膀胱癌所致[12]。膀胱癌患者血尿同时常伴破碎血块,严重时可出现大量血块充盈膀胱,引起患者排尿困难、尿潴留及剧烈的下腹部疼痛[13]。临床研究表明约 30%膀胱癌患者表现为浸润性癌,具有多发性、多中心性、高复发性等特点,且多数患者临床首次确诊时往往已浸润至深肌层并伴有淋巴结转移[14-16],仅凭外科手术治疗膀胱癌的临床疗效有限。目前,放化疗是控制膀胱癌发展、改善患者预后的主要治疗方式,由于膀胱解剖结构可与外界沟通的特殊性,因此灌注化疗可通过提高肿瘤局部药物浓度提高临床疗效[17,18]。

灌注化疗药物丝裂霉素在治疗过程中具有局部药物浓度高、全身副作用小等特点,可有效预防患者术后癌症复发[19]。然而,大量临床研究表明单独化学药物灌注治疗具有显著破坏患者机体免疫功能的作用,炎症影响患者术后的生存质量[20]。中医认为气虚、血虚、湿热等均是肿瘤发生发展的致病原因之一[21],既往研究表明中医药治疗在缓解患者尿频、尿急、尿痛、血尿及下膀胱区疼痛等方面疗效显著,可一定程度降低化疗药物诱发不良反应发生的风险[22,23]。本研究分析了益气活血汤联合灌注化疗用于中晚期膀胱癌患者术后治疗的临床疗效,结果显示观术后接受联合治疗的患者总缓解率显著高于单用灌注化疗者。益气活血汤组方中包含的人参、黄芪、麦冬门及党参具有显著的益气养阴功效,茯苓、白术、薏苡仁具有健脾利湿、积聚内停之功效,牡丹皮、大黄具有活血化瘀、驱散邪毒之作用,因此其辅助灌注化疗显著提高患者术后临床疗效[24-26]。本研究还分析了患者治疗期间不良反应的发生情况,结果显示益气活血汤联合灌注化疗治疗的患者胃肠不适、骨髓抑制的发生率显著低于单用灌注化疗者,由此说明益气活血汤可一定程度降低化疗诱发不良反应的发生率,大量研究表明肿瘤患者行放化疗的

临床疗效及不良反应的发生与患者机体免疫功能的变化密切相关[28]。中医治疗膀胱癌的主要治疗原则以扶本固正、祛邪利湿、益气补血为主，其中扶正赔本即为改善或巩固患者机体免疫力[27]。T 淋巴细胞亚群在肿瘤免疫监视中发挥至关重要的作用，其中 $CD4^+$ 可协助 B 淋巴细胞产生抗体，辅助其他 T 细胞亚群行抗肿瘤等生物学功能，$CD8^+$ 细胞可抑制 B 淋巴细胞产生抗体，发挥抑制淋巴细胞的生物学功能，二者在正常机体中相互协调，相互制约，发挥正常的免疫学功能，而 $CD4^+$ 和 $CD8^+$ 细胞在肿瘤患者机体含量及功能协调发生紊乱[29]。本研究分析了益气活血汤对接受灌注化疗的膀胱癌患者机体免疫功能的影响，结果显示益气活血汤联合灌注化疗的患者治疗后 $CD4^+$ 细胞含量及 $CD4^+/CD8^+$ 比值均较单用灌注化疗者显著升高，说明益气活血汤辅助灌注化疗可有效改善患者机体免疫功能。

本研究进一步分析了患者治疗期间生活质量的情况，结果显示：益气活血汤联合灌注化疗的患者治疗后的生活质量评分均显著高于单用灌注化疗者。罗松涛等报道益气活血汤联合化疗灌注可显著改善中晚期膀胱癌患者的生活质量[30]，其结果与本研究结果一致。由此可见益气活血汤联合灌注化疗有助于提高中晚期膀胱癌患者的生活质量，这可能与益气活血汤改善患者免疫功能，有效降低不良反应发生率有关。

综上所述，中晚期患者手术治疗后接受益气活血汤辅助灌注化疗可显著提高临床疗效，改善患者机体免疫功能及生活质量，有效降低化疗诱发不良反应的发生率，值得临床推广应用。

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