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健脾益气解毒方联合化疗治疗晚期结直肠癌的疗效评价

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摘要 目的:探讨健脾益气解毒方联合化疗治疗晚期结直肠癌的疗效及其对患者免疫功能、生活质量的影响。**方法:**选择 2010 年 6 月至 2015 年 12 月在我院进行治疗的晚期结直肠癌患者 80 例,随机分为两组,每组 40 例。对照组患者接受 FOLFIRI 化疗,观察组患者在对照组基础上服用健脾益气解毒汤。比较两组患者治疗的临床疗效、治疗前后机体免疫功能、生活质量的变化情况及治疗期间不良反应的发生情况。**结果:**治疗后,观察组患者治疗的疾病控制率、$CD4^+$ 以及 $CD4^+/CD8^+$、KPS 评分均显著高于对照组(P<0.05),中医证侯评分及脾虚证候评分、白细胞减少、Ⅰ-Ⅱ级中性粒细胞减少以及肝损伤等不良事件的发生率均显著低于对照组(P<0.05)。**结论:**健脾益气解毒汤联合化疗治疗晚期结直肠癌可有效提高临床疗效,改善患者免疫功能及生活质量。

关键词:晚期结直肠癌;健脾益气解毒汤;免疫功能;疗效;不良反应

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Curative Effect of Jianpi Yiqi Jiedu Decoction Combined with Chemotherapy on the Patients with Advanced Colorectal Cancer

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ABSTRACT Objective: To explore the curative effect of Jianpi Yiqi Jiedu decoction combined with chemotherapy on the patients with advanced colorectal cancer and effect on the immunity function and quality of life. **Methods:** 80 cases of patients with advanced colorectal cancer enrolled in our hospital from June 2010 to December 2015 were divided into two groups, the control group (n=40) was given FOLFIRI chemotherapy treatment, and the study group (n=40) adopted Jianpi yiqi jiedu decoction based on the control group. The clinical curative effect, immunity function and quality of life of patients before and after treatment, incidence of adverse reactions during treatment were compared between two groups. **Results:** After treatment, the disease control efficiency, content of $CD4^+$, $CD4^+/CD8^+$, KPS score of study group were significantly higher than those of the control group (P<0.05); the TCM and spleen deficiency syndrome integral, incidence of leukocyte reduction, Ⅰ-Ⅱ neutrophil depletion and liver function damage of patients in study group were significantly lower than those of the control group (P<0.05). **Conclusions:** Jianpi Yiqi Jiedu decoction combined with chemotherapy not only increase the curative effect, but also improve the immunity function and quality of life for patients with advanced colorectal cancer.

Key words: Advanced colorectal cancer; Jianpi Yiqi Jiedu decoction; Immunity function; Curative effect; Adverse reactions

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前言

结直肠癌是临床常见的消化道恶性肿瘤,其发病率在全球范围内仅次于肺癌、胃癌[1]。近几年,随着人们生活水平的提高以及饮食结构的变化,我国结直肠癌的发病率呈现上升趋势。据统计,该肿瘤在恶性肿瘤致死原因中位于第 5 位,严重威胁患者的生命健康[2]。由于我国人们日常定期体检意识较为淡薄,加之其发病早期临床症状并不明显,多数患者待确诊时往往已发展至中晚期,错过最佳的治疗时机,临床研究证实即使患者接受根治手术,其术后约半数患者仍旧可能发生复发或转移[3],因此放化疗成为临床控制结直肠癌发展并延长患者生命周期的有效治疗方法[4]。

FOLFIRI 是临床治疗晚期结直肠癌的标准化疗方案之一,但是患者对药物的耐药性以及强烈的毒副反应使得临床疗效大打折扣[5]。近几年,中医药联合化疗治疗肿瘤已广泛应用于临

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床，临床研究证实中药对肿瘤患者机体免疫力、临床疗效及预后均具有一定的改善作用[6,7]。本研究以在本院进行治疗的晚期结直肠癌患者为研究对象，探讨健脾益气解毒方联合 FOLFIRI 化疗方案治疗该肿瘤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 2010 年 6 月至 2015 年 12 月在我院进行治疗的晚期结直肠癌患者 80 例，所有患者均经影像学、病理学或细胞学检查确诊，且临床分期为Ⅲ-Ⅳ期。排除标准：经评估其 KPS 评分不足 60 分患者；患有严重心肝肾等功能疾病患者；对铂类及氟尿嘧啶类化疗药物过敏患者。所有患者均对本研究知情同意，且经过医院伦理委员会批准。所有患者按照随机数字表法分为两组，每组 40 例。对照组和观察组患者基本资料见表 1，两组患者性别、年龄、肿瘤类型及分化程度等基本资料比较差异均无统计学意义(P>0.05)，具有可比性。

表 1 两组患者一般资料的比较

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

Group		Control Group (n=40)	Study Group (n=40)
Gender (F/M)		23/17	24/16
Age (year)		63.4± 6.4	64.2± 6.1
Tumor type Colon cancer		22	23
Rectal cancer		16	15
Junction cancer of rectal and sigmoid colon		2	2
Differentiation	High differentiation	18	19
	Middle differentiation	8	9
	Low differentiation	14	12

1.2 治疗方法

所有患者的一线治疗与二线治疗方案均为 FOLFIRI 化疗，第 1 天：静脉注射 90 min 伊立替康(规格：40 mg/ 瓶，江苏恒瑞医药股份有限公司生产，国药准字 H20020687)180 mg/m^2+2 h 亚叶酸钙(0.1 g，江苏恒瑞医药股份有限公司生产，国药准字 H32022391)400 mg/m^2，第 1、2 天：静脉推注 5- 氟尿嘧啶(齐鲁制药有限公司生产，国药准字 H37021281)400 mg/m^2+ 静脉滴注 22 h 5- 氟尿嘧啶 2400 mg/m^2，每 2 周重复一次，共进行 4 次，化疗期间每天上午、下午静脉滴注 4 mg 托烷司琼 (5 mg/ 瓶，瑞阳制药有限公司生产，国药准字 H20060460)。观察组在此基础上服用健脾益气解毒汤剂，汤剂配方：陈皮 6 g，莪术、地鳖虫各 10 g，炒谷麦芽 12 g，党参、炒白术、云茯苓、仙鹤草各 15 g，山慈菇 20 g，黄芪、薏苡仁、半枝莲、蛇舌草各 30 g，水煎取汁 400 mL，每日 1 剂，早晚分服，连服 8 周，8 周后评价患者疗效。

1.3 观察指标及评价标准

评价两组患者的临床疗效：参照 RECIST 评价标准[8]，分为完全缓解(CR)、部分缓解(PR)、稳定(SD)以及进展(PD)，疾病控制率 =CR 率 +PR 率 +SD 率。采用流式细胞术分别检测患者治疗前后的 CD4$^+$、CD8$^+$ 的细胞水平并计算 CD4$^+$/CD8$^+$；依据《中药新药临床研究指导原则》[9] 评估两组患者治疗前后的中医证候积分；依据《中医虚证辨证参考标准》以及沈士肾气虚评分方法[10]评估患者治疗前后的脾虚证候积分；依据 Karnofsky 评分量表[11]计算患者治疗前后的 KPS 评分，评估患者的生活质量；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 检验分析，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，观察组患者治疗的控制效率为 75%，显著高于对照组(52.5%，P<0.05)。

2.2 两组治疗前后免疫功能的比较

由表 3 可见，两组患者经治疗后 CD4$^+$、CD4$^+$/CD8$^+$ 均较治疗前均显著升高 (P<0.05)；治疗后，观察组患者的 CD4$^+$ 以及 CD4$^+$/CD8$^+$ 均显著高于对照组(P<0.05)。

表 2 两组患者临床疗效的比较[例(%)]

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

Group	Number	CR	PR	SD	PD	DCR
Control Group	40	0 (0.0)	11 (27.5)	10 (25.0)	19 (47.5)	21 (52.5)
Study Group	40	0 (0.0)	17 (42.5)	13 (32.5)	10 (25.0)	30 (75.0)*

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

表 3 两组患者治疗前后免疫功能指标的比较

Table 3 The comparison of immunity indexes of patients before and after treatment between two groups

	Control Group(n=40)		Study Group(n=40)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
$CD4^+$ (%)	27.6± 3.5	28.9± 4.2*	28.1± 2.9	32.4± 3.6*#
$CD8^+$ (%)	21.1± 3.4	22.3± 2.9	21.4± 3.1	21.9± 3.1
$CD4^+/CD8^+$	1.0± 0.3	1.1± 0.2	1.0± 0.2	1.4± 0.3#

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

2.3 两组治疗前后中医证侯、脾虚证候评分及生活质量评分的比较

由表 4 可见，两组患者治疗后中医证侯评分均较治疗前显著降低(P<0.05)，KPS 评分较治疗前显著升高；治疗后，观察组患者的中医证侯评分及脾虚证候评分显著低于对照组(P<0.05)，KPS 评分显著高于对照组(P<0.05)。

表 4 两组患者治疗前后中医证侯、脾虚证候评分及 KPS 评分的比较

Table 4 The comparison of TCM and spleen deficiency syndrome integral and KPS score before and after treatment between two groups

	Control Group(n=40)		Study Group(n=40)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
TCM syndrome integral	14.6± 2.5	11.7± 3.1*	13.9± 1.9	7.2± 2.8*#
Spleen deficiency syndrome integral	13.5± 1.2	13.1± 1.4	13.8± 1.4	10.1± 1.3*#
KPS score	75.3± 4.8	77.8± 6.9*	76.2± 5.1	85.2± 6.3*#

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

2.4 两组不良反应发生情况的比较

由表 5 可见，观察组患者白细胞减少、Ⅰ-Ⅱ级中性粒细胞减少以及肝损伤等不良事件的发生率均显著低于对照组(P<0.05)。

表 5 两组患者治疗后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 (%)]

		Control Group(n=40)		Study Group(n=40)	
		Ⅰ-Ⅱ	Ⅲ-Ⅳ	Ⅰ-Ⅱ	Ⅲ-Ⅳ
Hematologic toxicity	Leukocyte reduction	15 (37.5)	10 (25.0)	5 (12.5)*	3 (7.5)*
	Neutrophil depletion	13 (32.5)	7 (17.5)	5 (12.5)*	3 (7.5)
	Thrombocytopenia	5 (12.5)	2 (5.0)	3 (7.5)	1 (2.5)
	Hemoglobin reduction	19 (47.5)	4 (10.0)	12 (30.0)	0 (0.0)
Liver function damage		18 (45.0)	0 (0.0)	7 (17.5)*	0 (0.0)
Renal damage		4 (10.0)	0 (0.0)	1 (2.5)	0 (0.0)
Nausea and vomiting		24 (60.0)	9 (22.5)	20 (50.0)	2 (5.0)

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

3 讨论

据报道，直肠癌患者的 5 年生存率为 60%，结肠癌更是在 50%左右徘徊[12,13]。多数早期(Ⅱ期)结直肠癌可通过手术治疗治愈，然而晚期(Ⅲ、Ⅳ期)结直肠癌患者仅通过手术治疗的获益极低，较高的复发率仍旧严重威胁患者的生命健康[14,15]。结直肠癌早期由于临床症状隐匿性较强，多数患者待确诊时往往已发展至晚期，部分原发灶、转移灶已不能通过手术治疗切除，因此放化疗成为提高晚期结直肠癌手术疗效及延长患者生存期的主要方法[16]。然而，患者在接收长期的放化疗后易出现耐药及毒副反应，比如血液毒副反应、神经毒性反应等，影响临床疗效及患者的生存质量[17-19]。

近几年，诸多研究证实我国中医药治疗结直肠癌的疗效显著，可一定程度改善患者的临床疗效及生活质量、降低不良反应的发生率[20,21]。我国中医认为结直肠癌属于＂肠风＂、＂脏毒＂、＂便血＂、＂肠僻＂、＂肠积＂、＂下痢＂、＂锁肛痔＂、＂积聚＂等范畴，其中肠风、脏毒产生的原因是由于脾胃虚弱，近几年随着中医临床辩证研究的深入，多数医家学者认为脾虚气弱、瘀毒结

结聚是结直肠癌发生、发展的主要病因[22]。唐·巢元方在《诸病源候论》中指出 " 凡脾胃不足,虚弱失调之人,多有积聚之病 ",临床无论通过手术、放化疗或肿瘤增大、转移,患者均可耗伤气血、加重脾虚,进而诱发复发转移或促进肿瘤生长[23]。本研究中,在放疗基础上服用健脾益气解毒汤药的患者治疗后的疾病控制效率显著高于单用放疗的患者,说明健脾益气、清热解毒辅助化疗可有效提高结直肠癌患者的临床疗效。

研究表明脾虚患者的细胞免疫和体液免疫均较为低弱,肿瘤发生率、转移发展率均较高[24,25],且肿瘤患者接受的手术放化疗可抑制骨髓淋巴干细胞的分化,降低淋巴细胞数量,一定程度上会影响机体的免疫功能[26,27]。$CD4^+$ 即辅助性 T 细胞,可协助 B 淋巴细胞分泌抗体调节其他 T 淋巴细胞的免疫应答,$CD8^+$ 是抑制性 T 淋巴细胞,其含量越高,免疫抑制越强,$CD4^+/CD8^+$ 的稳态是维持正常机体免疫应答的表现[28,29],本研究结果显示,在放疗基础上服用健脾益气解毒汤药的患者治疗后的 $CD4^+$ 细胞亚群含量以及 $CD4^+/CD8^+$ 显著高于单用放疗的患者,提示健脾益气解毒汤辅助化疗一定程度可改善患者的免疫功能。

脾与机体气血化生、抗病御邪等密切相关,脾虚可明显影响机体造血功能及其营养状态,脾虚症状综合积分可客观、全面的反映患者脾虚状态[30]。本研究结果显示:在放疗基础上服用健脾益气解毒汤药的患者脾虚证候积分显著低于单用放疗的患者,KPS 评分显著高于单用放疗的患者,提示化疗基础上服用健脾益气解毒汤可显著改善患者临床症状以及生活质量。此外,在放疗基础上服用健脾益气解毒汤药的患者白细胞减少、Ⅰ-Ⅱ级中性粒细胞减少以及肝损伤等不良事件的发生率显著低于单用放疗的患者,其原因可能与健脾益气解毒汤的功能作用相关,其健运脾气、生化气血、清热解毒、理气散结之功效显著改善患者体质及免疫力,有效对抗肿瘤发展,提高临床疗效及生活质量。

综上所述,健脾益气解毒汤联合化疗治疗晚期结直肠癌可有效提高临床疗效,改善患者免疫功能及生活质量。

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