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· 论 著 ·

厚朴通闭汤口服联合吡柔比星膀胱灌注化学治疗对非肌层浸润性膀胱癌术后患者疗效的随机对照研究

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[摘要] **目的** 观察厚朴通闭汤口服联合吡柔比星膀胱灌注化学治疗对非肌层浸润性膀胱癌术后患者的疗效。
方法 选择2018年1月至2019年12月于上海交通大学附属第一人民医院行经尿道膀胱肿瘤切除术治疗的非肌层浸润性膀胱癌患者95例, 随机分为观察组(49例)和对照组(46例), 对照组术后采用吡柔比星膀胱灌注化学治疗, 观察组在对照组基础上辅以厚朴通闭汤口服, 总疗程均为1年。所有患者术后均随访1年, 比较两组患者的膀胱癌复发情况、中医证候改善情况、生活质量、尿常规指标、血常规指标、肝肾功能指标、不良反应发生情况等。
结果 术后经过1年的辅助治疗, 观察组患者复发率(18.37%, 9/49)低于对照组(36.96%, 17/46), 整体中医证候改善率(79.59%, 39/49)高于对照组(41.30%, 19/46), 生活质量各项评分中情绪功能、疲倦、疼痛、总健康状况及尿路症状评分均优于对照组, 差异均有统计学意义($P < 0.05$); 观察组患者外周白细胞计数和丙氨酸转氨酶水平均低于对照组($P < 0.05$), 两组患者其他血常规及肝肾功能指标差异均无统计学意义($P > 0.05$); 两组患者尿白蛋白和红细胞水平差异均无统计学意义($P > 0.05$), 但观察组患者尿蛋白水平低于对照组($P < 0.05$)。治疗期间, 观察组总不良事件发生率(36.73%, 18/49)低于对照组(60.87%, 28/46), 差异有统计学意义($P < 0.05$)。
结论 厚朴通闭汤口服联合吡柔比星膀胱灌注化学治疗可预防非肌层浸润性膀胱癌患者术后肿瘤复发, 改善由肿瘤带来的中医证候, 提高患者的生活质量, 并减轻化学治疗相关不良反应。

[关键词] 膀胱肿瘤; 非肌层浸润性膀胱癌; 中西医结合疗法; 厚朴通闭汤; 吡柔比星; 化学治疗
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Houpo Tongbi decoction combined with pirarubicin intravesical chemotherapy in postoperative patients with non-muscle-invasive bladder cancer: a randomized control trial

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[Abstract] **Objective** To observe the efficacy of oral *Houpo Tongbi* decoction combined with pirarubicin intravesical chemotherapy in the treatment of postoperative patients with non-muscle-invasive bladder cancer (NMIBC). **Methods** Ninety-five NMIBC patients who underwent transurethral resection of bladder tumor (TURBT) in Shanghai General Hospital of Shanghai Jiao Tong University from Jan. 2018 to Dec. 2019 were randomly divided into observation group ($n=49$) and control group ($n=46$). The control group only received pirarubicin intravesical chemotherapy, while the observation group received oral *Houpo Tongbi* decoction combined with pirarubicin intravesical chemotherapy. The total course of treatment was 1 year. All patients were followed up for 1 year. The recurrence, improvement of traditional Chinese medicine (TCM) symptoms, quality of life, urine routine, blood routine, liver and kidney function and adverse events were compared between the 2 groups. **Results** After 1 year of adjuvant treatment, the recurrence rate in the observation group (18.37%, 9/49) was significantly lower than that in the control group (36.96%, 17/46)

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($P < 0.05$). The overall improvement rate of TCM symptoms was significantly higher in the observation group (79.59%, 39/49) than in the control group (41.30%, 19/46) ($P < 0.05$). The quality of life results showed that the emotional function, fatigue, pain, general health status and urinary tract symptom were significantly better in the observation group compared with the control group (all $P < 0.05$). The peripheral white blood cell count and alanine aminotransferase level in the observation group were significantly lower than those in the control group (both $P < 0.05$), and there were no significant differences in other blood routine or liver and kidney function indexes between the 2 groups (all $P > 0.05$). There were no significant differences in the levels of white blood cell or red blood cell in urine (both $P > 0.05$), while the urine protein level of the observation group was significantly lower than that of the control group ($P < 0.05$). During the treatment period, the total incidence of adverse events in the observation group (36.73%, 18/49) was significantly lower than that in the control group (60.87%, 28/46) ($P < 0.05$). **Conclusion** Houpo Tongbi decoction combined with pirarubicin intravesical chemotherapy can reduce the postoperative recurrence of NMIBC, alleviate TCM symptoms caused by tumor, improve quality of life, and reduce chemotherapy-related adverse events.

[**Key words**] urinary bladder neoplasms; non-muscle-invasive bladder cancer; integrated traditional Chinese and Western medicine; Houpo Tongbi decoction; pirarubicin; chemotherapy

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膀胱癌是世界第九大常见的恶性肿瘤,也是泌尿系统发病率最高的恶性肿瘤^[1]。国际癌症研究机构(International Agency for Research on Cancer, IARC)估计数据显示中国2020年有85 694人确诊膀胱癌^[2]。在新发的膀胱癌中,约75%为非肌层浸润性膀胱癌(non-muscle-invasive bladder cancer, NMIBC),其余为肌层浸润性膀胱癌^[3]。男性膀胱癌发病率为女性的3~4倍^[4],但有研究结果显示,女性患者被确诊时的病理等级相对更高^[5]。经尿道膀胱肿瘤切除术(transurethral resection of bladder tumor, TURBT)不仅是治疗NMIBC的标准术式,也是重要的诊断方法^[6]。然而,仍有50%左右的NMIBC患者术后会复发,且具有进展为肌层浸润性膀胱癌的可能,最终预后不良^[7-8]。因此,降低NMIBC患者TURBT术后的复发率并阻止其进展为肌层浸润性膀胱癌对预后至关重要。

术后化学治疗可在一定程度上减少膀胱癌复发^[9-12]。吡柔比星(pirarubicin)膀胱灌注是常用的术后化学治疗方案,效果较为确切^[13-14],但术后复发仍较常见,且其对膀胱黏膜刺激较大,可引发化学性膀胱炎等不良反应^[12,15]。中西医结合疗法是膀胱癌综合治疗的重要组成部分,中医药不但具有抗肿瘤作用,同时还可提高化学治疗效果并减少化学治疗特别是膀胱灌注化学治疗相关不良反应^[16]。上海交通大学附属第一人民医院将厚朴通闭汤应用于膀胱癌术后辅助治疗已近20年,并在临床上观察到其具有减毒增效的效果。本课题组

开展了一项随机对照试验,验证厚朴通闭汤联合吡柔比星膀胱灌注对TURBT术后NMIBC患者的治疗效果和安全性。

1 对象和方法

1.1 研究对象 根据药物临床试验质量管理规范原则,采用随机对照试验设计。前瞻性选择2018年1月至2019年12月于上海交通大学附属第一人民医院接受治疗的膀胱癌患者。纳入标准:(1)年龄为18~80岁,男女不限;(2)因膀胱癌行TURBT后,镜下均无肿瘤存留;(3)经肿瘤组织病理学明确诊断为NMIBC,临床分期为Ta~T1期、病理分级为低级别和高级别;(4)初发膀胱癌;(5)美国东部肿瘤协作组体力状况评分为0~2分;(6)无难以控制的泌尿道感染和肝肾等器官功能不全;(7)中医辨证属于膀胱湿热证或瘀毒蕴结证;(8)签署研究知情同意书。排除标准:

(1)临床与病理诊断为肌层浸润性膀胱癌或膀胱原位癌;(2)未行手术切除;(3)对试验药物过敏;(4)中医兼夹证型太多;(5)近3个月内参加过其他药物临床试验。本研究通过上海交通大学附属第一人民医院伦理委员会审批(2021KY069)。

1.2 治疗方法 采用随机数字表法将所有入组NMIBC患者分为观察组和对照组。两组患者均于TURBT术后24 h内行吡柔比星(深圳万乐药业有限公司,批号H10930105)膀胱灌注化学治疗。对照组:用50 mL生理盐水将50 mg吡柔比星溶解,经导尿管注入膀胱内,其间患者可变换

体位,每次持续20 min,每周1次,治疗8周后改为每月1次,总疗程为1年。观察组:在常规吡柔比星膀胱灌注化学治疗的基础上,给予厚朴通闭汤口服。厚朴通闭汤组成:厚朴6 g、黄芪15 g、白术9 g、女贞子15 g、地黄12 g、赤芍12 g、蒲公英30 g、土茯苓15 g、车前子15 g、龙葵15 g、蛇舌草15 g、白茅根30 g、苦参12 g、甘草梢9 g。对于湿浊明显的患者,在上述基础上加陈皮9 g、法半夏9 g、薏苡仁30 g;若存在阴虚内热,则加知母9 g、黄柏9 g、墨旱莲15 g;若存在尿频尿急明显,则加瞿麦12 g、篇蓄12 g、通草15 g;对于血尿明显的患者,则加仙鹤草30 g、花蕊石15 g、小蓟15 g。每剂煎煮成2袋,每袋150 mL。早晚各服用1次,每次1袋,3个月为1个疗程,连用4个或以上疗程。

1.3 肿瘤复发及生活质量评估 所有患者均随访1年。患者每3个月至医院随访1次,复查膀胱镜、尿液细胞学和泌尿系超声以明确肿瘤复发情况。综合各项检查结果,如有疑似复发者,予以活检或切除,最终以病理结果为复发诊断依据。采用欧洲癌症研究与治疗组织的癌症患者生活质量核心问卷(quality of life questionnaire core 30, QLQ-C30)和浅表性膀胱癌患者生活质量特异性量表(quality of life superficial bladder cancer-specific 24, QLQ-BLS24)评估患者的整体健康状况^[17]。

1.4 中医证候评估 膀胱癌术后患者中医证候分为4型^[18-19]。(1)湿热下注:小溲短赤,灼热,伴尿痛、尿急、尿频或排尿不畅,下腹胀痛,腰酸,舌苔黄腻,脉弦数;(2)气滞血瘀:小溲涩痛,或伴尿血(时多时少),小腹疼痛或胀痛,舌苔薄或腻,舌质紫暗,脉弦涩;(3)肾阴不足:小溲量少不畅,或有尿血(色淡红),神疲,腰酸,五心烦热,形体消瘦,盗汗,舌苔薄黄,舌质红绛,脉细数;(4)脾肾亏虚:小溲无力,或伴血尿,腰酸膝软,小腹下坠,面色少华,神疲乏力,头晕耳鸣,大便溏薄,舌质淡,舌苔薄腻,脉沉细。采用半定量方法,将上述各个证候按无、轻、中、重分别记为0、1、2、3分,计算每例患者治疗前的证候总积分和治疗后的证候总积分,评价其改善情况。以分值下降百分比[(治疗前分值-治疗后分值)/治疗前分值×100%]评估疗效,分值下降百分比≥70%为显效,30%~<70%为有效,<30%

为无效,显效和有效为中医证候改善。

1.5 安全性评估 在每次随访中记录患者所发生的不良事件,如严重的尿路刺激症状和严重血尿等的发生情况。记录尿常规检查结果,监测尿路感染、镜下血尿和蛋白尿的发生情况。记录患者血常规和肝肾功能指标以评估患者一般身体状况,明确口服厚朴通闭汤是否会对身体造成额外负担或肝肾毒性。

1.6 统计学处理 采用SPSS 26.0软件对数据进行分析。服从正态分布的计量资料以 $\bar{x}\pm s$ 表示,组间比较采用独立样本 t 检验,组内比较使用配对 t 检验。计数资料以例数和百分数表示,组间比较采用 χ^2 检验。等级资料组间比较采用秩和检验。检验水准(α)为0.05。

2 结果

2.1 两组患者基线资料比较 根据纳入、排除标准,共105例患者纳入研究,其中6例患者因停药而被剔除,4例患者因失访而被剔除,最终有95例患者入组。95例患者中男74例、女21例,年龄为35~80岁,初发临床分期Ta期52例、T1期43例,初发病理分级低级别48例、高级别47例。对照组46例,男38例、女8例,年龄为(62.72±10.35)岁,初发临床分期Ta期24例、T1期22例,初发病理分级低级别22例、高级别24例;观察组49例,男36例、女13例,年龄为(63.87±10.21)岁,初发临床分期Ta期28例、T1期21例,初发病理分级低级别26例、高级别23例。两组患者的性别构成、年龄、初发临床分期及初发病理分级差异均无统计学意义(P 均>0.05)。

2.2 两组患者复发情况比较 以术后随访膀胱镜活检或切除标本病理活检阳性为复发诊断标准,术后经过3个月及6个月辅助治疗,观察组病理活检阳性者分别为2例(4.08%)及6例(12.24%),对照组分别为4例(8.70%)及10例(21.74%),两组间差异均无统计学意义(P 均>0.05);术后经过1年的辅助治疗,观察组病理活检阳性者为9例(18.37%),对照组为17例(36.96%),观察组复发率低于对照组,差异有统计学意义(P <0.05)。

2.3 两组患者中医证候改善情况比较 术后经过1年的辅助治疗,观察组中39例(79.59%)患者

表现出中医证候改善(显效和有效),其中8例患者为显效;对照组中19例(41.30%)患者表现出中医证候改善。观察组的整体中医证候改善率高于对照组,差异有统计学意义($P < 0.05$)。在4种

中医证候改善方面,观察组气滞血瘀的改善优于对照组,差异有统计学意义($P < 0.01$);两组中湿热下注、肾阴不足和脾肾亏虚的改善情况差异均无统计学意义(P 均 > 0.05)。见表1。

表1 两组NMIBC患者术后辅助治疗1年后中医证候改善情况比较

Tab 1 Comparison of improvement of TCM symptoms in NMIBC patients between 2 groups 1 year after postoperative adjuvant treatment

TCM symptom	Control group			Observation group			χ^2 value	P value
	N	Improved	Not improved	N	Improved	Not improved		
Dampness-heat diffusing downward	12	6	6	15	12	3	1.519	0.218
Stagnation of <i>qi</i> and blood stasis	14	5	9	13	12	1	6.990	0.008
Deficiency of kidney <i>yin</i>	12	5	7	9	8	1	3.067	0.080
Deficiency of spleen and kidney	8	3	5	12	7	5	0.208	0.648

Observation group: The patients received oral *Houpo Tongbi* decoction combined with pirarubicin intravesical chemotherapy; Control group: The patients received pirarubicin intravesical chemotherapy. NMIBC: Non-muscle-invasive bladder cancer; TCM: Traditional Chinese medicine.

2.4 两组患者生活质量的比较 各组患者的总体生活质量评分见表2和表3。术后经过1年的辅助治疗,观察组患者的情绪功能、总健康状况得分均高于治疗前,疲倦、疼痛、失眠得分均低于治疗前,差异均有统计学意义(P 均 < 0.05);对照组的总健康状况得分也高于治疗前,差异有统计

学意义($P < 0.05$)。术后经过1年的辅助治疗,两组患者的经济困难得分均高于治疗前,差异均有统计学意义(P 均 < 0.05)。治疗后观察组患者的情绪功能和总健康状况得分均高于对照组,疲倦、疼痛、尿路症状得分均低于对照组,差异均有统计学意义(P 均 < 0.05)。

表2 两组NMIBC患者术后辅助治疗1年后QLQ-C30评分比较

Tab 2 Comparison of QLQ-C30 scores in NMIBC patients between 2 groups 1 year after postoperative adjuvant treatment

Group	$\bar{x} \pm s$							
	Physical function	Role function	Emotional function	Cognitive function	Social function	Fatigue	Nausea/vomiting	Pain
Control group $n=46$								
Pre-treatment	60.8±13.7	66.8±12.2	58.5±13.7	75.2±17.4	39.6±15.9	53.2±18.6	12.9±7.2	57.3±18.9
Post-treatment	61.2±13.9	70.2±14.2	63.8±15.9	71.1±16.2	41.8±17.1	55.8±22.3	12.1±6.4	53.1±17.7
Observation group $n=49$								
Pre-treatment	61.4±15.5	69.5±13.6	57.2±18.1	73.5±12.6	40.2±17.9	55.4±21.2	13.2±6.9	55.3±13.7
Post-treatment	63.7±15.3	68.1±17.8	71.3±15.2 ^{*△}	75.0±14.3	40.4±17.3	46.6±16.9 ^{*△}	12.2±6.6	44.6±17.1 ^{*△}
Group	Dyspnoea	Insomnia	Appetite loss	Constipation	Diarrhoea	Financial difficulties	General health	
Control group $n=46$								
Pre-treatment	7.6±7.1	62.2±13.8	56.8±14.2	55.6±17.8	38.9±12.3	58.4±23.5	34.1±17.4	
Post-treatment	8.3±7.2	63.2±14.4	54.8±15.9	58.8±16.4	34.6±15.5	69.1±15.6 [△]	42.5±16.4 [△]	
Observation group $n=49$								
Pre-treatment	8.5±5.6	65.3±17.9	55.6±12.3	60.3±13.2	34.2±17.1	60.2±20.4	38.6±14.3	
Post-treatment	8.9±6.7	57.6±14.6 [△]	55.8±16.3	59.8±20.3	37.1±18.2	70.3±19.9 [△]	49.6±13.8 ^{*△}	

Observation group: The patients received oral *Houpo Tongbi* decoction combined with pirarubicin intravesical chemotherapy; Control group: The patients received pirarubicin intravesical chemotherapy. ^{*} $P < 0.05$ vs the control group post-treatment; [△] $P < 0.05$ vs the same group pre-treatment. NMIBC: Non-muscle-invasive bladder cancer; QLQ-C30: Quality of life questionnaire core 30.

表 3 两组 NMIBC 患者术后辅助治疗 1 年后 QLQ-BLS24 评分比较

Tab 3 Comparison of QLQ-BLS24 scores in NMIBC patients between 2 groups 1 year after postoperative adjuvant treatment

Group	Urinary symptoms	Treatment issues	Flatulence	Future worries	$\bar{x} \pm s$
					Sexual function
Control group $n=46$					
Pre-treatment	55.6 ± 18.9	64.4 ± 18.7	10.1 ± 6.6	68.7 ± 17.9	17.2 ± 8.5
Post-treatment	61.3 ± 18.8	63.4 ± 17.9	13.9 ± 6.4	70.0 ± 16.7	16.9 ± 7.4
Observation group $n=49$					
Pre-treatment	51.1 ± 16.8	65.5 ± 23.1	11.1 ± 6.9	72.3 ± 12.1	16.9 ± 10.3
Post-treatment	49.9 ± 17.3*	66.9 ± 14.3	11.6 ± 8.3	69.5 ± 15.8	18.1 ± 11.2

Observation group: The patients received oral *Houpo Tongbi* decoction combined with pirarubicin intravesical chemotherapy; Control group: The patients received pirarubicin intravesical chemotherapy. * $P < 0.05$ vs the control group post-treatment. NMIBC: Non-muscle-invasive bladder cancer; QLQ-BLS24: Quality of life superficial bladder cancer-specific 24.

2.5 两组患者尿常规指标比较 术后经过 1 年的辅助治疗, 两组患者的尿白细胞、红细胞、蛋白水平与治疗前相比差异均无统计学意义 ($P > 0.05$)。治疗后观察组患者的尿白细胞、红细胞

水平与对照组相比差异亦无统计学意义 ($P > 0.05$)，但尿蛋白水平低于对照组 ($P < 0.05$)。见表 4。

表 4 两组 NMIBC 患者术后辅助治疗 1 年后尿常规指标比较

Tab 4 Comparison of urine routine indexes of NMIBC patients between 2 groups 1 year after postoperative adjuvant treatment

Index	Control group $N=46$					Observation group $N=49$					Z value	P value
	-	+	++	+++	++++	-	+	++	+++	++++		
White blood cell												
Pre-treatment	40	4	2	0	0	41	6	2	0	0	-0.423	0.672
Post-treatment	36	7	1	1	1	43	3	2	0	1	-1.167	0.243
Red blood cell												
Pre-treatment	39	2	1	4	0	37	9	1	0	2	-0.940	0.347
Post-treatment	37	3	1	3	2	43	6	0	0	0	-1.180	0.238
Protein												
Pre-treatment	40	3	2	0	1	44	2	1	2	0	-0.402	0.688
Post-treatment	37	3	3	2	1	46	2	1	0	0	-2.033	0.042

Observation group: The patients received oral *Houpo Tongbi* decoction combined with pirarubicin intravesical chemotherapy; Control group: The patients received pirarubicin intravesical chemotherapy. NMIBC: Non-muscle-invasive bladder cancer.

2.6 两组患者血常规和肝肾功能比较 术后经过 1 年的辅助治疗, 两组患者的血常规和肝肾功能指标与治疗前相比差异均无统计学意义 ($P > 0.05$)，且均处于正常参考值范围内。治疗后观察组患者的外周血白细胞计数低于对照组, 差异有统计学意义 ($P < 0.05$)；两组患者血红蛋白和血小板计数差异均无统计学意义 ($P > 0.05$)。治疗后观察组患者丙氨酸转氨酶水平低于对照组, 差异有统计学意义 ($P < 0.05$)；其余各项肝肾功能指标在两组间差异均无统计学意义 ($P > 0.05$)。见表 5。

2.7 两组患者不良反应发生情况比较 在随访期间, 观察组 18 例 (36.73%) 患者发生不良事件, 其中 9 例 (18.37%) 发生膀胱刺激征, 7 例 (14.29%) 发生血尿, 2 例 (4.08%) 发生尿道狭窄。对照组 28 例 (60.87%) 患者发生不良事件, 其中 13 例 (28.26%) 出现膀胱刺激征, 11 例 (23.91%) 出现血尿, 4 例 (8.70%) 出现尿道狭窄。观察组总不良事件发生率低于对照组, 差异有统计学意义 ($P < 0.05$)。

表 5 两组 NMIBC 患者术后辅助治疗 1 年后血常规和肝肾功能指标比较

Tab 5 Comparison of blood routine and liver and kidney function indexes of NMIBC patients between 2 groups 1 year after postoperative adjuvant treatment

Group	$\bar{x} \pm s$				
	WBC/(L ⁻¹ , ×10 ⁹)	Hemoglobin/(g·L ⁻¹)	Platelet/(L ⁻¹ , ×10 ⁹)	ALT/(U·L ⁻¹)	AST/(U·L ⁻¹)
Control group n=46					
Pre-treatment	6.02 ± 1.59	134.10 ± 13.26	193.90 ± 62.32	28.13 ± 17.01	23.76 ± 10.04
Post-treatment	6.03 ± 1.18	132.30 ± 14.96	177.30 ± 45.90	29.31 ± 11.07	23.10 ± 6.27
Observation group n=49					
Pre-treatment	5.70 ± 1.33	135.60 ± 13.03	205.60 ± 36.51	25.14 ± 9.39	21.08 ± 5.51
Post-treatment	5.44 ± 0.68*	134.00 ± 9.75	192.90 ± 43.87	23.72 ± 9.05*	21.22 ± 4.53
Group	Creatinine/(μmol·L ⁻¹)	Urea/(mmol·L ⁻¹)	Uric acid/(μmol·L ⁻¹)	Bilirubin/(μmol·L ⁻¹)	
Control group n=46					
Pre-treatment	71.90 ± 24.53	5.56 ± 1.26	357.10 ± 74.56	12.89 ± 4.71	
Post-treatment	72.83 ± 32.22	5.31 ± 1.33	362.30 ± 64.51	12.57 ± 4.30	
Observation group n=49					
Pre-treatment	69.56 ± 17.50	5.61 ± 1.20	365.10 ± 69.25	11.68 ± 4.37	
Post-treatment	69.65 ± 14.83	5.26 ± 1.51	373.10 ± 88.27	12.71 ± 4.12	

Observation group: The patients received oral *Houpo Tongbi* decoction combined with pirarubicin intravesical chemotherapy; Control group: The patients received pirarubicin intravesical chemotherapy. *P<0.05 vs the control group post-treatment. NMIBC: Non-muscle-invasive bladder cancer; WBC: White blood cell; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

3 讨论

膀胱癌是泌尿系统中发病率最高的恶性肿瘤, 其危险因素包括高龄、男性、吸烟等^[20]。作为高复发率的肿瘤, 膀胱癌病死率居所有恶性肿瘤的第 13 位^[21]。根据现有的研究结果, 接受单药腔内化学治疗的患者复发率低于只接受 TURBT 手术的患者, 但 5 年复发率仍然很高, 约为 44.8%^[10]。吡柔比星是一种常用的蒽环类化学治疗药物, 通过下调细胞中的存活蛋白 (survivin) 基因表达、增强 caspase 3 活性以促进肿瘤细胞凋亡, 起到抑制膀胱癌细胞的作用^[22-23]。与核苷同系物吉西他滨相比, 患者对吡柔比星的反应率更高, 且使用吡柔比星进行膀胱灌注化学治疗患者的中位总生存期更长^[24]。接受吡柔比星膀胱灌注化学治疗与 TURBT 联合治疗的膀胱癌患者比单纯行 TURBT 治疗的患者肿瘤复发率显著降低^[25], 故吡柔比星作为一线膀胱灌注化学治疗药物被广泛接受。单纯性辅助化学治疗往往遵循一级动力学原理, 不能杀死所有肿瘤细胞, 因此术后辅助治疗不仅需要依靠化学药物, 还需联合其他治疗方法。既往研究表明, 预灌注肿瘤细胞来源的微粒 (tumor cell-derived microparticle) 可通过多种途径提高膀胱内化学治疗的疗效^[26]。中药如姜黄素等对膀胱癌的治疗有

积极作用^[27-28], 应考虑将中药作为膀胱癌术后辅助治疗的措施。

国医大师张镜人教授认为膀胱癌多由于湿浊下注膀胱, 气化不利, 与瘀血蕴而生热成毒所致, 乃本虚标实之证。脾肾亏虚是本, 贯穿膀胱癌的始终, 湿热下结膀胱、络阻化火生毒、血脉受损为标, 本虚标实处于动态变化之中^[29]。厚朴通闭汤方中厚朴运脾燥湿导滞以绝浊毒之源, 为君药; 黄芪、白术、女贞子健脾益肾, 补虚以固本, 土茯苓、车前子清热利湿, 以化浊, 共为臣药; 生地黄、赤芍、白茅根养阴清热, 宁络以止血, 蒲公英、苦参、龙葵、蛇舌草清热解毒, 甘草梢清热兼以调和诸药, 共为佐使药。全方补泄并用, 气血通调, 共奏扶正祛邪之功, 适合膀胱癌术后患者使用。

现代药理学研究证实, 厚朴的有效成分和厚朴酚可通过抑制 zeste 基因增强子同源物 2 (enhancer of zeste homolog 2, EZH2) /miRNA-143 信号通路实现对膀胱癌细胞的杀伤作用^[30]; 和厚朴酚可通过抑制类固醇受体共激活因子 3 (steroid receptor coactivator-3, SRC-3) 及其下游靶基因, 抑制膀胱癌细胞发生上皮间质转化 (epithelial-mesenchymal transition, EMT), 从而发挥抗肿瘤作用^[31]。和厚朴酚还可诱导上皮钙黏素 (E-cadherin) 的表达, 同时抑制神经钙黏素 (N-cadherin) 的表达, 进而

抑制膀胱癌细胞发生 EMT^[31-32]。EMT 是肿瘤发生、进展及转移的重要环节,包括上皮标志物的丢失和间质标志物的表达,目前认为 EMT 是一个动态过程^[33-34]。厚朴通闭汤可能通过以上机制抑制 EMT 过程,从而发挥抗肿瘤作用。

本研究旨在探讨中西医结合治疗 NMIBC 的疗效和安全性,明确中西医结合治疗 NMIBC 的价值。在疗效方面,膀胱癌术后患者经过 1 年的辅助治疗后观察组患者的复发率低于(18.37%, 9/49)低于对照组(36.96%, 17/46),表明联合使用厚朴通闭汤辅助治疗可起到抑制肿瘤复发的作用。观察组患者的整体中医证候改善率(79.59%, 39/49)高于对照组(41.30%, 19/46),说明此方有助于改善患者的中医证候。观察组患者多项生活质量指标更佳,情绪功能和总健康状况得分均高于对照组,疲倦、疼痛及尿路症状等负面指标得分均低于对照组。尽管随着治疗时间的延长两组患者均出现了经济负担加重的情况,但观察组患者的总体生活质量高于对照组,说明长期服用厚朴通闭汤辅助治疗可以达到改善生活质量的效果。

在安全性方面,观察组患者的总体不良事件发生率(36.73%, 18/49)低于对照组(60.87%, 28/46),提示厚朴通闭汤可减轻吡柔比星膀胱灌注化学治疗造成的不良反应。观察组患者总体表现出更低的尿蛋白水平,表明厚朴通闭汤可能起到减轻炎症刺激或减少蛋白排泄的作用,其具体机制有待进一步研究。观察组和对照组患者的血常规和肝肾功能指标在治疗前后均无明显差异,虽然观察组白细胞计数和丙氨酸转氨酶水平低于对照组,但两组所有指标均处于正常参考值范围内,说明联合使用厚朴通闭汤不会对患者造成骨髓抑制或肝肾功能损害等不良影响。

综合以上各项结果可见,厚朴通闭汤联合吡柔比星膀胱灌注化学治疗比单纯使用吡柔比星膀胱灌注化学治疗能够减少 NMIBC 患者 TURBT 术后肿瘤复发,改善中医证候和总体生活质量,减轻蛋白尿的同时降低不良事件发生率,具有较高的安全性,且不会对身体造成额外的负担。

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