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清肺散结丸与长春瑞滨和顺铂联用对晚期非小细胞肺癌的疗效观察 *

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摘要 目的：观察清肺散结丸与长春瑞滨（vinorelbine, NVB）和顺铂（cisplatin, DDP）联合治疗晚期非小细胞肺癌的近期疗效及毒副作用，为临床用药提供参考。**方法**：选取 2010 年 11 月 -2012 年 3 月我院收治的晚期非小细胞肺癌患者 146 例，随机分为对照组和联合组，每组各 73 例。对照组常规给予长春瑞滨和顺铂（NP 方案）治疗，联合组在对照组基础上加以清肺散结丸治疗。观察两组患者的客观有效率、疾病控制率、生活质量改善率和毒副反应的发生情况。**结果**：对照组患者的客观有效率为 42.5%，联合组为 46.6%，差异无统计学意义（P>0.05）；联合组疾病控制率为 85.0%，明显高于对照组的 65.8%(P<0.05)；联合组生活质量改善情况为 68.5%，明显高于对照组的 41.1%(P<0.05)；联合组Ⅱ度以上白细胞减少的发生率为 54.8%，对照组为 75.3%；联合组Ⅲ度以上白细胞减少的发生率为 17.8%，对照组为 37.0%，差异显著具有统计学意义(P<0.05)；联合组恶心呕吐的发生率为 24.7%，显著优于对照组的 49.3%(P<0.05)。**结论**：NP 方案联用清肺散结丸治疗晚期 NSCLC 能够使患者获益并提高患病期间生活质量，降低骨髓移植和消化系统毒副反应发生。

关键词：清肺散结丸；顺铂；长春瑞滨；非小细胞肺癌

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Effect of Qingfeisanjie Capsule Combined with Cisplatin and Vinorelbine on the Treatment of Advanced Non-small Cell Lung Cancer*

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ABSTRACT Objective: To investigate the clinical effects and adverse reactions of Qingfeisanjie capsule combined with Cisplatin and vinorelbine on the treatment of advanced non-small cell lung cancer in order to provide some references for the clinical research. **Methods:** 146 patients with the advanced NSCLC who were treated in our hospital from November 2010 to March 2012 were selected and randomly divided into the control group and the combination group with 73 cases in each group. The patients in the control group were treated by the conventional method of Cisplatin and Vinorelbine, while the patients in the combination group were treated by Qingfeisanjie capsule combined with Cisplatin and Vinorelbine. Then the response rate, disease control, improvement of life quality and the incidence of adverse reactions were observed and compared between two groups. **Results:** The response rate of the control group was 42.5%, and 46.6% in combination group with no significant difference. The disease control of the combination group was 85.0% which was higher than 65.8% of the control group (P<0.05); The improvement of life quality in the combination group was 68.5% which was higher than 41.1% of the control group (P<0.05); The reduction of Ⅱ-Ⅳ leukopenia in the combination group was 54.8% which was better than 75.3% in the control group, and the reduction of Ⅲ-Ⅳ leukopenia in the combination group was 17.8% which was better than 37.0% in the control group with statistically significant differences (P<0.05); The incidence of nausea and vomiting in combination group was 24.7% which was lower than 49.3% in the control group (P<0.05). **Conclusion:** Qingfeisanjie capsule could help the patients with advanced NSCLC to improve the life quality and reduce the adverse reactions.

Key words: Qingfeisanjie capsule; Cisplatin; Vinorelbine; Non-small Cell Lung Cancer

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肺癌(Lung cancer)是我国高发病率及高致死率的恶性肿瘤之一。随着医疗卫生水平的提高,肺癌预后较以往得到一定的改善,但其五年生存率仍徘徊于40%。非小细胞肺癌(Non-small cell lung cancer, NSCLC)约占肺癌的75%~80%[1],其中60%~70%的患者在确诊时已属晚期,错失最佳治疗时机。晚期肺癌患者中位生存时间仅为5~6个月,1年生存率仅10%[2]。目前,晚期非小细胞肺癌的治疗方案以化疗为主。长春瑞滨联合顺铂(NP)作为晚期NSCLC患者的一线化疗方案广泛应用于临床[3],但严重的消化道、骨髓移植等毒副反应在一定程度上限制其临床效果[4-6]。寻求高效、低毒的化疗方案的同时,减轻毒副反应、提高疗效显得尤为重要。近年来,中药配伍化疗的研究进展显示,此类联用能够改善化疗带来的不良反应,提高患者的生活质量,并在一定程度上提高疗效[7-9]。本文通过观察我院应用清肺散结丸联合长春瑞滨及顺铂治疗晚期非小细胞肺癌的近期疗效、生活质量的改善及对毒副反应的影响,以探讨其临床应用价值。

1 资料与方法

1.1 一般资料

选取我院2010.11~2012.03收治的晚期非小细胞肺癌患者146例。纳入标准:①入院时经胸部CT、细胞学和病理学检查确诊;②有客观评价指标(影像检查病灶≥ 1 cm,体检病灶≥ 2 cm);③预计生存期≥ 3个月;④Kamofsky评分> 70分;⑤全部为初次化疗或一个月内未使用抗癌药。排除标准:①无影像学及病理明确诊断或不符合晚期NSCLC患者;②心、肝、肾等主要脏器功能异常或不全;③精神状态异常;④非自愿参加本研究者。化疗前及化疗3周后予以胸片或CT检查,并行腹部B超、γ核素扫描、血常规、肝肾功能检查,以明确临床分期及作为疗效评定的依据。严格按照以上标准,共有158例Ⅲb期及Ⅳ期NSCLC患者入选,其中146例可评价疗效。所选患者随机分为联合组(清肺散结丸+NP方案)与对照组(NP方案)。两组患者的年龄、性别、病理类型和分期等一般资料无显著差异,具有可比性。所有患者均知情同意。见表1。

表1 两组患者的临床资料

Table 1 Clinical Characteristics of patients in two groups

	Control Group	Combination Group
Gender		
Male	40	57
Female	33	16
Median Age	51(38~66)	55(44~68)
Histological Grade		
Squamous carcinoma	36	40
Adenocarcinoma	33	28
Adenosquamous carcinoma	4	3
Large cell carcinoma	0	2
Clinical stage		
Ⅲb	24	33
Ⅳ	49	40

1.2 治疗方案

对照组:第1天、第8天NVB 25 mg/m^{2}加生理盐水40 ml静推6~10 min;第1~3天DDP 30 mg/m^{2}加生理盐水500 ml静滴,每三周为1个周期,共3个周期。NVB每次给药后以生理盐水100 ml加入地塞米松10 mg冲洗,以减轻对血管壁刺激及静脉炎的发生。

联合组:在对照组NP方案的基础上给予口服清肺散结丸,1次3 g,2次/天,1个月为一疗程,并保证连续治疗不少于3个疗程。

1.3 疗效及毒副反应评价

观察各组患者的近期疗效,采用WTO统一评价标准:完全缓解(CR)、部分缓解(PR),病情稳定(SD)和病情进展(PD);客观有效率(RR)=(CR+PR)/病例数× 100%;疾病控制率(DC)=(CR+PR+SD)/病例数× 100%;生活质量以Kamofsky评分标准予以评价,治疗后Kamofsky评分增加大于20分认为生活质量显著改善;增加10-20分认为生活质量得到改善;前后评分增加或减少值<10分为稳定;评分减少或超过10分认为生活质量下降;生活质量改善率=(显著改善+改善)/病例数× 100%;毒性评价参考WHO抗癌药物急性与亚急性毒性标准分为0~Ⅳ度。观察两组白细胞和血小板数目、肝功能损害和胃肠道反应等。

1.4 统计学方法

采用SPSS14.0软件进行统计分析。计数资料采用卡方检验,计数等级资料采用秩合检验,所有检验均为双侧检验,以$P<0.05$为差异具有统计学意义。

2 结果

2.1 两组患者的近期疗效比较

对照组完全缓解2例,部分缓解29例,病情稳定17例,病情进展25例,客观有效率为42.5%,疾病控制率为65.8%,中位缓解期为5.0个月;联合组完全缓解1例,部分缓解33例,病情稳定28例,病情进展11例,客观有效率为46.6%,疾病控制率为85.0%,中位缓解期为5.5个月。对比两组客观有效率,差异无统计学意义($P>0.05$);比较两组疾病控制率,差异显著具有统计学意义($P<0.05$)。见表2。

表 2 两组患者的疗效比较

Table 2 Comparison of clinical effects of patients between two groups

	Cases	CR	PR	SD	PD	Response	Disease control	Medium response
Control Group	73	2	29	17	25	42.5%	65.8%	5.0
Combination Group	73	1	33	28	11	46.6%	85.0%	5.5

2.2 生活质量改善情况对比

对照组生活质量改善率为 41.1%,联合组为 68.5%,联合组比对照组改善显著(P<0.05)。见表 3。

表 3 两组生活质量改善情况比较

Table 3 Comparison of improvement of life quality between two groups

	Case	Significant improvement	Improvement	Stable	Downgrade	Rate
Control Group	73	10	20	34	9	41.1%
Combination Group	73	21	29	19	4	68.5%

2.3 毒副反应比较

研究中观察了各组白细胞减少、血小板减少、贫血、恶心呕吐及肝功能异常等指标。对照组与联合组Ⅱ度以上白细胞减少发生率分别为 75.3%和 54.8%,差异显著(P<0.05);Ⅲ度以上白细胞减少发生率为 37.0%和 17.8%,差异显著(P<0.05)。此外,对照组和联合组恶心呕吐的发生率分别为 49.3%和 24.7%, 联合组显著低于对照组恶心呕吐的发生率(P<0.05)。见表 4。

表 4 两组化疗不良反应比较

Table 4 Comparison of the major toxicity of patients between two groups

	Combination Group(n=73)					Control Group(n=73)				
	0	Ⅰ	Ⅱ	Ⅲ	Ⅳ	0	Ⅰ	Ⅱ	Ⅲ	Ⅳ
Leukopenia	12	21	27	13	0	2	16	28	24	3
Thrombocytopenia	61	7	5	0	0	62	8	3	0	0
Anemia	66	3	4	0	0	65	6	1	1	0
Nausea and vomiting	55	11	7	0	0	37	18	15	3	0
Dysfunction of liver	70	2	1	0	0	69	3	1	0	0

3 讨论

含铂药物作为治疗 NSCLC 的一线药物, 单药有效率在 16%~20%,而以铂类药物为基础的化疗方案往往能显著改善患者生存期。既往研究表明三药联合并不好于铂类药物为基础的两药联合,且有更为严重的毒副反应[10,11]。中医认为,肺为娇脏,易受邪毒侵袭,致使肺气肃降失司,郁滞不宣,脉络不畅,气血瘀滞,毒瘀互结,久而形成肿块[12]。因此,肺癌的发生与正气虚损和邪毒入侵关系密切。正气内虚,脏腑阴阳失调,是罹患肺癌的基础[13,14]。清肺散结丸在肺癌治疗中能够针对正气缺虚而进行益气补血、扶正祛邪及平衡脏腑阴阳,从患者整体予以调整,提高机体抗癌能力与适应力。此外,清肺散结丸可激发机体细胞免疫与体液免疫功能、保护造血系统,能够显著改善患者生活质量。对于化疗药物而言,多药联合往往弊大于利,难以耐受的骨髓抑制及消化系统症状常导致患者不得不降低药物剂量或停药或改用其他治疗方案,严重影响患者的预后情况[15-17]。清肺散结丸为中成药,主要成分包括灵芝、冬虫夏草、阿胶、绞股蓝浸膏、苦玄参浸膏、川贝母、珍珠、法半夏、牛黄等 11 味中药,主要功效为:扶正祛邪、活血化瘀、清热解毒、温阳化湿、化痰,提高机体免疫功能作用。其药物自身毒副作用低,且还可通过中药的调理作用,保护机体在接受大剂量化疗时免受或少受化疗药物带来的不良反应。

本研究发现, 清肺散结丸在联合 NP 方案对晚期 NSCLC 患者进行治疗时,其Ⅱ度以上白细胞减少发生率显著低于对照组(单独 NP 方案)(54.8% vs.75.3%, P<0.05);而Ⅲ度以上的白细胞减少发生率同样优于对照组(17.8% vs. 37.0%, P<0.05);此外对恶心呕吐的发生率控制,联用清肺散结丸组也占有显著优势(24.3% vs. 49.7%, P<0.05)。结果证实,清肺散结丸在控制铂类药物为基础的两药联合化疗导致的骨髓移植及消化系统毒副作用中具有较好的作用。根据 Kamofsky 评分评价两组患者的生活质量改善情况,我们发现联用清肺散结丸的患者比对照组患者的生活质量改善更为明显。我们对比两组患者的客观有效率无显著差异,结果说明是否联用清肺散结丸对客观有效率没有影响,且两组的中位缓解期差异也不显著(5.0 vs. 5.5);联用联合组的疾病控制率优于对照组(65.8% vs. 85.0%, P<0.05)。我们认为,虽然清肺散结丸与长春瑞滨及顺铂联用对患者远期预后没有明显作用,但可提高患病期间的生活质量及自身机体的免疫功能,在一定程度上抵抗了肿瘤的进展及扩散。

目前,针对中药联用传统化疗方案治疗肺癌的研究已逐步展开并获得了一定成果,王婉茹[18]等以艾迪注射液(成分包括

黄芪、人参、斑蝥及刺五加等）治疗晚期 NSCLC，有效率为63.3%显著高于化疗组 36.7%（P<0.05）。陆红[19]等以香菇多糖注射液治疗晚期 NSCLC，结果显示试验组 $CD3^+$、$CD4^+$ 及 $CD3^+/CD4^+$ 变化值均高于对照组，差异具有统计学意义。蔡美[20]等在观察中药益肺饮对老年晚期非小细胞肺癌患者的临床疗效中发现，其能明显改善患者的临床症候，提高生活质量，稳定流涕，且毒副反应轻，耐受性较好。综上所述，中药辅助化疗往往能给临床肿瘤医生提供独特的视野，以低廉的成本和毒性负担换取较为显著的疗效及生存质量的改善，这将是抗肿瘤药物未来的前进方向，而大规模、多中心的随机双盲对照试验仍是其未来研究的重心。但目前此类药物应用于临床并获得成功的文献报道并不多，我们需要在今后的临床实践中进一步证实，研究出更多可提高肺癌治疗效果的中药来辅助化疗，使患者更加受益。

参 考 文 献（References）

[1] 宋恕平，梁军，苗志敏.中国临床肿瘤教育专辑（2005）[M]. 青岛：中国海洋出版社,2005:111
Zhou Shu-ping, Liang Jun, Miao Zhi-min. Chinese clinical oncology education album(2005)[M]. Qingdao: China Ocean Press,2005:111

[2] Aiqin GU, Chunlei SHI, Liwen XIONG, et al. Efficacy and safety evaluation of icotinib in patients with advanced non-small cell lung cancer[J]. Chinese Journal of Cancer Research,2013,25(1):90-94

[3] Belani CP, Schreeder MT, Steis RG, et al. Cetuximab in combinationwith carboplatin and docetaxel for patients with metastatic or advanced stage nonsmall cell lung cancer: a multicenter phase 2 study[J]. Cancer, 2008, 113(9): 2512-2517

[4] Cortes J, Rodriguez J, Calvo E, et al. Paclitaxel, cisplatin, and vinorelbine combination chemotherapy in metastatic non-small-cell lung cancer[J]. Am J Clin Oncol, 2004,27(3):299-303

[5] Stewart DJ, Tomiak E, Shamji FM, et al. Phase II study of alternating chemotherapy regimens for advanced non-small cell lung cancer[J]. Lung Cancer, 2004,44(2):241-249

[6] CHANG JW, Tsao TC, YANG CT, et al. A randomized study of gemcitabine plus cisplatin and vinorelbine plus cisplatin in patients with advanced non-small-cell lung cancer [J]. Chang Gung Med J, 2008,31(6):559-566

[7] LI DY, YU TT, BAI H, et al. Clinical study on effect of compound granule prescription of thunberg fritillary bulb in relieving post-chemotherapy bone marrow suppression in RAL patients [J]. China Journal of Chinese Materia Medica,2012,37(20):3155-3157

[8] LO LC, CHEN CY, CHEN ST, et al. Therapeutic efficacy of traditional Chinese medicine, Shen-Mai San, in cancer patients undergoing chemotherapy or radiotherapy: study protocol for a randomi zed, double-blind, placebo-controlled trial[J]. Trials,2012,13:232

[9] XU L, LI H, XU Z, et al. Multi-center randomized double-blind controlled clinical study of chemotherapy combined with or without traditional Chinese medicine on quality of life of postoperative non-small cell lung cancer patients [J]. BMC Complement Altern Med,2012,12:112

[10] Rosati G, Rossi A, Nicolella G, et al. Second-line chemotherapy with paclitaxel, cisplatin and gemcitabine in pre-treated sensitive cisplatin-based patients with advanced non-small cell lung cancer[J]. Anticancer Res,2000,20(3B):2229-2233

[11] Comella P, Frasci G, Panza N, et al. Randomized trial com paring cisplatin, gemcitabine, and vinorelbine with either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non-small-cell lung cancer: interim analysis of a phase III trial of the Southern Italy Cooperative Oncology Group[J]. J Clin Oncol,2000,8(7):1451-1457

[12] 杨咏梅，梁久菊. 中医疗法治疗 68 例支气管肺癌临床分析 [J]. 中医临床研究,2012,4(11):61-62
Yang Yong-mei, Liang Jiu-ju. Clinical analysis of treating 68 cases of lung cancer in TCM[J]. Clinical Journal of Chinese Medicine, 2012,4 (11):61-62

[13] 邵丽，邹勇. 中医药治疗肺癌的研究进展[J]. 中国中医药现代远程教育, 2013,11(2):164-165
Shao Li, Zou Yong. Research progress of Chinese medicine in treat with lung cancer [J]. Chinese Medicine Modern Distance Education Of China, 2013,11(2):164-165

[14] 单建国，李平，苏丽，等. 中医对晚期肺癌的认识及治疗现状 [J].中医药临床杂志,2013, 25(2):186-188
Shan Jian-guo, Li Ping, Su Li, et al. Knowledge and treatment of advanced lung cancer in traditional Chinese medicine [J]. Clinical Journal of Traditional Chinese Medicine,2013,25(2):186-188

[15] 陈声池，张长其，陈映雪. 热疗联合长春瑞滨和顺铂方案治疗晚期非小细胞肺癌临床疗效[J]. 中国肿瘤防治杂志,2008, 15(10): 778-779
Chen Sheng-chi, Zhang Chang-qi, Chen Ying-xue. Vinorelbine and DDP combined with hyperthermia in the treatment of advanced non-small cell lung cancer [J]. Chinese Journal of Cancer Prevention and Treatment,2008, 15(10): 778-779

[16] WANG J, LIU F, HUANG DX, et al. Post-operative treatment with cisplatin and vinorelbine in Chinese patients with non-small cell lung cancer: a clinical prospective analysis of 451 patients [J]. Asian Pac J Cancer Prev,2012,13(9):4505-4510

[17] JIANG Y, LIU LS, LI CJ. Effect of Chinese medicine comprehensive regimen as the maintenance therapy on time to progression and quality of life of patients with advanced non-small-cell lung cancer[J]. Chinese Journal Of Integrated Traditional And Western Medicine, 2011,31(10):1311-1316

[18] 王婉茹. 艾迪注射液联合 NP 化疗治疗晚期非小细胞肺癌临床观察[J].辽宁中医药大学学报,2008, 10(2): 125-126
Wang Wan-ru. Clinical evaluation of Aidi injection combined with cisplatin and vinorelbine chemotherapy for advanced non-small cell lung cancer [J]. Journal of Liaoning Medical University, 2008, 10 (2): 125-126

[19] 陆红，王淑琴，张祥梅. 香菇多糖注射液联合 NP 方案治疗晚期非小细胞肺癌 63 例临床分析[J].新疆医科大学学报,2008,31(1):92-93
Lu Hong, Wang Shu-qin, Zhang Xiang-mei. Clinical analysis of Lentinas combined with cisplatin and vinorelbine chemotherapy in the treatment of 63 cases with advanced non-small cell lung cancer[J]. Journal of Xinjiang University,2008,31(1):92-93

[20] 蔡美，田莹，宁鹤丽. 中药益肺饮与化疗治疗老年晚期非小细胞肺癌的临床对比观察[J]. 湖南中医药大学学报, 2013,33(3):65-68
Cai Mei, Tian Ying, Ning He-li. Comparative study of clinical effects of Yifei Decoction and chemotherapy on elderly non-small-cell lung cancer patients in advanced stage [J]. Journal of Traditional Chinese Medicine University of Hunan, 2013, 33(3):65-68