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复方苦参注射液对放疗肺损伤的临床疗效及安全性观察*

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摘要 目的:探究复方苦参注射液对放疗性肺损伤防护作用及安全性。**方法:**选取我院胸外科收治的肺癌患者 112 例,随机分为两组,其中对照组 57 例,予常规单纯放疗治疗;实验组 55 例,在常规放疗治疗的同时加用复方苦参注射液 5 mL,溶于 0.9% 氯化钠注射液 250 mL,日一次静滴,至放疗结束。治疗结束后对比后两组患者放射性肺炎的比率、放射性肺纤维化比率及血浆 TGF- β 1 和 TNF- α 值。**结果:**①放疗治疗前两组血浆 TGF- β 1 和 TNF- α 值无明显差异,无统计学意义($P>0.05$),放疗治疗后实验组血浆 TGF- β 1 和 TNF- α 值较对照组明显下降,差异有统计学意义($P<0.05$),肺纤维化比率较对照组明显减低,差异有统计学意义($P<0.05$);②放疗治疗后实验组放射性肺炎的比率明显低于对照组,差异有统计学意义($P<0.05$);**结论:**复方苦参注射液够明显预防由于放射性治疗带来的肺损伤,对临床具有指导意义,值得临床推广。

关键词:苦参;放疗性肺损伤;转化生长因子- β 1;肿瘤坏死因子- α

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Clinical Efficacy and Safety of Fufangkushen Injection on Radiation-induced Lung Injury*

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ABSTRACT Objective: To explore the protective role of Fufangkushen injection on radiation-induced lung injury and its safety.

Methods: 112 lung cancer patients admitted to the Department of Thoracic Surgery in our hospital were selected and were randomly divided into two groups. 57 patients in control group received conventional radiotherapy and treatment; 55 cases in the experimental group were treated in the conventional radiotherapy combined with Compound Kushen injection 5 mL, dissolved in 0.9% Sodium Chloride Injection 250 mL intravenous drip, once a day, to the end of radiotherapy. Ratios of radiation pneumonitis, radiation pulmonary fibrosis ratio and plasma TGF- β 1 and TNF- α value were compared between the two groups after treatment. **Results:** TGF- β 1 and α values had no significant differences between the two groups before treatment, with no statistical significance ($P>0.05$); after radiotherapy, TGF- β 1 and TNF- α plasma TNF-decreased significantly in the experimental group, compared with that in the control group, and the difference was statistically significant ($P<0.05$); what's more, ratio of lung fibrosis, compared with that in the control group, decreased significantly, and there were statistically significant differences ($P<0.05$); after radiotherapy, ratio of radioactive pneumonia was in the experimental group was significantly lower than that in the control group, and the difference was statistically significant. **Conclusions:** Fufangkushen injection is effective in protecting the patients against radiation-induced lung damage, and it is worthy of clinical promotion.

Key words: Fufangkushen injection; Radiation-induced lung damage; TGF- β 1; TNF- α

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前言

放射性肺损伤是指放射线治疗胸部恶性肿瘤后,引起肺组织损伤的非感染性炎症反应,是胸部恶性肿瘤放射治疗中最常见、最重要的毒副反应。放疗性肺损伤包括早期的放射性肺炎和晚期的放射性肺纤维化,放射性肺炎一般在放疗结束后 1-3 个月发生,而放射性肺纤维化出现在放疗结束后 6 个月^[1]。由于放射性肺损伤为放疗治疗的迟发反应,一旦发生往往不可逆

转,严重时甚至加速患者的死亡。因此,研究放射性肺损伤的发病机制及其有效地防治方法对于肿瘤的放射治疗具有重要意义^[2]。中医无放疗性肺损伤这一病名,属"咳嗽"、"肺痿"、"喘证"等范畴。随着世界医疗技术的发展,人们更加重视疾病的防治及预后,然而对于本病,目前尚无有效的治疗和预防的方法。临床多采用抗生素配合糖皮质激素治疗,但不良反应较多,降低了患者的生活质量^[3]。研究发现^[4,5]:中药苦参碱具有抗炎、抗氧化、抗肿瘤、抗纤维化、抗心律失常、镇静、镇痛及免疫调节

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等方面的药物活性,尤其是在治疗组织纤维化方面发挥重要作用,受到诸多学者地关注。本研究在肺癌患者放疗治疗的同时应用中药复方苦参注射液,观察放疗结束后患者放射性肺炎发生的比率,放射性肺纤维化发生的比率及放疗结束后患者血浆 TGF- β 1 和 TNF- α 值,来探究复方苦参注射液对放疗肺损伤的防护效果,现报道如下。

1 资料与方法

1.1 一般资料

选取 2012 年 12 月至 2013 年 10 月与我院以原发性肺癌为诊断而收入院患者者 112 例,均经细胞学或者病理学确诊,根据 1997 年 UICC 新修订的肺癌 TNM 分期,分期为Ⅱ期-Ⅲ期,卡氏评分在 60 分以上。采用随机数字表分为实验组和对照组。实验组 55 例,其中男 48 例,女 8 例,平均年龄 59.12 ± 8.37 岁,鳞癌 27 例,腺癌 13 例,小细胞癌 11 例,大细胞癌 6 例;对照组 57 例,其中男 46 例,女 10 例,平均年龄 58.94 ± 8.65 岁;鳞癌 25 例,腺癌 15 例,小细胞癌 9 例,大细胞癌 7 例。两组患者的一般资料相仿,差异无统计学意义($P > 0.05$)。

1.2 诊断标准

放射性肺炎的诊断:①有胸部放射线治疗病史;②放疗结束或者放疗过程中后 1-3 个月内出现发热、咳嗽、活动后气短等症状;③X 线片或肺部 CT 检查见密度增高影或条索样炎症性改变;④排除肺部病原性感染、肿瘤进展等其他原因。

放射性肺纤维化的诊断:①有胸部放射线治疗病史;②放疗结束后 6 个月出现呼吸困难、病理性呼吸音及干湿啰音或捻发音;③X 线片或肺部 CT 检查见弥漫性线条状、结节状、云絮样、网状阴影、肺容积缩小;④肺功能衰竭表现^[6]。

1.3 纳入标准

符合原发性肺癌的诊断标准;分期为Ⅱ期-Ⅲ期;年龄 48-62 岁;患者自愿参与本实验,并签署知情同意书;经所在单位伦理学相关机构的批准^[7]。

1.4 排除标准

心肝肾功能严重疾病;肺部病原性感染;血液病;神志异常;近期服用抗癌细胞药物及常年接触放射性物质的患者等。

1.5 治疗方法

两组均采用 6MV-X 线照射,每次 200 cGy,每周 5 次,肺的照射体积均满足 $V_{20} < 30\%$,脊髓剂量不超过 40 Gy,肿瘤的累积剂量为 DT60-70 Gy。两组放疗方案、剂量比较无差异,均无统计学意义($P > 0.05$)。实验组在常规放射治疗的同时加用复方苦参注射液(山西振东制药股份有限公司,国药准字 Z14021231,每支装 5 mL)5 mL,溶于 0.9% 氯化钠注射液 250 mL,日一次静点,至放疗结束。注意事项:用药期间,禁食生冷辛辣等刺激性食物,戒烟酒,保持患者情绪稳定。

1.6 观察指标及检测方法

从放射治疗第一天开始详细观察并记两组患者录咳嗽、咳痰、气促、胸闷、呼吸困难等症状;放疗前、放疗结束时和放疗后 3、6 个月行肺部 CT 检查;放疗前和结束时均抽取静脉血 3 mL,测定血浆转化生长因子- β 1(TGF- β 1)和肿瘤坏死因子- α (TNF- α)值,使用由美国 Adlitteram Diagnostic Laboratories 公司生产的试剂盒,均采用 ELISA 法检测。

1.7 判定指标

放射性肺损伤的评价:根据 RTOG 分级标准将急性放射性肺损伤分为 0~5 级,临床症状 ≥ 1 级者诊断为急性放射性肺损伤, ≥ 2 级者诊断为严重放射性肺损伤。胸部 CT 表现为放射性肺损伤改变。

1.8 统计学方法

采用统计学软件 SPSS19.0 进行统计学分析,计量资料采用 t 检验,计数资料采用卡方检验处理,以 $P < 0.05$ 为差异显著,有统计学意义。

2 结果

2.1 两组患者放射性肺炎发生率比较

放疗结束时及结束后 3、6 个月实验组放射性肺炎的比率明显低于对照组,差异有统计学意义($P < 0.05$),如表 1。

表 1 放疗结束后患者放射性肺炎发生率比较(例,%)

Table 1 Comparison of the incidence rate of radiation pneumonitis between two groups (n,%)

Group	n	At the end of radiotherapy	3 months after radiotherapy	6 months after radiotherapy
Experimental group	55	2(3.57)*	3(5.36)*	5(8.93)*
Control group	57	7(12.5)	15(26.78)	17(30.36)

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

2.2 两组放射性肺纤维化比率比较

放疗结束时,实验组放射性肺纤维化比率较对照组明显减

低,差异有统计学意义($P < 0.05$),如表 2。

表 2 两组放射性肺纤维化比率比较情况(例,%)

Table 2 Comparison of the radioactive pulmonary fibrosis between two groups(n, %)

Group	n	At the end of radiotherapy	3 months after radiotherapy	6 months after radiotherapy
Experimental group	55	0	1(0.79)*	7(12.5)*
Control group	57	0	6(10.71)	13(23.21)

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

2.3 两组患者治疗前后血浆 TGF-β1 和 TNF-α 值比较

治疗前两组血浆 TGF-β1 和 TNF-α 值无明显差异,无统计

学意义($P>0.05$);治疗后实验组血浆 TGF-β1 和 TNF-α 值较对照组明显下降,差异有统计学意义($P<0.05$),如表 3。

表 3 两组患者治疗前后血浆 TGF-β1 和 TNF-α 值比较($\bar{x} \pm s$)

Table 3 Comparison of the level of plasma TGF-beta 1 and TNF- alpha before and after treatment($\bar{x} \pm s$)

Group	TGF-β1(ng/mL)		TNF-α(ng/mL)	
	Before treatment	After treatment	Before treatment	After treatment
Experimental group	4.67± 2.73	6.17± 2.51*	1.78± 0.45	2.13± 0.78*
Control group	4.75± 2.57	12.67± 2.67	1.98± 0.56	6.87± 0.65

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

3 讨论

放射性肺损伤仍是胸部及胸壁恶性肿瘤患者放疗后常见且严重的并发症,不但影响病人的生活质量,严重时还会危及生命。目前,关于放射性肺损伤的发生机制主要有:细胞因子学说、毛细血管内皮细胞损伤学说、肺泡上皮损伤学说、自由基产生过多学说、基因学说等,对其发生机制仍不十分明确,且临床上缺乏理想的放射保护剂预防和治疗放射性肺损伤^[8-11]。近年来,临床研究显示,含有苦参碱的岩舒注射液辅助肺癌放疗,具有明显提高疗效、减轻放射对肺部损伤的作用。一项关于苦参碱的动物实验显示,苦参碱能够减轻小鼠急性放射性肺损伤,且其防护作用优于单参和川芎嗪^[12-15]。随着中医学的继承和发展,学者们将预防和治疗放射性肺损伤的目光转移到中医身上。中医对于本病具有整体调节、局部治疗、标本兼治、多靶点、多成分的特点和优势。在中医辨证论治理论体系的指导下运用中药制剂,复方或单味中药或者有效成分治疗本病均能取得较理想的效果。

放射性肺损伤隶属于中医的“咳嗽”、“肺痿”等病症范畴。肺脏清虚娇嫩而高位,本易受寒热燥湿诸邪侵袭。放射线为热毒燥邪,胸部恶性肿瘤行放射线治疗,放射线的热毒燥邪直中脏腑血络,灼伤机体津液,损伤正气和阴血,热燥之邪灼伤肺阴,炼液成痰;虚热内盛,正气虚弱,无力推动血脉,阴津津伤,不能养血,血液黏稠,致瘀血内生,肺络阻滞;胸部恶性肿瘤本为痰凝瘀毒阻滞,瘀毒与热毒燥邪交织,致气血津液更加虚弱^[6]。本虚标实,气阴两伤、瘀热毒互结为本病的主要病机。气阴津液损伤、瘀毒阻肺,肺不得濡养,致肺失宣发肃降。故有早期放射性肺损伤干咳、咳少量黏液样痰、胸痛、气促等症状出现;肺属金,肾属水,金水相生,肺虚日久,不能输布津液下达于肾,肾水源竭;肾水既亏,水不制火,则虚火上炎而烁肺金,形成肺肾两亏。肾水乏源,失于濡养,则肾不纳气,气不归元,导致临床表现为呼吸困难的晚期放射性肺纤维化的形成,甚者出现呼吸衰竭而死亡^[17-19]。热毒燥邪主要灼伤肺气阴津液,而导致肺肾功能失调,故对放射性肺损伤治则主要为养阴润肺,滋肾壮水。复方苦参注射液提取苦参与土茯苓中的主要中药有效成分,具有清热润燥、凉血解毒的功效,能够治疗肺热引起的一系列疾病。现代药理研究发现复方苦参注射液的有效成分为苦参碱及氧化苦参。文献报道苦参碱能够抑制肿瘤细胞中线粒体酶的活性,诱导肿瘤细胞的分化与凋亡,同时能够调节机体免疫,对肿

瘤细胞具有抑制作用^[20]。本实验结果显示,放疗结束时及结束后 3、6 个月实验组放射性肺炎的比率明显低于对照组,差异有统计学意义($P<0.05$);治疗后实验组血浆 TGF-β1 和 TNF-α 值较对照组明显下降,差异有统计学意义($P<0.05$),结果说明复方苦参注射液能够有效的防护放射线给肺组织带来的损伤,能够抑制放疗后血浆 TGF-β1 和 TNF-α 的过度表达,能有效降低放射性肺损伤的发生几率。目前,虽普遍认为肺纤维化一旦发生往往不可逆转,但亦有部分学者认为肺纤维化的过程是可逆的,但本实验表明放疗结束后 3、6 个月实验组放射性肺纤维化比率也明显低于对照组,差异有统计学意义($P<0.05$),其作用机制可能是通过抑制 CTGF 和 TGF-β1 的表达,从而影响了上述细胞因子的生物学作用,最终显示出肺间质的胶原成分减少,肺纤维化减轻的结果。

综上所述,复方苦参注射液能够明显预防和减轻放射性肺损伤,为一种高效、低毒副作用、安全的防治方法。此实验给放射性肺损伤带来了新的思路,同时也给中医的发展和应带来了更广阔的前景。但本实验随访时间较短,对于本病预后还需大量的临床研究来证实。

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(上接第 3037 页)

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