doi: 10.13241/j.cnki.pmb.2019.09.023

重组人血管内皮抑制素联合胸腺肽对肺癌合并恶性胸腔积液患者血清炎症因子和免疫功能的影响*

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摘要 目的:研究重组人血管内皮抑制素联合胸腺肽对肺癌合并恶性胸腔积液患者血清炎症因子和免疫功能的影响。**方法:**选择2015年1月～2017年12月我院收治的60例肺癌合并恶性胸腔积液患者,并将其随机分成两组。对照组将60 mg重组人血管内皮抑制素经引流管缓慢注入患者的胸腔内,观察组联合将300 mg胸腺肽经引流管缓慢注入患者的胸腔内。治疗8周后,对比两组的治疗有效率,治疗前后的血清白介素-6、肿瘤坏死因子-α以及白介素-23水平、每分钟最大通气量(Maximum ventilation per minute,MVV)、1秒钟用力呼气量占用力肺活量比值（forced expiratory volume in one second to forced vital capacity ratio,FEV1/FVC)、$CD8^+$、$CD4^+$及$CD4^+/CD8^+$的改变情况。**结果:**治疗后,观察组的有效率为86.67%,明显高于对照组(P<0.05)。两组治疗后的MVV和FEV1/FVC均较治疗前明显升高(P<0.05),且观察组MVV和FEV1/FVC均明显高于对照组(P<0.05)。两组治疗后的血清白介素-6、肿瘤坏死因子-α以及白介素-23水平均较治疗前明显降低(P<0.05),且观察组以上指标均显著低于对照组(P<0.05)。观察组治疗后的$CD4^+/CD8^+$以及$CD4^+$均明显高于对照组(P<0.05),$CD8^+$明显低于对照组(P<0.05)。**结论:**重组人血管内皮抑制素联合胸腺肽可以改善减轻肺癌合并恶性胸腔积液患者的免疫功能,减轻机体的炎症状态,改善肺功能,提高治疗效果。

关键词:重组人血管内皮抑制素;胸腺肽;肺癌;恶性胸腔积液;免疫功能;炎症因子

中图分类号:R734.2 **文献标识码:**A **文章编号:**1673-6273(2019)09-1711-04

Effect of Recombinant Human Endostatin Combined with Thymosin on the Serum Inflammatory Factors and Immune Function of Lung Cancer Patients with Malignant Pleural Effusion*

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ABSTRACT Objective: To study the effect of recombinant human vascular endostatin combined with thymosin on the serum inflammatory factors and immune function of lung cancer patients with malignant pleural effusion. **Methods:** 60 cases of lung cancerpatients complicated with malignant pleural effusion who were treated in our hospital from January 2015 to December 2017 were selected and randomly divided into two groups. The control group was given 60 mg recombinant endostatin into the thoracic cavity through the drainage tube, and the observation group was given 300 mg thymosin through the drainage tube. After 8 weeks of treatment, the effectiveness, the changes of serum levels of interleukin-6, TNF-α, interleukin-23, MVV, FEV1/FVC, $CD8^+$, $CD4^+$, $CD4^+/CD8^+$ before and after treatment were compared between two groups. **Results:** After treatment, the effective rate of observation group was 86.67%, which was significantly higher than that of the control group (P<0.05). The MVV and FEV1/FVC of both groups after treatment were significantly higher than those before treatment (P<0.05), and the MVV and FEV1/FVC of observation group were significantly higher than those in the control group (P<0.05). The levels of serum interleukin -6, tumor necrosis factor -αand interleukin -23 after treatment in both groups were significantly lower than those before treatment (P<0.05), and the above indexes were significantly lower in the observation group than those in the control group (P<0.05). The $CD4^+/CD8^+$ and $CD4^+$ of observation group after treatment were significantly higher than those of the control group (P<0.05), and $CD8^+$ was significantly lower than that of the control group (P<0.05). **Conclusion:** Recombinant human vascular endostatin combined with thymosin can improve the immune function of lung cancerpatients with malignant pleural effusion, it can relevel the inflammatory response, improve the lung function and the therapeutic effect.

Key words: Recombinant human endostatin; Thymosin; Lung cancer; Malignant pleural effusion; Immune function; Inflammatory factors

Chinese Library Classification(CLC): R734.2 Document code: A

Article ID: 1673-6273(2019)09-1711-04

* 基金项目:新疆维吾尔自治区自然科学基金项目(2015211c149)

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(收稿日期:2018-08-30 接受日期:2018-09-23)

前言

肺癌是引发恶性胸腔积液的主要原因之一,占其所有引发因素的24%~42%,以肺腺癌最为多见[1]。临床上控制恶性胸腔积液的常用药物主要包括三种:硬化剂(引起胸膜粘连,产生化学胸膜炎,从而是胸膜腔消灭)、细胞生长抑制剂(减小恶性肿瘤的体积,从而有效控制胸腔积液)和生物免疫反应调节剂(增强以及调节机体固有的抗癌功能,杀伤及抑制癌细胞)[2-4]。胸腔内置管引流以及胸腔内灌注给药联合使用被认为是治疗恶性胸腔积液的标准治疗方案。重组人血管内皮抑制素可以抗血管生成因子以及促血管生成因子之间的平衡得以重新建立,有效诱导肿瘤血管的正常化。重组人血管内皮抑制素以及胸腺肽均为肺癌合并恶性胸腔积液患者行胸腔置管引流手术常用的辅助治疗药物[5,6]。胸腺肽具有促进T细胞成熟、激活细胞免疫的效果,但尚未见两种药物联合使用的研究报道。鉴于此,本研究主要探讨了重组人血管内皮抑制素联合胸腺肽对肺癌合并恶性胸腔积液患者的临床疗效。

1 资料与方法

1.1 一般资料

选择2015年1月～2017年12月我院收治的60例肺癌合并恶性胸腔积液患者，入院后经病理组织学检查确诊为肺癌,并经胸片、常规查体、胸部CT、胸水细胞学检查以及胸腔超声等确诊为恶性胸腔积液,排除对重组人血管内皮抑制素联合胸腺肽不耐受的患者,非肺癌所致恶性胸腔积液的患者,合并造血系统、肝、心、肾等较为严重的原发疾病的患者。随机分为两组。观察组30例,男18例,女12例;年龄53~84岁,平均(67.23± 8.35)岁;病理类型:腺癌10例,大细胞未分化癌2例,鳞癌18例;部位:右肺13例,左肺16例,双肺1例;胸腔积液量:大量11例,中等量19例;肺癌分型:周围型20例,中心型10例。对照组30例,男17例,女13例;年龄52~84岁,平均(68.14± 7.92)岁;病理类型:腺癌10例,大细胞未分化癌1例,鳞癌19例;部位:右肺12例,左肺17例,双肺1例;胸腔积液量:大量20例,中等量10例;肺癌分型:周围型19例,中心型11例。所有患者均签署知情同意书。

1.2 治疗方法

两组均行胸腔内置管引流术,并且在灌注药前半小时肌内注射20 mg甲氧氯普胺(批号:国药准字H32020191,生产厂家:江苏天士力帝益药业有限公司,规格:5 mg)以预防胃肠道反应,肌内注射25 mg盐酸异丙嗪(批号:国药准字H31022033,生产厂家:上海禾丰制药有限公司,规格:2 mL: 50 mg)以预防过敏。对照组将60 mg重组人血管内皮抑制素(批号:国药准字S20050088,生产厂家:山东先声麦得津生物制药有限公司,规格:15 mg/2.4× 10^5 U/3 mL/ 支) 经引流管缓慢注入患者的胸腔内,每周给药1次。观察组联合将300 mg胸腺肽(批号:国药准字H20003652,生产厂家:广东京豪医药科技开发有限公司,规格:2 mL: 10 mg)经引流管缓慢注入患者的胸腔内,每周给药1次。两组均治疗8周。定期复查胸部CT、胸片和B超。

1.3 观察指标

比较两组的临床治疗有效率,评估标准[7]:① 完全缓解:经过治疗后,患者的B超检测结果表明胸腔积液全部消失,且持续时间超过1个月;② 部分缓解:经过治疗后,患者的胸腔积液量降低幅度大于50%,胸腔压迫症状得到显著的缓解,且持续时间超过1个月;③ 疾病稳定:经过治疗后,患者的胸腔积液量增多小于25%或者减少小于50%;④ 疾病进展:经过治疗后,患者的胸腔积液量与治疗前相比增加超过25%,积液压迫胸腔的症状更为严重。

分别在治疗前后，于清晨采集4 mL静脉血，采取ELISA双抗体夹心法测定血清白介素-6、肿瘤坏死因子-α以及白介素-23水平,试剂盒均购自上海基免科技有限公司。采用德国耶格肺功能仪检测每分钟最大通气量(MVV)以及用力呼气量占用力肺活量比值(FEV1/FVC)。采用美国BD Accuri C6流式细胞仪检测两组治疗前后的$CD4^+/CD8^+$、$CD8^+$以及$CD4^+$等细胞免疫功能。

1.4 统计学分析

采用SPSS19.0软件进行统计学分析，组间和组内对比用方差分析和t检验,组间率的比较用x^2检验,以P<0.05为差异有统计学意义。

2 结果

2.1 两组临床疗效对比

治疗后,观察组的有效率为86.67%,明显高于对照组(P<0.05),见表1。

表1 两组临床疗效对比[例(%)]

Table 1 Comparison of the clinical effect between two groups[n(%)]

Groups	n	Complete remission	Partial remission	Stability of the disease	Disease progression	The total effect rate
Observation group	30	10 (33.33)	16 (53.33)	3 (10.00)	1 (3.33)	86.67 *
Control group	30	7 (23.33)	14 (46.67)	7 (23.33)	2 (6.67)	70.00

Note: Compared with the control group, *P<0.05.

2.2 两组治疗前后肺功能对比

两组治疗后的MVV和FEV1/FVC均较治疗前明显升高(P<0.05)，且观察组MVV和FEV1/FVC明显高于对照组(P<0.05),见表2。

2.3 两组治疗前后血清炎症因子水平对比

两组治疗后的血清白介素-6、肿瘤坏死因子-α以及白介素-23水平均较治疗前明显降低(P<0.05),且观察组以上指标均显著低于对照组(P<0.05),见表3。

表 2 两组治疗前后肺功能的对比($\bar{x}\pm s$)

Table 2 Comparison of the pulmonary function before and after treatment between two groups($\bar{x}\pm s$)

Groups	n	MVV		FEV1/ FVC	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	30	74.31± 10.25	83.38± 12.41*#	54.39± 10.18	82.57± 11.59*#
Control group	30	73.29± 10.54	78.25± 11.23#	55.27± 10.34	74.38± 10.32#

Note: Compared with the control group, *P<0.05; compared with before treatment, #P<0.05.

表3 两组治疗前后血清炎症因子水平对比($\bar{x}\pm s$)

Table 3 Comparison of the serum inflammatory factor levels before and after treatment between two groups($\bar{x}\pm s$)

Groups	n	IL-6 (ng/mL)		IL-23 (pg/mL)		TNF-α (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	89.34± 5.73	33.19± 4.32 *#	129.34± 13.25	43.63± 8.89*#	152.17± 17.35	48.73± 6.14*#
Control group	30	89.25± 5.68	57.64± 5.59#	129.73± 13.52	75.64± 9.32#	152.94± 18.63	86.73± 8.25#

Note: Compared with the control group, *P<0.05; compared with before treatment, #P<0.05.

2.4 两组治疗前后免疫功能对比

两组治疗后的 $CD4^+/CD8^+$ 以及 $CD4^+$ 均较治疗前明显升高 (P<0.05),$CD8^+$ 较治疗前明显降低 (P<0.05), 且观察组 $CD4^+/CD8^+$ 以及 $CD4^+$ 明显高于对照组,而 $CD8^+$ 显著低于对照组(P<0.05),见表 4。

表 4 两组治疗前后免疫功能对比($\bar{x}\pm s$)

Table 4 Comparison of the immune function before and after treatment between two groups ($\bar{x}\pm s$)

Groups	n	$CD4^+/CD8^+$		$CD8^+$(%)		$CD4^+$(%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	1.02± 0.14	1.59± 0.31*#	30.78± 6.42	23.59± 5.38*#	29.45± 6.31	37.47± 8.38*#
Control group	30	1.03± 0.17	1.34± 0.25#	30.62± 6.53	26.72± 6.14#	29.57± 6.62	33.69± 7.25#

Note: Compared with the control group, *P<0.05; compared with before treatment, #P<0.05.

3 讨论

随着生活环境的迅速变化,尾气、工业化以及粉尘污染等现象日益加剧,肺癌的发病率逐渐升高。相关统计数据表明大约有一半左右的复发或者晚期肺癌患者会合并产恶性胸腔积液[8]。恶性胸腔积液形成的机制是由于恶性肿瘤转移至或直接侵犯胸膜上而导致,是胸膜渗透压升高、淋巴引流受到阻塞和毛细血管的通透性增加等多种机制共同作用的结果[9-11]。大量的胸腔积液能对患者呼吸功能和预后情况造成严重的不良影响。临床治疗恶性胸腔积液的手段多种多样,包括胸腔镜治疗、热疗、胸膜固定术和胸腔穿刺等,但尚无标准的治疗方案[12-14]。

胸腔内灌注给药可以对肿瘤细胞进行直接杀伤,且能促进胸膜黏连闭锁,明显抑制胸腔积液的形成。随着硬化剂、化疗药物、中药制剂以及生物反应调节剂等胸腔灌注药物种类的逐渐增多,胸腔灌注给药联用胸腔置管引流在临床恶性胸腔积液的治疗获得广泛的应用,而且多种药物联合灌注的效果更佳[15-17]。重组人血管内皮抑制素能对肿瘤血管的增殖进行显著抑制,从而发挥抗肿瘤的效果,其对乳腺癌、肺癌、结直肠癌、恶性黑色素瘤和肝癌等多种恶性肿瘤均有效[18,19]。胸腺肽有效成分包括胸腺生成素、胸腺素 α1、血清胸腺因子和胸腺体液因子等,可以促进 T 细胞成熟,通过促进低免疫功能以及抑制高免疫功能来发挥免疫调节效果,从而能使患者机体病态的异常反应转变成正常状态下的保护性免疫反应,而且可以使机体外周的 T 细胞成熟得以激活,使机体的内部环境得到明显的改善,从而缓解患者的临床症状[20-22]。

研究表明炎症是肺癌等恶性肿瘤的本质特征之一[23,24]。本研究结果显示两组治疗后的血清炎症因子水平均较治疗前明显降低,且观察组显著低于对照组,表明胸腔引流手术联合重组人血管内皮抑制素能减轻患者的全身炎症反应,联合给予胸腺肽治疗能使其症状得到进一步的缓解。分析原因认为,趋化因子如白介素 -6、肿瘤坏死因子 -α 以及白介素 -23 等能促进肺癌患者的肿瘤细胞发生扩散以及增殖,从而诱导全身炎症反应。重组人血管内皮抑制素具有较为显著的抗肿瘤效果,联合给予胸腺肽治疗,可以进一步降低趋化因子的释放,阻止白细胞与 IL28、TNF-α 等炎症因子之间的相互作用,降低白细胞和炎症因子对组织造成的损伤,最终减轻炎症反应对机体肺功能产生的损害。

细胞免疫功能抑制可以对肿瘤转移和复发造成重要影响,T 淋巴细胞具有中心调控肿瘤免疫功能的效果,在抗肿瘤免疫反应中发挥主导作用[25-27]。随着恶性胸腔积液的逐渐进展,患者的体液免疫功能会明显降低, 而且化疗在杀伤肿瘤细胞的同时,也会对正常细胞造成损伤[28-30]。本研究结果显示观察组治疗后的 $CD4^+/CD8^+$ 以及 $CD4^+$ 均明显高于对照组,$CD8^+$ 明显低于对照组,表明重组人血管内皮抑制素联合胸腺肽可以有效减轻肺癌合并恶性胸腔积液患者的免疫功能损伤。分析其原因为,胸腺肽可以显著促进 T 细胞成熟、激活细胞的免疫功能。

综上所述,重组人血管内皮抑制素联合胸腺肽可以改善减轻肺癌合并恶性胸腔积液患者的免疫功能,减轻机体的炎症状

态,改善肺功能,提高治疗效果。

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