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重组人血管内皮抑制素注射液联合洛铂对恶性胸腔积液患者生活质量及免疫功能的影响*

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摘要 目的:探讨重组人血管内皮抑制素注射液联合洛铂对恶性胸腔积液患者生活质量及免疫功能的影响。**方法:**选择2015年3月至2017年3月期间我院收治的恶性胸腔积液患者56例为研究对象,按照不同的治疗方式分为研究组($n=28$)和对照组($n=28$)。对照组给予洛铂治疗,研究组给予重组人血管内皮抑制素注射液联合洛铂治疗。比较两组患者治疗前后生活质量变化、免疫功能变化、临床疗效和不良反应发生情况。**结果:**研究组患者生活质量改善率高于对照组($P<0.05$)。治疗前,两组免疫功能指标含量经统计分析差异无统计学意义($P>0.05$),与治疗前比较,两组治疗后4周 $CD3^+$ 、 $CD4^+$ 、 $CD4^+/CD8^+$ 、NK含量均升高, $CD8^+$ 含量降低,且研究组 $CD3^+$ 、 $CD4^+$ 、 $CD4^+/CD8^+$ 、NK含量较对照组升高, $CD8^+$ 含量较对照组降低($P<0.05$)。研究组总有效率为78.57%,与对照组的46.43%比较差异有统计学意义($P<0.05$)。两组患者心脏反应、呕吐、恶心、血小板减少、白细胞减少、贫血、乏力发生率比较差异均无统计学意义($P>0.05$)。**结论:**重组人血管内皮抑制素注射液联合洛铂治疗恶性胸腔积液具有较好的疗效,其可以改善患者生活质量,提高免疫功能,且不会增加患者不良反应,值得临床推广。

关键词:恶性胸腔积液;重组人血管内皮抑制素;洛铂;生活质量;免疫功能

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Effect of Recombinant Human Endostatin Injection Combined with Lobaplatin on Quality of Life and Immune Function in Patients with Malignant Pleural Effusion*

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ABSTRACT Objective: To investigate the effect of Recombinant Human Endostatin Injection combined with lobaplatin on the quality of life and immune function in patients with malignant pleural effusion. **Methods:** A total of 56 patients with malignant pleural effusion, who were treated in the second People's Hospital in Jingmen from March 2015 to March 2017, were selected and divided into study group ($n=28$) and control group ($n=28$) according to the different treatment methods. The control group was given chemotherapy with lobaplatin, and the study group was treated with Recombinant Human Endostatin Injection combined with lobaplatin. The changes of the quality of life, the changes of immune function before and after treatment, the clinical effect and the occurrence of adverse reactions were compared between the two groups. **Results:** Improvement rate of quality of life of the patients in the study group was higher than that of the control group ($P<0.05$). Before treatment, there was no significant difference in the contents of immune function indexes between the two groups by statistical analysis ($P>0.05$). Compared with those before treatment, the contents of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ and NK in the two groups 4 weeks after treatment were increased, while the content of $CD8^+$ was decreased, the contents of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ and NK in the study group were higher than those in the control group, and the content of $CD8^+$ in the study group was lower than that in the control group ($P<0.05$). The total effective rate of the study group was 78.57%, compared with the 46.43% of the control group, the difference was statistically significant ($P<0.05$). There was no significant difference in the incidence of cardiac reactions, vomiting, nausea, thrombocytopenia, aleucocytosis, anemia and fatigue between the two groups ($P>0.05$). **Conclusion:** Recombinant Human Endostatin Injection combined with lobaplatin has a good effect in the treatment of malignant pleural effusion. It can improve the quality of life of the patients, improve the immune function, and it will not increase the adverse reaction of the patients, which is worthy of clinical promotion.

Key words: Malignant pleural effusion; Recombinant human endostatin injection; Lobaplatin; Quality of life; Immune function

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前言

恶性胸腔积液是伴随晚期恶性肿瘤而存在的一种并发症,其多发于肺癌、乳腺癌等患者中^[1,2]。恶性胸腔积液患者多表现为贫血、消瘦乏力、气促、干嗽、胸痛等症状,并且症状将随积液的增加而加重,对患者的生活质量造成严重影响^[3,4]。临床上,胸腔引流是胸腔积液的常规处理方式,但是反复的胸腔引流操作将导致大量蛋白质随积液流出体外,严重降低患者的免疫功能,加速了机体的衰竭^[5,6]。有研究报道^[7,9],经导管引流积液后行化疗药物及生物制剂灌注是治疗恶性胸腔积液的有效方法,此方法可以降低胸腔内积液的产生速度,从而抑制病情的进展,进而改善患者的生活质量和免疫功能,但是对于使用何种化疗药物和生物制剂却存在争议。洛铂是继顺铂和卡铂之后新开发的第3代铂类抗肿瘤药物,主要用于治疗非小细胞肺癌、乳腺癌等,具有较好的抗癌性和水溶性,同时不良反应少^[10]。重组人血管内皮抑制素是一种新型的抗肿瘤药物,其一般与化疗药物同时使用,多用于非小细胞肺癌的治疗,具有毒性低、抗癌普广等特点^[11]。为了探讨重组人血管内皮抑制素注射液联合洛铂对恶性胸腔积液患者的治疗效果,本研究从患者的生活质量和免疫功能两方面进行分析,旨在为恶性胸腔积液治疗药物的选择提供依据,现进行如下阐述。

1 资料与方法

1.1 一般资料

选择2015年3月至2017年3月期间我院收治的恶性胸腔积液患者56例为研究对象,纳入标准:(1)经胸部CT或B超确诊为恶性胸腔积液;(2)预计生存期超过3个月;(3)伴有气促、干嗽、胸闷等症状;(4)患者自愿参与本研究,并签署知情同意书。排除标准:(1)患者卡氏评分(Karnofsky performance status, KPS) < 60分者;(2)合并有造血系统疾病以及重要脏器功能障碍者;(3)近一个月内接受过化疗者;(4)孕妇或哺乳期妇女;(5)意识障碍或精神疾病者。将入选患者按照治疗方式的不同分为研究组(n=28)和对照组(n=28)。研究组男18例,女10例;年龄35-75岁,平均(55.78±3.56)岁;病理类型:腺癌16例,腺鳞癌3例,鳞癌9例。对照组男20例,女8例;年龄34-78岁,平均(54.39±3.78)岁;病理类型:腺癌17例,腺鳞癌4例,鳞癌7例。比较两组患者以上资料差异无统计学意义($P>0.05$),均衡可比。本研究符合我院伦理委员会的相关规定,并获得批准。

1.2 方法

行胸腔灌注前半小时,所有患者均给予奥美拉唑和盐酸昂丹司琼等药物治疗以预防恶心、呕吐。在B超的引导下定位好穿刺点后,将单腔中心静脉导管置入患者胸腔,并逐步分次进行积液引流操作,引流量根据患者耐受程度而定,一般控制在500-1000 mL/次,当患者胸腔内积液量不能再进行引流操作或完全消失时,对照组给予注射用洛铂(海南长安国际制药有限公司;国药准字:H20050308)治疗,30 mg/m²,1次/周,连续治疗3周。研究组患者在对照组的基础上给予重组人血管内皮抑制素注射液(山东先声生物制药有限公司;国药准字:S20050088)治疗,45 mg/m²,1次/周,连续治疗3周。药物注射

完成后,叮嘱患者在一小时内频繁变换体位,以保证药物与胸膜表面充分接触,从而促进药物能够有效的被吸收。治疗期间常规监测肝肾功能、血常规、心电图等。

1.3 观察指标

1.3.1 生活质量^[12] 治疗前、治疗后4周对两组患者的生活质量进行评价,参照KPS评分标准,分为三个等级(改善、稳定、降低)。改善:治疗后4周,KPS评分增加幅度不少于10分;稳定:治疗后4周,KPS评分增加幅度少于10分或减少幅度少于10分;降低:治疗后4周,KPS评分减少幅度不少于10分。

1.3.2 免疫功能 治疗前、治疗后4周清晨采集两组患者外周静脉血5 mL,采用流式细胞仪(贝克曼库尔特,型号:Gallios)及免疫标记法(相关试剂盒购于上海酶联科技生物有限公司)测定CD3⁺、CD4⁺、CD8⁺、自然杀伤细胞(Natural killer cells, NK)含量,并根据结果计算CD4⁺/CD8⁺比值。所有操作严格按照试剂盒说明书进行。

1.3.3 疗效评价^[13] 依据世界卫生组织制定的恶性胸腔积液疗效评价标准:(1)完全缓解(Complete remission, CR):患者气促、干嗽、胸痛等症状完全缓解,胸腔内积液完全消失,且持续时间超过4周;(2)部分缓解(Partial remission, PR):患者气促、咳嗽、胸闷等症状基本缓解,胸腔内积液减少超过一半,且持续时间超过4周;(3)稳定(Stable disease, SD):患者气促、咳嗽、胸闷等症状有所缓解,胸腔内积液减少小于一半,且持续时间超过4周;(4)进展(Progression disease, PD):患者气促、咳嗽、胸闷等症状加重,胸腔内积液增加超过25.00%。总有效率=(CR+PR)/总例数*100%。

1.3.4 不良反应 比较两组不良反应情况。

1.4 统计学方法

采用SPSS 22.0统计软件进行数据分析,免疫功能指标含量等计量资料采用均数±标准差表示,实施t检验,总有效率、不良反应率、生活质量改善率等计数资料采用率表示,实施 χ^2 检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组生活质量改善情况比较

与对照组相比,研究组患者生活质量改善率升高($P<0.05$),两组患者稳定率和降低率比较均无统计学差异($P>0.05$)。见表1。

2.2 两组免疫功能指标比较

治疗前,两组免疫功能指标含量经统计分析差异无统计学意义($P>0.05$),与治疗前比较,两组治疗后4周CD3⁺、CD4⁺、CD4⁺/CD8⁺、NK含量均升高,CD8⁺含量降低,且研究组CD3⁺、CD4⁺、CD4⁺/CD8⁺、NK含量较对照组升高,CD8⁺含量较对照组降低($P<0.05$)。见表2。

2.3 两组治疗疗效比较

研究组总有效率高于对照组($P<0.05$)。见表3。

2.4 两组不良反应比较

研究组患者心脏反应、呕吐、恶心、血小板减少、白细胞减少、贫血、乏力发生率与对照组比较差异均无统计学意义($P>0.05$)。见表4。

表 1 两组生活质量改善情况比较[n(%)]

Table 1 Comparison of improvement of quality of life between two groups[n(%)]

Groups	n	Improvment	Stabilization	Reduction
Study group	28	19(67.86)	7(25.00)	2(7.14)
Control group	28	11(39.29)	10(35.71)	7(25.00)
χ^2		4.595	0.760	3.310
<i>P</i>		0.032	0.383	0.069

表 2 两组免疫功能指标比较($\bar{x} \pm s$)Table 2 Comparison of immune function indexes between two groups($\bar{x} \pm s$)

Groups	n	Time	CD3 ⁺ (%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺	NK(%)
Study group	28	Before treatment	57.93± 4.79	26.43± 3.23	30.89± 3.77	0.87± 0.23	13.05± 3.98
		4 weeks after treatment	69.55± 4.99* [#]	39.12± 3.90* [#]	19.66± 3.02* [#]	2.05± 0.19* [#]	20.13± 3.02* [#]
Control group	28	Before treatment	57.88± 4.86	26.51± 3.45	30.67± 3.59	0.86± 0.21	13.07± 3.68
		4 weeks after treatment	63.26± 4.77*	33.45± 3.37*	25.45± 3.12*	1.32± 0.18*	16.56± 3.33*

Note: compared with before treatment, * $P < 0.05$, compared with the control group, [#] $P < 0.05$.

表 3 两组治疗疗效比较[n(%)]

Table 3 Comparison of therapeutic effect between two groups[n(%)]

Groups	n	CR	PR	SD	PD	Total effective rate
Study group	28	6(21.43)	16(57.14)	3(10.71)	3(10.71)	22(78.57)
Control group	28	3(10.72)	10(35.71)	10(35.71)	5(17.86)	13(46.43)
χ^2						6.171
<i>P</i>						0.013

表 4 两组不良反应比较[n(%)]

Table 4 Comparison of adverse reactions between two groups[n(%)]

Groups	n	Cardiac reactions	Vomiting	Nausea	Thrombocytopenia	Aleukocytosis	Aanemia	Fatigue
Study group	28	0(0.00)	7(25.00)	11(39.29)	10(35.71)	6(21.43)	8(28.57)	10(35.71)
Control group	28	2(7.14)	9(32.14)	12(42.86)	13(46.43)	7(25.00)	10(35.71)	11(39.29)
χ^2		2.074	0.350	0.074	0.664	0.100	0.327	0.076
<i>P</i>		0.150	0.554	0.786	0.415	0.752	0.567	0.783

3 讨论

机体胸腔处于正常状态时,人体脏器层与胸膜壁层之间只存在少量的液体,其作用是防止胸膜腔粘连和促进胸膜壁与其他脏器层之间的润滑^[14,15]。而当机体存在肿瘤时,肿瘤侵犯胸膜壁层和脏器层的毛细血管,以致其通透性增强,此时大量蛋白质、红细胞进入胸腔,从而引发胸腔积液^[16-18]。恶性胸腔积液患者如不及时治疗,其生存期一般在 7 至 10 个月,严重威胁患者生命健康,因此,恶性胸腔积液早期治疗显得尤为重要^[19]。临床上多采用抽取积液后行腔内灌注化疗药物和生物制剂的方式治疗恶性胸腔积液,化疗药物可以直接杀死肿瘤细胞,进而消除胸腔内积液^[20,21]。然而,经局部的化疗之后,患者胸膜将受到损伤,其粘连和纤维化程度将加重,同时部分患者还会对某些药物产生抗药性,因此,治疗恶性胸腔积液患者药物的选择至

关重要^[22,23]。

本研究中,研究组总有效率及生活质量改善率高于对照组($P < 0.05$),提示重组人血管内皮抑制素注射液联合洛铂对恶性胸腔积液的效果优于单用洛铂治疗。重组人血管内皮抑制素是一种血管生成抑制类生物制剂,其可以抑制肿瘤和胸膜内新生血管的形成,减少血管生成因子的增殖、分化,从而降低新生血管的通透性,进而降低蛋白质、红细胞等进入胸腔的几率,减少了积液的产生^[24,25]。与单纯的洛铂治疗相比,两者的联合使用在直接杀死肿瘤细胞的同时还通过降低血管通透性来减少积液进入胸腔,从而改善患者临床症状,提高其生活质量,因而,两者的联合使用治疗效果更好。CD3⁺、CD4⁺、CD8⁺、NK 均是免疫反应的重要指标,其水平的变化将严重影响机体的免疫功能;同时免疫功能的降低是肿瘤进展、转移的首要因素^[26]。CD3⁺是 T 淋巴细胞的代表;CD4⁺是辅助 T 淋巴细胞的代表;CD8⁺是

抑制 T 淋巴细胞的代表;而 NK 则能够识别靶细胞,是抗肿瘤和抗感染的重要免疫调节细胞^[27]。本研究结果显示,与治疗前比较,两组治疗后 4 周 CD3⁺、CD4⁺、CD4⁺/CD8⁺、NK 含量均升高,CD8⁺ 含量降低,且研究组 CD3⁺、CD4⁺、CD4⁺/CD8⁺、NK 含量较对照组升高,CD8⁺ 含量较对照组降低($P<0.05$),说明两药的联合使用对患者免疫功能的改善作用更好。洛铂等化疗药物是通过直接杀死肿瘤细胞产生作用,然而化疗药物在杀死肿瘤细胞的同时,也会杀死部分免疫细胞,同时其骨髓抑制作用将导致 T 淋巴细胞水平的下降,进而影响患者的免疫功能^[28]。重组人血管内皮抑制素则只是通过增强血管的通透性来产生作用,可以减少化疗药物的对机体免疫细胞的损伤。有报道显示^[29],重组人血管内皮抑制素联合洛铂对机体免疫功能的影响可能是两者的协同作用产生的效果。本研究结果还显示,研究组患者心脏反应、呕吐、恶心、血小板减少、白细胞减少、贫血、乏力发生率与对照组比较差异无统计学意义($P>0.05$)。说明两药的联合使用不会增加患者的不良反应。相比于顺铂等化疗药物,洛铂对患者的不良反应有所减少,但是其骨髓抑制作用将导致血红细胞、白细胞不同程度的减少,从而引起患者发生血液学毒性反应以及肠道反应^[30]。重组人血管内皮抑制素本身毒性少,其与洛铂联合使用不会增加对患者血液毒性以及肠道反应的影响,具有较好的安全性。

综上所述,与单用洛铂化疗,重组人血管内皮抑制素注射液联合洛铂治疗恶性胸腔积液具有更好的疗效,其在改善患者生活质量、提高免疫功能方面效果均优于洛铂的单独使用,但是在不良反应方面两种用药方案并无差异,因此,两者的联合使用是临床治疗恶性胸腔积液较好的药物选择方案,值得临床推广。

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