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阿帕替尼联合多西他赛对多线治疗晚期非小细胞肺癌患者血清肿瘤标志物、免疫功能及生活质量的影响*

丁婷婷¹ 芮晓艳¹ 范洪峰¹ 张艳喜¹ 陈 军¹ 徐 锐²

(1 安徽医科大学滁州临床学院 / 滁州市第一人民医院呼吸内科 安徽 滁州 239000;

2 安徽医科大学第一附属医院呼吸科 安徽 合肥 230022)

摘要 目的:分析阿帕替尼联合多西他赛用于多线治疗晚期非小细胞肺癌患者的临床效果。**方法:**选择我院 2017 年 1 月到 2019 年 8 月共 86 例晚期非小细胞肺癌患者为研究对象,按照随机抽签法分为对照组、观察组各 43 例,地塞米松预处理后,对照组仅应用多西他赛治疗,观察组联合应用阿帕替尼与多西他赛治疗,3 周为 1 个治疗周期,均治疗 4 个周期。比较两组治疗前、治疗 4 周期后血清肿瘤标志物水平、免疫功能及生活质量及不良反应发生情况。**结果:**观察组治疗 4 周期后总缓解率为 44.19%(19/43),高于对照组总缓解率 23.26%(10/43)($P<0.05$);治疗 4 周期后两组患者细胞角蛋白 19 片段抗原 21-1(CYFRA21-1)、癌胚抗原(CEA)、糖蛋白抗原 125(CA125)、鳞状上皮细胞癌抗原(SCC)水平、 $CD8^+$ 、生命质量测定量表 EORTC QLQ-C30(QLQ-C30)中的功能及症状总得分均较治疗前降低,且观察组低于对照组($P<0.05$); $CD3^+$ 、 $CD4^+$ 、 $CD4^+/CD8^+$ 水平及 QLQ-C30 的总体健康状况及生活质量总得分均高于治疗前,且观察组高于对照组($P<0.05$),两组患者治疗期间的不良反应发生率无差异($P>0.05$)。**结论:**阿帕替尼联合多西他赛用于多线治疗晚期非小细胞肺癌患者,可在一定程度上提高缓解率,其改善血清肿瘤标志物水平的效果更优,有助于提高患者机体免疫功能和生活质量,且短期内不会增加不良反应。

关键词:晚期非小细胞肺癌;阿帕替尼;多西他赛;多线治疗;肿瘤标志物;免疫功能;生活质量

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Effect of Apatinib Combined with Docetaxel on Serum Tumor Markers, Immune Function and Quality of Life in Patients with Multiline Therapy for Advanced Non-small Cell Lung Cancer*

DING Ting-ting¹, RUI Xiao-yan¹, FAN Hong-feng¹, ZHANG Yan-xi¹, CHEN Jun¹, XU Ru²

(1 Department of Respiratory Medicine, Chuzhou Clinical College of Anhui Medical University/The First People's Hospital of Chuzhou, Chuzhou, Anhui, 239000, China;

2 Department of Respiration, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230022, China)

ABSTRACT Objective: To analyze the effect of apatinib combined with docetaxel in the treatment of patients with advanced non-small cell lung cancer. **Methods:** From January 2017 to August 2019, a total of 86 patients with advanced non-small cell lung cancer who were treated in our hospital were selected as the research object, according to the random draw method, they were divided into control group and observation group, 43 cases in each group. After pretreatment with dexamethasone, the control group was used only application docetaxel treatment, observation group was used apatinib combined with docetaxel treatment. 3 weeks were a treatment cycle, all of which were 4 cycles. The serum tumor markers levels, immune function and quality of life and adverse reactions of two groups before treatment and 4 cycles after treatment were compared. **Results:** The total remission rate of the observation group at 4 cycles after treatment was 44.19%(19/43), which was higher than 23.26% (10/43) of the control group ($P<0.05$). The levels of cytokeratin-19-fragment antigen 21-1 (CYFRA21-1), carcinoembryonic antigen (CEA), glycoprotein antigen 125 (CA125) and squamous cell carcinoma antigen (SCC), $CD8^+$, quality of life measurement scale EORTC QLQ-C30(QLQ-C30) function and symptoms total scores of the two groups at 4 cycles after treatment were lower than those before treatment, and those of observation group were lower than those of control group ($P<0.05$). The levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ and QLQ-C30 general health and quality of life total scores were higher than those before treatment, and those of the observation group were higher than those of the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Apatinib combined with docetaxel for the multiline treatment of patients with advanced non-small cell lung cancer can improve the remission rate to a certain extent, improve the level of serum tumor markers, help improve the immune function and quality of life of patients, and will not increase adverse reactions in the short term.

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作者简介:丁婷婷(1985-),女,本科,主治医师,研究方向:肺癌及肺部疾病诊治,E-mail: jyttsa09@163.com

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前言

在全部因癌症导致的死亡患者中,肺癌患者的死亡率第一,肺癌患者的5年生存率不超过五分之一,肺癌含小细胞、非小细胞肺癌两类,后者占比重更大^[1]。肺癌由于早期缺乏典型临床表现,部分被误诊为普通呼吸系统疾病,在治疗上未给予足够重视,使得大多数肺癌患者在最终确诊时病变已经进入中晚期^[2]。临床将TNM分期为IIIb-IV期的肺癌视为晚期肺癌,晚期肺癌患者基本已经错过最佳的手术时机,部分肿瘤甚至已发生转移,因而放疗、化疗成为重要的辅助治疗方法^[3]。含铂双药化疗是针对晚期非小细胞肺癌常用的一线化疗方案,但一些患者因为治疗中出现耐药,使得化疗效果不理想,最终化疗失败,需要接受二线或者三线化疗^[4]。二线标准化疗方案多为多西他赛或培美曲塞单一应用,有效率也较低,所以,临床需要探求更为有效、安全的化疗方案以治疗二线化疗失败的患者。阿帕替尼为抗血管生成剂,可血管内皮细胞生长因子受体-2(Vascular endothelial growth factor receptor-2, VEGFR-2)中的腺苷三磷酸(Adenosine triphosphate, ATP)高度选择性结合,抑制 VEGFR-2 的激活,实现对肿瘤新生血管的阻断,促使肿瘤细胞凋亡^[5]。鉴于此,本研究探讨了阿帕替尼联合多西他赛多线治疗对晚期非小细胞肺癌患者血清肿瘤标志物,免疫功能及生活质量的影响,旨在为晚期非小细胞肺癌患者的多线化疗用药选择提供参考依据,现作以下报道。

1 资料与方法

1.1 一般资料

选择我院2017年1月到2019年8月共86例晚期非小细胞肺癌患者为研究对象,纳入标准:(1)诊断参考非小细胞肺癌诊断标准^[6];(2)TNM分期为IIIb-IV期的晚期非小细胞肺癌;(3)预计生存时间超过3个月;(4)既往接受一线含铂双药化疗后病情仍继续进展;(5)对化疗可耐受。排除标准:(1)合并急性血液系统感染者;(2)对本研究药物过敏者;(3)伴有心、肝、肾等脏器功能严重障碍者;(4)存在精神异常或交流障碍者;(5)处于妊娠期或哺乳期的女性患者。以随机抽签法分为2组,每组43例,观察组男、女分别31例、12例,年龄31岁到77岁,年龄平均(61.19±10.81)岁;病理类型:腺癌23例,鳞癌15例,其他5例。对照组男、女分别30例、13例,年龄34岁到80岁,年龄平均(62.28±11.72)岁;病理类型:腺癌21例,鳞癌17例,其他5例。两组性别、年龄、病理类型比较,差异无统计学意义($P>0.05$),病例同质性较好。两组患者均签署了知情同意书,我院伦理委员会已批准本次研究。

1.2 治疗方法

全部患者化疗开始前均选择8 mg 醋酸地塞米松(芜湖康奇制药有限公司,规格:0.75 mg/片,国药准字H34021783)口服治疗,每天服用2次,共服用3天。对照组单一应用多西他赛治疗,多西他赛注射液(江苏恒瑞医药股份有限公司,规格:

1 mL:20 mg,国药准字H20163032),剂量:60 mg/m²,静脉滴注,3周为一个治疗周期,1周期滴注1次。观察组联合应用多西他赛与阿帕替尼治疗,多西他赛注射液用法及剂量同对照组,另给予甲磺酸阿帕替尼片(江苏恒瑞医药股份有限公司,规格:0.25 g/片(以阿帕替尼计),国药准字H20140103)0.75 g/天,餐后半小时口服,尽量保证治疗期间每天服药时间一致,3周为1个治疗周期。全部患者治疗期间均接受营养支持、胃黏膜保护剂等对症支持治疗,两组均治疗4个周期。

1.3 观察指标

1.3.1 疗效评价 根据实体瘤疗效评价(RSCIST)标准进行评估^[7]:(1)完全缓解(Complete response, CR):与治疗前比较,治疗4周期后目标病灶全部消失;(2)部分缓解(Partial response, PR):与治疗前比较,治疗4周期后目标病灶长径总和减小超过50%;(3)稳定(Stable disease, SD):与治疗前比较,治疗4周期后目标病灶长径总和减小25%-50%;(4)进展(Progress disease, PD):与治疗前比较,治疗4周期后目标病灶长径总和增加超过25%或有新病灶出现。总缓解率=CR+PR。

1.3.2 血清肿瘤标志物 分别在治疗前、治疗4周期后抽取患者清晨空腹状态下5 mL 静脉血,在1500 r/min速度下进行10分钟离心处理,离心半径10 cm,分离上清后利用酶联免疫吸附法测定两组患者鳞状上皮细胞癌抗原(Squamous cell carcinoma antigen, SCC)、细胞角蛋白19片段抗原21-1(cytokeratin-19-fragment antigen21-1, CYFRA21-1)、糖蛋白抗原125(Glycoprotein antigen 125, CA125)、癌胚抗原(Carcinoembryonic antigen, CEA)水平,试剂盒购自罗氏公司,操作严格按照说明书进行。

1.3.3 免疫功能 分别在治疗前、治疗4周期后抽取所有患者空腹静脉血3 mL,测定两组患者CD3⁺、CD4⁺、CD8⁺、CD4⁺/CD8⁺水平,均利用流式细胞仪(美国贝克曼CyttoFLEX型)进行检测。

1.3.4 生活质量 分别在治疗前、治疗4周期后采用癌症患者生命质量测定量表EORTC QLQ-C30(QLQ-C30)中文版^[8]对患者生活质量进行评价,量表共30个条目,1~28条目(功能及症状)按"从来没有"、"有一点"、"较多"、"很多"得分1-4分,得分越高,说明生活质量越差;条目29、30(整体生活质量和健康状况)采用1-7级评分法,根据患者回答的选项得分1-7分,得分越高,生活质量越高。

1.4 统计学方法

统计学分析采用SPSS23.0软件完成,计数资料以%表示, χ^2 检验,计量资料以($\bar{x} \pm s$)表示,t检验, $P<0.05$ 证实差异具备统计学意义。

2 结果

2.1 治疗效果

观察组治疗4周期后总缓解率为44.19%(19/43),高于对照组的23.26%(10/43),差异比较有统计学意义($P<0.05$),见表1。

表 1 两组总缓解率比较 [例(%)]

Table 1 Comparison of total remission rates between the two groups [n(%)]

Groups	n	CR	PR	SD	PD	Total response rate
Observation group	43	2(4.65)	17(39.53)	18(41.86)	6(13.95)	19(44.19)
Control group	43	0(0.00)	10(23.26)	13(30.23)	20(46.51)	10(23.26)
χ^2						4.214
P						0.040

2.2 肿瘤标志物

观察组与对照组治疗前 CYFRA21-1、CEA、CA125、SCC 指标水平比较无差异 ($P>0.05$), 治疗 4 周期后各指标水平平均

较治疗前下降 ($P<0.05$), 观察组治疗 4 周期后各指标水平均低于对照组, 差异有统计学意义 ($P<0.05$), 见表 2。

表 2 两组治疗前、治疗 4 周期后血清肿瘤标志物水平比较 ($\bar{x} \pm s$)

Table 2 Comparison of serum tumor markers between the two groups before and 4 cycles after treatment ($\bar{x} \pm s$)

Groups	n	CYFRA21-1($\mu\text{g/L}$)		CEA($\mu\text{g/L}$)		CA125(ng/mL)		SCC(ng/mL)	
		Before treatment	4 cycles after treatment	Before treatment	4 cycles after treatment	Before treatment	4 cycles after treatment	Before treatment	4 cycles after treatment
Observation group	43	7.53 $\pm$ 1.65	3.86 $\pm$ 0.82*	23.84 $\pm$ 4.32	8.69 $\pm$ 1.35*	65.36 $\pm$ 6.82	21.45 $\pm$ 2.13*	5.23 $\pm$ 0.58	1.52 $\pm$ 0.32*
Control group	43	7.49 $\pm$ 1.38	5.52 $\pm$ 1.21*	22.43 $\pm$ 4.29	13.57 $\pm$ 2.47*	63.82 $\pm$ 6.39	38.45 $\pm$ 4.29*	5.29 $\pm$ 0.60	2.49 $\pm$ 0.41*
t		0.122	7.447	1.519	11.368	1.081	23.274	0.471	12.230
P		0.903	0.000	0.133	0.000	0.283	0.000	0.639	0.000

Note: compared with before treatment, * $P<0.05$.

2.3 免疫功能

观察组与对照组治疗前 $\text{CD}3^+$ 、 $\text{CD}4^+$ 、 $\text{CD}8^+$ 、 $\text{CD}4^+/\text{CD}8^+$ 指标水平比较差异无统计学意义 ($P>0.05$), 治疗 4 周期后两组 $\text{CD}3^+$ 、 $\text{CD}4^+$ 、 $\text{CD}4^+/\text{CD}8^+$ 水平均较治疗前升高, $\text{CD}8^+$ 水平较治

疗前下降 ($P<0.05$), 观察组治疗 4 周期后 $\text{CD}3^+$ 、 $\text{CD}4^+$ 、 $\text{CD}4^+/\text{CD}8^+$ 水平高于对照组, $\text{CD}8^+$ 水平低于对照组 ($P<0.05$), 见表 3。

表 3 两组治疗前后免疫功能比较 ($\bar{x} \pm s$)

Table 3 Comparison of immune function between the two groups before and after treatment ($\bar{x} \pm s$)

Groups	n	$\text{CD}3^+(\%)$		$\text{CD}4^+(\%)$		$\text{CD}8^+(\%)$		$\text{CD}4^+/\text{CD}8^+$	
		Before treatment	4 cycles after treatment	Before treatment	4 cycles after treatment	Before treatment	4 cycles after treatment	Before treatment	4 cycles after treatment
Observation group	43	63.42 $\pm$ 5.75	69.63 $\pm$ 7.49*	31.06 $\pm$ 5.29	35.99 $\pm$ 5.21*	32.26 $\pm$ 4.19	25.42 $\pm$ 5.49*	0.96 $\pm$ 0.21	1.42 $\pm$ 0.32*
Control group	43	62.19 $\pm$ 5.34	66.43 $\pm$ 6.82	30.85 $\pm$ 5.33	33.42 $\pm$ 5.79*	31.47 $\pm$ 4.23	28.39 $\pm$ 5.68*	0.98 $\pm$ 0.23	1.18 $\pm$ 0.28*
t		1.028	2.071	0.183	2.164	0.870	2.465	0.003	3.701
P		0.307	0.041	0.855	0.033	0.387	0.016	0.997	0.000

Note: compared with before treatment, * $P<0.05$.

2.4 生活质量

观察组与对照组治疗前 QLQ-C30 各评分差异无统计学意义 ($P>0.05$), 治疗 4 周期后两组功能及症状评分均低于治疗前, 总体健康状况及生活质量评分均高于治疗前 ($P<0.05$), 观察组治疗 4 周期后 QLQ-C30 评分改善情况优于对照组 ($P<0.05$), 见表 4。

2.5 不良反应发生情况

治疗期间, 对照组出现血液毒性反应 (白细胞减少、粒细胞减少、血小板减少) 13 例, 发生率为 30.23% (13/43), 非血液毒性反应 (蛋白尿、乏力、高血压等) 15 例, 发生率为 34.88% (15/43), 均为 I-II 级; 观察组出现血液毒性反应 16 例, 发生率为 37.21% (16/43), 非血液毒性反应 18 例, 发生率为 41.86% (18/43), 均为 I-II 级。两组血液毒性反应与非血液毒性反应发生率相比均无统计学意义 ($\chi^2=0.468, 0.443, P=0.494, 0.506$)。

表 4 两组治疗前后 QLQ-C30 得分的比较($\bar{x} \pm s$, 分)Table 4 Comparison of QLQ-C30 scores between the two groups before and after treatment($\bar{x} \pm s$, scores)

Groups	n	Function and symptoms total scores		General health and quality of life total scores	
		Before treatment	4 cycles after treatment	Before treatment	4 cycles after treatment
Observation group	43	80.62 $\pm$ 12.34	62.35 $\pm$ 7.49*	5.34 $\pm$ 2.15	8.83 $\pm$ 1.22*
Control group	43	81.54 $\pm$ 10.19	70.83 $\pm$ 9.16*	5.73 $\pm$ 1.94	6.99 $\pm$ 1.15*
t	-	0.487	4.700	0.883	7.197
P	-	0.628	0.000	0.380	0.000

Note: compared with before treatment, * $P < 0.05$.

3 讨论

手术治疗晚期非小细胞肺癌效果不佳,化疗成为重要治疗方法,化疗对于控制晚期非小细胞肺癌的肿瘤细胞转移、增殖以及延长患者生存时间具有重要意义^[9-11]。随着研究的不断深入,可用于晚期非小细胞肺癌化疗的药物有多种,但受到多种因素的影响,一些患者接受一线化疗后无法获得预期疗效,部分二线化疗也存在着毒性明显、药物作用时间短的不足,所以临床需要不断探求安全、有效的多线化疗方案^[12-14]。多西他赛属于化疗中应用广泛的一类紫杉类抗肿瘤药物,其可通过调节肿瘤细胞微管蛋白的聚合与解聚,并进一步形成稳定性高的非功能微管蛋白束,发挥对癌细胞增殖与分裂的有效抑制作用^[15-17]。不少研究都证实,多西他赛是多种晚期癌症最可行的支持治疗药物,能够使晚期癌症患者生存时间得到明显延长^[18-20]。但也有研究发现,多西他赛单一应用对肿瘤的缓解率低,同时持续用药还会有明显毒副反应,部分患者甚至因为无法耐受而出现治疗中断、治疗失败的情况^[21]。本研究观察组联合应用的阿帕替尼为小分子抗血管生成药物,其不仅能够通过阻断肿瘤病灶微血管形成发挥抗肿瘤效果,还具备逆转耐药基因的效应,能够减轻化疗导致的耐药情况,使化疗的实施获得更高的成功率^[22,23]。研究发现阿帕替尼用于化疗中安全性高,针对接受一线化疗失败的肺癌,在多线化疗中联合应用阿帕替尼能够获得较单药更突出的效果^[24]。

本研究观察组患者经过 4 周期的治疗后其肿瘤总缓解率明显更高,提示多西他赛联合阿帕替尼用于晚期非小细胞肺癌患者的治疗,可更好地抑制肿瘤细胞的增殖,促进肿瘤细胞凋亡,有更好的抗肿瘤效果。CYFRA21-1 为肺泡上皮细胞凋亡时的重要产物,其水平上升表明预后不佳^[25,26]。肺癌组织中 CEA 的阳性率超过 80%,其水平上升表明肿瘤细胞增殖活跃,水平得到控制表明肿瘤细胞减少^[27]。CA125、SCC 也是肺癌患者重要肿瘤标志物,其水平变化与病情程度有相关性,水平越高提示病情越严重^[28]。本研究观察组治疗 4 周期后 CYFRA21-1、CEA、CA125、SCC 各血清肿瘤标志物水平均明显低于对照组,提示两种治疗方案均有效,且联合使用多西他赛、阿帕替尼的改善效果更明显。本研究观察组治疗 4 周期后 CD3⁺、CD4⁺、CD4⁺/CD8⁺ 水平高于对照组,CD8⁺ 水平较对照组更低,治疗 4 周期后 QLQ-C30 得分得到明显改善,提示多西他赛联合阿帕替尼在非小细胞肺癌治疗中可更明显改善晚期非小细胞肺癌患者的免疫功能,分析观察组免疫功能改善更优的原因,肿瘤患者机体的免疫功能受到明显抑制,CD4⁺/CD8⁺ 是典型的表现,而阿帕替尼的抗肿瘤血管生成作用使肿瘤微环境得以改

变,从而各种免疫细胞的构成得到改善,一定程度上解除了免疫抑制状态,增强了机体自身的免疫功能^[29],因此上述免疫功能指标得以改善。患者免疫功能的提升使得身体各项机能提高,患者的日常生活能力得到一定恢复,从而观察组患者生活质量获得较好的改善,两种药物联合应用能够叠加药物的抗肿瘤效应,多西他赛可抑制癌细胞的增殖分裂,阿帕替尼减少了病灶内新微血管生成,隔断了癌细胞的营养供应,同时阿帕替尼的应用还能够使机体对治疗药物有更高的敏感性,保证药效的更大程度发挥,因而整体疗效更优^[30]。此外本研究中的不良反应均为 I - II 级,可能是治疗方案中阿帕替尼剂量较为合理,且治疗时间尚短,因此没有出现严重的不良反应,说明联合治疗的短期安全性较好。值得注意的是,若长期服用阿帕替尼,出现 III 级以上的不良反应时,应暂停用药,待不良反应有所缓解再行服药。

综上所述,阿帕替尼与多西他赛联合用于晚期非小细胞肺癌患者多线治疗中能够提高临床疗效,其对晚期非小细胞肺癌患者血清肿瘤标志物水平、机体免疫功能、生活质量的改善效果优于多西他赛单药治疗,且短期内不会增加不良反应。

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