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参附注射液联合奥西替尼治疗晚期 EGFR 阳性非小细胞肺癌患者疗效及对患者免疫功能的影响 *

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摘要 目的:探讨分析参附注射液联合奥西替尼治疗晚期 EGFR 阳性非小细胞肺癌(Non-small cell lung cancer, NSCLC)患者疗效及对患者免疫功能的影响。**方法:**选择 2018 年 6 月~2020 年 12 月我院收治的 EGFR 突变阳性晚期 NSCLC 患者 96 例,随机分为观察组 50 例、对照组 46 例,对照组给予奥西替尼口服治疗,观察组在对照组基础上给予参附注射液,两组均治疗 16 周。比较两组治疗临床疗效、免疫功能指标及患者生活质量评分结果。**结果:**治疗前,两组 T 淋巴细胞亚群水平和 EORTC-QLQ-C30 评分差异均无统计学意义($P>0.05$);治疗后,与对照组相比,观察组患者治疗有效率、CD4⁺/CD8⁺ 比值、功能领域及总体健康状况评分均显著增加,而外周血 CD8⁺ 水平、症状领域评分均显著降低($P<0.05$)。**结论:**参附注射液联合奥西替尼治疗晚期 EGFR 阳性 NSCLC 患者可有效提高临床治疗效果,改善患者机体免疫功能并提高患者生活质量,值得临床推广。

关键词:参附注射液;奥西替尼;晚期肺癌;EGFR 阳性;非小细胞肺癌;疗效;免疫功能

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Efficacy of Shenfu Injection Combined with Osimertinib in the Treatment of Patients with Advanced EGFR-positive NSCLC and Its Effect on the Immune Function of Patients*

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ABSTRACT Objective: To investigate and analyze the therapeutic effect of Shenfu injection combined with osimertinib in the treatment of patients with advanced EGFR-positive non-small cell lung cancer and its effect on the immune function of patients. **Methods:** A total of 96 EGFR mutation-positive advanced NSCLC patients admitted to our hospital from June 2018 to December 2020 were randomly divided into observation group of 50 cases and control group of 46 cases. The control group was given oral treatment with osimertinib, and the observation group Shenfu injection was given on the basis of the control group, and both groups were treated for 16 weeks. The clinical efficacy, immune function indicators and patient quality of life scores were compared between the two groups. **Results:** Before treatment, there was no significant difference in the levels of T lymphocyte subsets and EORTC-QLQ-C30 scores between the two groups ($P>0.05$); After treatment, compared with the control group, the observation group patients' treatment effectiveness, CD4⁺/CD8⁺ ratio, functional areas and overall health status scores were significantly increased, while the peripheral blood CD8⁺ level and symptom area scores were significantly reduced ($P<0.05$). **Conclusion:** Shenfu injection combined with Osimertinib in the treatment of patients with advanced EGFR-positive NSCLC can effectively improve the clinical treatment effect, improve the immune function of the patient and improve the quality of life of the patient, and it is worthy of clinical promotion.

Key words: Shenfu injection; Osimertinib; Advanced lung cancer; EGFR positive; Non-small cell lung cancer; Curative effect; Immune function

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肺癌是我国最为常见的一种恶性肿瘤,同时也是目前最为主要的癌症死亡原因之一。根据肺癌的类型,可将其分为小细胞肺癌以及 NSCLC,其中 NSCLC 约占所有肺癌的 80%^[1,2]。由于肺癌的发病较为隐匿,相关调查研究显示,约有 57% 的患者

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在初诊时已经发生并已处于疾病的晚期阶段,而且出现远处转移^[3]。对于此类晚期患者,临床多采用含铂类药物化疗方案,但临床治疗的局限性以及化疗期间其严重不良反应影响了患者的临床获益。目前针对肿瘤细胞分子改变的分子靶向治疗成为学者研究的重点,美国国立综合癌症网络目前已经将表皮生长因子受体-酪氨酸激酶抑制剂(EGFR-TKI)作为EGFR突变晚期NSCLC患者的一线治疗方案^[4,5]。但是晚期NSCLC患者因体质状况不佳等原因难以耐受化疗,因此采取有效的措施促进患者免疫功能恢复对延长患者总体生存时间、提高患者生活质量具有着重要价值^[6,7]。本研究具体探讨了参附注射液联合

化疗治疗晚期EGFR阳性NSCLC患者的疗效及对其免疫功能的影响。

1 资料与方法

1.1 临床资料

选择2018年6月~2020年12月我院收治的EGFR突变阳性晚期NSCLC患者96例作为研究对象,并将其随机分为观察组(n=50)和对照组(n=46)。两组一般资料差异无统计学意义($P>0.05$),如下表。本研究经本院伦理委员会审批通过且患者自愿签署知情同意书。

表1 临床资料
Table 1 Clinical Data

Clinical data	Observation group(n=50)	Control group(n=46)	t/χ^2	P
Gender				
Male	31	32	0.608	0.436
Female	19	14		
Age(year)	69.38±6.59	70.21±5.98	0.644	0.521
Pathology type				
Adenous cancer	29	25	0.130	0.719
Squamous cancer	21	21		
KPS Score (points)	75.46±6.28	74.93±7.22	0.385	0.702
ECOG score				
0	7	9	0.666	0.506
1	33	29		
2	10	8		

1.2 纳入标准与排除标准

纳入标准:①符合《中国原发性肺癌诊疗规范(2015年版)》诊断标准^[8];②按照美国癌症联合会(AJCC)关于NSCLC肿瘤分期系统(TNM)分期标准^[9],均为TNM分期IV期患者;③EGFR基因检测为突变阳性;④预计生存期≥6个月;⑤患者骨髓、肝、脑、肾等脏器功能正常。

排除标准:①对本研究药物过敏患者;②合并精神疾病患者;③合并其他严重感染性疾病患者;④合并造血功能异常患者;⑤合并其他原发性恶性肿瘤患者;⑥出现大量心包积液、胸腔积液无法控制患者。

1.3 方法

对照组:给予奥西替尼(泰瑞沙)(阿斯利康制药有限公司,批准文号:国药准字J20180027)80 mg/d口服,1次/d,连续服用16周。

观察组:在对照组基础上将60~80 mL参附注射液(华润三九(雅安)药业有限公司,批准文号:国药准字Z51020664)加入5% 250 mL葡萄糖注射液进行静脉滴注,1次/d,28 d为一疗程,连续治疗4疗程。

1.4 观察指标

1.4.1 疗效评价标准 按照WHO实体瘤近期疗效客观评价标准对患者近期治疗情况进行分析^[10],完全缓解(CR):所测量

病灶均消失,且持续4周以上;部分缓解(PR):患者可测量的病灶缩小在50%以上,且持续4周以上;稳定(SD):患者可测量的病灶缩小<50%或增大<25%,且持续4周以上;进展(PD):患者可测量病灶增大25%以上或出现新的病灶。治疗有效率=CR+PR。

1.4.2 外周血T淋巴细胞亚群 分别于入院后次日和治疗后次日,空腹状态下抽取两组患者外周血,采用流式细胞术检测外周血T淋巴细胞亚群(CD3⁺、CD4⁺、CD8⁺细胞)变化,计算占比及CD4⁺/CD8⁺比值。

1.4.3 生活质量 分别于治疗前后采用欧洲癌症研究与治疗组织生活质量核心量表(EORTC-QLQ-C30)^[11]对患者生活质量进行评估分析。

1.5 统计学分析

采用SPSS 25.0进行数据分析,计量资料比较采用t检验,计数资料比较采用 χ^2 检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 临床疗效

观察组患者治疗有效率显著高于对照组($P<0.05$),见表2。

2.2 外周血T淋巴细胞亚群

治疗前后对照组各T淋巴细胞亚群占比及比值均无显著

变化($P>0.05$), 观察组患者治疗后 $CD8^+$ 水平较治疗前显著降低($P<0.05$), $CD4^+/CD8^+$ 比值较治疗前显著升高($P<0.05$)。治疗前两组 T 淋巴细胞亚群占比及 $CD4^+/CD8^+$ 比值差异

无统计学意义($P>0.05$); 治疗后与对照组相比, 观察组治疗后 $CD8^+$ 水平显著降低, $CD4^+/CD8^+$ 比值显著增加($P<0.05$), 见表 3。

表 2 临床疗效[n(%)]
Table 2 Clinical efficacy[n(%)]

Groups	n	CR	PR	SD	PD	Effective rate
Observations	50	5(10.00)	32(64.00)	13(26.00)	0(0.00)	37(74.00)
Control group	46	1(2.17)	24(52.17)	21(45.65)	0(0.00)	25(54.35)
χ^2	-	-	-	-	-	4.045
P	-	-	-	-	-	0.044

表 3 外周血 T 淋巴细胞亚群
Table 3 T lymphocyte subsets of lymphocytes in peripheral blood

Groups	Period	$CD3^+$ (%)	$CD4^+$ (%)	$CD8^+$ (%)	$CD4^+/CD8^+$
Observation group (n=50)	Before treatment	48.32±6.47	31.53±5.12	30.33±4.28	1.05±0.31
	After treatment	49.02±7.21	32.31±6.84	26.78±2.40*	1.28±0.29*
	t	0.511	0.646	5.110	3.832
	P	0.611	0.520	0.000	0.000
Control group (n=46)	Before treatment	48.93±5.28	30.48±4.67	30.19±3.27	1.02±0.25
	After treatment	47.95±6.47	30.12±6.58	31.28±4.18	0.93±0.32
	t	0.809	0.303	1.393	1.503
	P	0.421	0.763	0.167	0.136

Note: Compared with the control group for the same period, * $P<0.05$.

2.3 EORCT-QLQ-C30 评分

治疗前两组患者 EORCT-QLQ-C30 评分评分无显著差异($P>0.05$), 治疗后观察组患者功能领域及总体健康状况评分较治疗前显著升高($P<0.05$), 治疗后两组患者症状领域评分较治

疗前显著降低($P<0.05$)。

与对照组治疗后相比, 观察组治疗后患者功能领域、总体健康状况领域评分显著增加, 而症状领域评分显著降低($P<0.05$), 见表 4。

表 4 治疗前后 EORCT-QLQ-C30 评分比较(分)
Table 4 Comparison of EORCT-QLQ-C30 scores before and after treatment(points)

Groups	Period	Functional areas	Symptoms field	Overall health status
Observation group (n=50)	Before treatment	54.58±5.28	40.82±4.75	65.48±5.06
	After treatment	61.39±6.02*	29.07±4.06*	70.21±5.17*
	t	6.014	13.296	4.623
	P	0.000	0.000	0.000
Control group(n=46)	Before treatment	55.10±6.21	39.95±5.11	65.92±6.44
	After treatment	56.38±7.02	34.65±4.98	65.47±5.94
	t	0.926	5.039	0.348
	P	0.357	0.000	0.728

Note: Compared with the control group for the same period, * $P<0.05$.

3 讨论

NSCLC 是临床常见的一种高发病率和高致死率的恶性肿瘤。对于 NSCLC 的临床治疗, 目前仍以使用铂类化疗药物为

主, 但是由于其疗效进入了平台期, 且化疗的毒副反应较大, 患者的耐受程度相对较差^[12]。多项研究显示, EGFR 与肿瘤的发生、分化、黏附、迁移、转化、存活和凋亡均明显相关^[13,14]。学者报道证实^[15,16], 对于 EGFR 敏感突变阳性的晚期 NSCLC 患者而

言,大多可受益于 EGFR-TKI 治疗,从而有效提高了患者的临床治疗疗效,延长患者生存期,但是由于 EGFR-TKI 治疗后可出现耐药,而发生 EGFR-TKI 耐药后治疗的难度将进一步加大,因此如何提高 EGFR-TKI 的治疗效果已经成为目前研究的热点以及难点。

参附注射液原方来源于参附汤,主治阳气暴脱、手足逆冷、头晕气短、汗出脉微等症,具有补先天、益后天之功^[7]。研究发现,参附注射液对正气受损、脾肾亏虚相关恶性肿瘤患者具有良好的疗效,同时由于参附注射液可促进骨髓干细胞增殖、明显改善骨髓造血微循环、刺激正常巨噬细胞增殖从而促进血小板生成等相关作用,故可有效降低恶性肿瘤化疗期间不良反应发生情况,提高患者对治疗的耐受度^[18-20]。奥西替尼是 EGFR 阳性 NSCLC 患者的治疗方式之一,可明显延长患者肿瘤复发时间以及生存时间,但是对于晚期 NSCLC 患者或老年患者而言,抗肿瘤治疗可导致机体出现免疫功能的紊乱,从而影响患者生活质量^[21-23]。

为了进一步提高晚期 EGFR 阳性 NSCLC 患者 EGFR-TKI 治疗疗效,并改善患者免疫功能功能,本研究通过参附注射液联合奥西替尼对晚期 EGFR 阳性非小细胞肺癌进行治疗,其免疫功能相关结果显示:参附注射液治疗后,与对照组相比,观察组患者治疗有效率、CD4⁺/CD8⁺ 比值均显著增加,而外周血 CD8⁺ 水平显著降低($P<0.05$),与 Garon EB^[24]和 Shu CA^[25]的相关研究报道结果相似,提示参附注射液联合使用可通过改善患者外周血 T 淋巴细胞水平,从而增强患者免疫功能,并发挥良好的治疗效果。结合相关研究^[26,27]分析其作用机制可能在于:参附注射液中红参提取物具有明显的抗肿瘤、清除自由基、增强 NK 细胞活力作用,同时可有效促进抗原结合细胞的增多,对机体免疫功能具有显著的促进作用;另外,方中附子的散寒作用也可以间接增强患者的机体免疫功能,而免疫功能的改善是延长晚期恶性肿瘤患者生存时间、提高临床治疗获益率的重要措施^[28-30]。此外,本研究结果显示,治疗后观察组患者功能领域、总体健康状况领域评分显著高于对照组,而症状领域评分显著低于对照组($P<0.05$),表明:参附注射液联合 EGFR-TKI 治疗,可有效改善患者的生活质量,结合前文结果分析:参附注射液联合 EGFR-TKI 治疗对 NSCLC 患者生活质量的改善主要考虑与参附注射液提高机体免疫功能,提高临床治疗疗效,并减轻患者临床症状、改善机体功能以及增强患者对治疗的信心等多种因素相关。本研究不足之处在于:由于本研究纳入样本量相对较小,且观察时间相对较短,研究结果可能存在一定的偏差,提示后续研究将进一步增加样本量,延长观察时间,从而获得更为可靠的临床研究数据。

综上所述,参附注射液联合奥西替尼治疗晚期 EGFR 阳性 NSCLC 患者可有效提高临床治疗效果,改善患者机体免疫功能并提高患者生活质量,值得临床推广。

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