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吉非替尼联合 GP 化疗方案治疗晚期非小细胞肺癌的效果及对血清 CEA、SCC、NSE、CYFRA21-1 水平的影响 *

任宝恒[1] 万 伟[2△] 周庆元[1] 宋利明[1] 向 静[1] 丁 亮[3]

（1 西安交通大学附属汉中 3201 医院呼吸与危重症医学科 陕西 汉中 723000；
2 西安市长安医院肿瘤科 陕西 西安 710016；3 西安市长安医院临床药学室 陕西 西安 710016）

摘要 目的：研究吉非替尼联合吉西他滨和顺铂(GP)化疗方案治疗晚期非小细胞肺癌的效果及对血清癌胚抗原(Carcinoembbryonic antigen,CEA)、鳞状细胞癌相关抗原(Squamous cell carcinoma,SCC)、神经元特异烯醇化酶(Neuron-specific enolase,NSE)、细胞角蛋白 19 片段(Cytokeratin-19-fragment,CYFRA21-1)水平的影响。**方法：**选取 2016 年 6 月 ~2018 年 6 月我院收治的晚期非小细胞肺癌患者 110 例，采用随机数字表法将患者分为两组，每组 55 例。对照组患者给予 GP 化疗方案，观察组在对照组的基础上给予吉非替尼。比较两组患者的临床治疗效果，治疗前后血清肿瘤标志物水平和生活质量的变化以及不良反应发生情况。**结果：**治疗后，观察组疾病控制率为 86.67%，对照组为 74.55%，观察组显著高于对照组($P<0.05$)；两组治疗后血清 CEA、SCC、NSE 和 CYFRA21-1 水平均较治疗前显著下降，且观察组以上指标均显著低于对照($P<0.05$)；两组治疗后 FACT-L 各项评分包括躯体状况、社会家庭状况、情感状况、肺癌特异性模块和功能状况评分均较治疗前显著升高，且观察组以上指标均显著高于对照($P<0.05$)。治疗期间，观察组患者白细胞减少、血小板减少、肝肾功能异常的发生率显著低于对照组($P<0.05$)，两组贫血、恶心呕吐的发生率比较无统计学差异($P>0.05$)。**结论：**与 GP 化疗方案相比，吉非替尼联合 GP 化疗方案可更显著提高晚期非小细胞肺癌患者的治疗效果，改善其生活质量，且安全性较高，可能与其降低血清 CEA、SCC、NSE 和 CYFRA21-1 水平有关。

关键词：吉非替尼；GP 化疗方案；晚期非小细胞肺癌；效果

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Efficacy of Gefitinib Combined with GP Chemotherapy in the Treatment of Advanced Non-small Cell lung Cancer and Its Effect on the Serum CEA, SCC, NSE and CYFRA21-1 Levels*

REN Bao-heng[1], WAN Wei[2△], ZHOU Qing-yuan[1], SONG Li-ming[1], XIANG Jing[3], DING Liang[3]

(1 Respiratory and critical care medicine, Hanzhong 3201 hospital affiliated to xi 'an jiaotong university, Hanzhong, Shaanxi, 723000, China;
2 Oncology department, Chang 'an hospital in xi 'an, shaanxi province, Xi'an, Shaanxi, 710016, China;
3 Xi'an Chang'an Hospital Clinical Pharmacy, Xi'an, Shaanxi, 710016, China)

ABSTRACT Objective: To study the efficacy of gefitinib combined with gemcitabine and cisplatin (GP) chemotherapy in the treatment of advanced non-small cell lung cancer and its effect on serum carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC), Effects of neuron-specific enolase (NSE) and Cytokeratin-19-fragment (CYFRA21-1) levels. **Methods:** 110 patients with advanced non-small cell lung cancer admitted to our hospital from June 2016 to June 2018 were selected. The patients were divided into two groups with random number table method, with 55 patients in each group. The control group was given GP chemotherapy, and the observation group was given gefitinib on the basis of the control group. The clinical effects, changes of serum tumor markers and quality of life before and after treatment, as well as the occurrence of adverse reactions were compared between the two groups. **Results:** After treatment, the disease control rate was 86.67% in the observation group and 74.55% in the control group, which was significantly higher than that in the control group ($P<0.05$). There was no significant difference in CEA, SCC, NSE and CYFRA21-1 levels in the two groups before treatment ($P>0.05$). After treatment, the above indicators were significantly decreased in two groups, and in the observation group was significantly lower than the control group ($P<0.05$). The FACT-L scores of the two groups before treatment included physical condition, social family status, emotional status, lung cancer specific module and functional status, and there was no significant difference ($P>0.05$). After treatment, these scores were significantly increased in two groups, and the observation group was significantly higher than the control group ($P<0.05$). During the treatment period, the incidence of leukopenia, thrombocytopenia, liver and kidney dysfunction in the observation group was significantly lower than that in the control group ($P<0.05$), and there was no statistical difference in the incidence of anemia, nausea and vomiting between the two groups ($P>0.05$). **Conclusion:** Compared with GP chemotherapy, gefitinib

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作者简介：任宝恒(1972-)，男，本科，副主任医师，主要研究方向：肺癌的临床诊治，E-mail: renbaoheng1972@126.com

△ 通讯作者：万伟(1983-)，男，本科，主治医师，主要研究方向：消化道，肺癌，食管癌，E-mail: wanwei211@163.com，电话：13689261210

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combined with GP chemotherapy can significantly improve the treatment of patients with advanced non-small cell lung cancer, improve their quality of life, and have higher safety, which may reduce serum CEA, SCC, NSE and CYFRA21-1 level is related.

Key words: Gefitinib; GP chemotherapy; advanced non-small cell lung cancer; Efficacy

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前言

肺癌是我国发病率和死亡率最高的恶性肿瘤,其发病率近年来呈现逐年上升的态势,已经成为威胁人类健康的重大公共卫生问题[1-3]。非小细胞肺癌是肺癌常见的病理类型,约占所有肺癌的 80 %[4,5]。由于该病早期的临床症状不典型,约 2/3 的患者就诊时已发展为中晚期,不宜采用手术治疗,患者的 10 年生存率仅为 7 %左右,5 年生存率不到 15 %, 且患者的预后较差[6,7]。晚期非小细胞肺癌的治疗以延长患者的生存期和提高生活质量为主。目前,临床治疗主要采用放疗和化疗。在常用的化疗方案中,以铂类制剂为基础的化疗药物可显著降低晚期患者的死亡率,但药物副反应较大,患者的依从性差[8-10]。

吉非替尼是一种选择性表皮生长因子受体抑制剂,可显著抑制肿瘤血管的生成、转移及生长,并促进肿瘤细胞凋亡,临床效果较好[11,12]。肿瘤标志物是肿瘤细胞或组织合成表达或由宿主细胞释放的一类物质,可用于肿瘤的诊断、预后评估和性质判断,在临床中已得到广泛应用[13]。近年来,越来越多的肿瘤标志物被发现,CEA 在多种恶性肿瘤中均有不同程度的升高,是临床评价肺癌常用的指标;SCC 在肺鳞癌的诊断中具有重要的价值, 同时还能够反应化疗的效果;NSE 在肺癌中有较高的特异性和敏感性, 有助于诊断和分期, 及检测患者不良预后;CYFRA21-1 在肺癌患者的血清中显著升高, 可以预测化疗反应和预后情况[14,15]。因此,本研究主要探讨了吉非替尼联合 GP 化疗方案治疗晚期非小细胞肺癌的效果及对血清 CEA、SCC、NSE、CYFRA21-1 水平的影响,以期为晚期非小细胞肺癌的治疗提供更多的参考依据。

1 资料与方法

1.1 一般资料

选取我院收治的 110 例晚期非小细胞肺癌患者,研究时间段为 2016 年 6 月 ~2018 年 6 月。纳入标准:① 经病理活检确诊为非小细胞肺癌;② 临床分期为Ⅲ~Ⅳ期;③ 卡氏功能状态评分(Karnofsky performance status, KPS)评分≥ 70 分;④ 入组前未接受过放化疗、靶向治疗等抗肿瘤治疗者;⑤ 预计生存期长于 3 个月者。排除:① 合并其他恶性肿瘤者;② 合并精神神经异常及不能配合治疗者;③ 哺乳期及妊娠期妇女。将所有患者随机分为两组, 每组各 55 例。对照组中, 男 29 例, 女 26 例; 年龄 41~65 岁,平均 55.38± 3.46 岁;肿瘤分期:ⅢB 期 30 例,Ⅳ期 25 例; 观察组中, 男 30 例, 女 25 例; 年龄 40~63 岁, 平均 54.89± 3.21 岁;肿瘤分期:ⅢB 期 28 例,Ⅳ期 27 例。两组一般资料比较差异均无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组给予 GP 化疗方案, 第 1 d 和第 8 d 静脉滴注吉西他滨(南京正大天晴制药有限公司,国药准字 H20093404)1000 mg/(m^2·d),30 min 内滴完,第 2 d 给予顺铂(南京制药厂有限公司,国药准字 H20030675)75 mg/m^2,静滴,21 d 为一个化疗疗程。观察组在对照组的基础上给予吉非替尼片(齐鲁制药(海南)有限公司,国药准字 H20163465),口服,250 mg/ 次,1 次 /d。两组均治疗 2 个疗程。

1.3 观察指标

① 临床治疗效果。② 血清肿瘤标志物水平,分别于治疗前和治疗后 1 个月抽取两组患者的空腹静脉血 5 mL,2000 rpm 离心后分离血清, 采用全自动电化学发光免疫分析仪测定 CEA、SCC、NSE、CYFRA21-1 水平, 试剂盒均由深圳新产业公司提供。③ 生存质量, 采用肺癌治疗功能评价量表(Functional Assessment of Cancer Therapy-Lung, FACT-L)进行评价,得分高表示患者的状况好。④ 不良反应的发生情况。

1.4 疗效评定标准

完全缓解(Complete response, CR):肿瘤消失且持续 1 个月以上;部分缓解(Partial response, PR):肿瘤体积缩小 50%以上;病情稳定 (Stable disease, SD): 肿瘤体积缩小 50%以下或增大 25%以下; 病情进展 (Progression disease, PD): 肿瘤体积增大 25%以上或出现新病灶。以 CR+PR+SD 计算疾病控制率(Disease control rate, DCR)。

1.5 统计学方法

数据采用 SPSS16.0 进行统计学分析,计数资料以率(%)表示,组间比较行卡方检验,计量资料以($\bar{x}\pm s$)表示,组间比较行 t 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组治疗效果的比较

治疗后,观察组疾病控制率为 86.67%,对照组为 74.55%,观察组显著高于对照组(P<0.05),见表 1。

表 1 两组临床治疗效果比较[例(%)]

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

Groups	Cases	CR	PR	SD	PD	DCR
Control group	55	16(29.09)	10(18.18)	15(27.27)	15(27.27)	41(74.55)
Observation group	55	25(45.45)	15(27.27)	10(18.18)	5(9.09)	50(86.67)
x^2						5.153
P						0.023

2.2 两组患者治疗前后血清肿瘤标志物水平的比较

治疗后，两组 CEA、SCC、NSE 和 CYFRA21-1 水平均较治疗前显著下降，且观察组以上指标均显著低于对照($P<0.05$)，见表 2。

表 2 两组患者治疗前后血清肿瘤标志物水平比较($\bar{x}\pm s$)

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

Index	Control group(n=55)		Observation group (n=55)	
	Before treatment	After treatment	Before treatment	After treatment
CEA(ng/mL)	13.28± 3.85	9.32± 2.53*	13.87± 3.91	5.14± 1.57*#
SCC(ug/L)	25.61± 7.32	18.94± 5.07*	26.04± 7.85	12.06± 3.47*#
NSE(ng/mL)	24.81± 7.01	16.58± 4.36*	25.13± 7.54	12.08± 3.37*#
CYFRA21-1(ng/mL)	5.32± 1.06	4.13± 0.85*	5.84± 1.31	2.46± 0.74*#

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

2.3 两组治疗前后生存质量评分的比较

治疗后，两组患者的 FACT-L 各项评分包括躯体状况、社会家庭状况、情感状况、肺癌特异性模块和功能状况均较治疗前著升高，且观察组以上指标均显著高于对照($P<0.05$)，见表3。

表 3 两组患者治疗前后的生存质量比较($\bar{x}\pm s$，分)

Table 3 Comparison the quality of life between two groups before and after treatment($\bar{x}\pm s$, score)

Index	Control group(n=55)		Observation group (n=55)	
	Before treatment	After treatment	Before treatment	After treatment
Body condition	19.21± 5.37	21.85± 5.84*	19.84± 5.79	34.28± 6.47*#
Social/family condition	18.26± 5.37	21.54± 6.01*	18.86± 5.69	25.32± 7.18*#
Emotional condition	11.02± 3.07	15.58± 4.11*	11.85± 3.12	18.94± 4.78*#
Lung cancer specific module	27.85± 7.43	30.95± 8.12*	28.02± 7.81	35.27± 9.57*#
Function condition	14.56± 4.02	18.67± 5.53*	14.89± 4.57	22.58± 6.03*#

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

2.4 两组不良反应发生情况的比较

观察组白细胞减少、血小板减少、肝肾功能异常的发生率均显著低于对照组($P<0.05$)，而两组贫血、恶心呕吐的发生率比较无统计学差异($P>0.05$)，见表 4。

表 4 两组患者的不良反应发生情况比较[例(%)]

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

Groups	Cases	Anemia	Leukopenia	Thrombocytopenia	Nausea and vomiting	Abnormal liver and kidney function
Control group	55	35(29.09)	30(27.27)	32(27.27)	45(27.27)	13(74.55)
Observation group	55	31(45.45)	13(18.18)	11(18.18)	40(9.09)	2(86.67)
x^2	-	0.606	11.034	16.838	1.294	9.340
P	-	0.463	0.001	<0.001	0.255	0.002

3 讨论

肺癌的病因较复杂，目前尚未完全阐明，有研究显示肺癌的发生与长期大量吸烟、环境因素、遗传、电离辐射等密切相关[16]。目前，临床治疗早期非小细胞肺癌的有效方法为手术治疗，但早期诊断较困难，大部分患者在确诊时已出现扩散转移[17,18]。晚期肺癌患者以全身化疗为主，GP 化疗方案是治疗非小细胞肺癌的标准方案，包括顺铂和吉西他滨，顺铂可干扰癌细胞 DNA 的复制和转录，还可抑制肿瘤细胞分裂，进而起到广谱抗癌的作用 [19-21]。与吉西他滨联合应用可使顺铂更稳定的嵌入 DNA 中，进而干扰 DNA 的修复[22]。但该化疗方案的不良反应较多，患者的依从性差。因此，需要寻找更为有效安全的治疗方法。

吉非替尼是一种靶向药物，其治疗机制与化疗药物不同，可直接作用于靶点，针对性强，不易影响机体的健康细胞。吉非替尼可阻断肿瘤细胞增殖的信号传导，抑制其有丝分裂及增殖，促进肿瘤细胞凋亡，还能够抑制肿瘤细胞的转移、侵袭及肿瘤新生血管的形成[23,24]。本研究显示观察组疾病的控制率显著高于对照组，说明吉非替尼与 GP 化疗方案联合应用的抗肿瘤效果更佳，提示联合吉非替尼，在 GP 化疗方案有效的抑制肿瘤细胞的分裂产生广谱的抗癌作用的基础上，提高了治疗的靶向性，同时吉非替尼能够抑制表皮生长因子受体发生磷酸化，影响肿瘤细胞的侵袭、增值、凋亡等一系列信号转导。吉非替尼

也能保护患者的骨髓，维持患者的造血功能，提高免疫力[25]，从而抑制肿瘤的发生和发展，提高肿瘤的控制率。

CEA 是一种细胞表面糖蛋白，是最早发现的与肺癌相关的广谱肿瘤标志物，其水平变化可反映患者的病情进展情况和治疗效果[26,27]。CYFRA21-1 是一种细胞角蛋白，在肿瘤细胞分化的过程中脱落[28]。SCC 存在于肺鳞状上皮细胞癌的细胞浆中，其酸性部分仅见于恶性肿瘤组织中[29]。NSE 是一种糖代谢酶，主要存在于神经组织及神经元细胞中，非小细胞肺癌患者的 NSE 水平显著升高，可作为该病的诊断、评价手术效果及检测病情指标[30]。本研究显示治疗后吉非替尼联合 GP 方案可显著降低患者上述指标水平，也提示吉非替尼联合 GP 方案可通过改善血清 CEA、SCC、NSE 和 CYFRA21-1 水平，显著提高非小细胞肺癌的临床疗效，可能是由于吉非替尼通过降低血清 CEA、SCC、NSE 和 CYFRA21-1 水平，抑制肿瘤细胞的转移和增值，降低了化疗后患者的血液学毒性反应，从而提高化疗效率。本研究结果还显示吉非替尼联合 GP 化疗方案可显著改善患者的生存质量，这可能与其可降低血清肿瘤标志物有关。另外，观察组白细胞减少、血小板减少和肝肾功能异常的发生率较低，说明吉非替尼治疗非小细胞肺癌的安全性较好[31]。

综上所述，与 GP 化疗方案相比，吉非替尼联合 GP 化疗方案可更显著提高晚期非小细胞肺癌患者的治疗效果，改善其生活质量，且安全性较高，可能与其降低血清 CEA、SCC、NSE 和 CYFRA21-1 水平有关。

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