doi: 10.13241/j.cnki.pmb.2018.23.017

沙利度胺联合吉非替尼靶向治疗非小细胞肺癌的临床效果观察*

王 宏[1] 夏永寿[2] 加 静[3] 张 燕[1] 王 瑛[4△]

(1 空军军医大学唐都医院肿瘤科 陕西 西安 710038;2 西安市长安医院血液科 陕西 西安 710016;
3 西安医学院第二附属医院肿瘤内科 陕西 西安 710038;4 空军军医大学唐都医院呼吸科 陕西 西安 710038)

摘要 目的:探讨沙利度胺联合吉非替尼靶向治疗非小细胞肺癌的临床效果。**方法:**选取 2014 年 1 月 -2016 年 12 月我院收治的非小细胞肺癌患者 79 例,按照治疗方法的不同分为对照组 40 例、观察组 39 例。对照组进行常规非小细胞肺癌治疗,观察组在手术前给予沙利度胺联合吉非替尼靶向治疗后行常规治疗。比较两组临床疗效,6 个月、1 年生存率,并记录观察组患者不良反应的发生情况。**结果:**观察组化疗的化疗缓解率(71.79 %)显著高于对照组(52.50 %)(P<0.05)。观察组患者在治疗期间出现了不同程度的白细胞减少、、恶心呕吐、关节痛、脱发、肝功能损伤等不良反应,患者对以上症状均可耐受,给予对症治疗后均自行缓解。观察组患者 6 个月、1 年生存率均显著高于对照组(P<0.05)。**结论:**沙利度胺联合吉非替尼靶向治疗 NSCLC 患者的疗效较好,能显著提高患者生存率。

关键词:非小细胞肺癌;沙利度胺;吉非替尼

中图分类号:R734.2 **文献标识码:**A **文章编号:**1673-6273(2018)23-4474-04

Therapeutic Effect of Thalidomide Combined with Gefitinib on Non-small Cell Lung Cancer*

WANG Hong[1], XIA Yong-shou[2], JIA Jing[3], ZHANG Yan[1], WANG Ying[4△]

(1 Department of Oncology, Tangdu Hospital of Air Force Military Medical University, Xi'an, Shaanxi, 710038, China; 2 Department of Hematology, Chang'an Hospital of Xi'an City, Xi'an, Shaanxi, 710016, China; 3 Department of Medical Oncology, The Second Affiliated Hospital of Xi'an Medical University, Xi'an, Shaanxi, 710038, China; 4 Department of Pneumology, Tangdu Hospital of Air Force Military Medical University, Xi'an, Shaanxi, 710038, China)

ABSTRACT Objective: To explore the clinical efficacy of thalidomide combined with gefitinib in the treatment of non-small cell lung cancer. **Methods:** Selected 79 NSCLC patients admitted to our hospital from January 2014 to December 2016. All patients were divided into control group (n=40) and observation group (n=39) by treatment methods. The control group received NSCLC routine treatment. The observation group was given thalidomide combined with gefitinib targeted therapy before surgery, then received routine treatment. The clinical efficacy, 6 months and 1 year survival rates between two groups were compared. The incidence of adverse reactions in the observation group was recorded. **Results:** The chemotherapy remission rate in the observation group (71.79 %) was significantly higher than that in the control group (52.50 %) (P<0.05). The patients in the observation group experienced various adverse reactions such as neutropenia, nausea and vomiting, joint pain, hair loss, and liver function impairment during the treatment period. Patients can tolerate the above symptoms, and they all relieve themselves after symptomatic treatment. The 6-month and 1-year survival rates in the observation group were significantly higher than those in the control group (P<0.05). **Conclusions:** Thalidomide combined with gefitinib is effective in the treatment of NSCLC patients and can significantly improve the survival rate of patients. It is worth further study.

Key words: Non-small cell lung cancer; Thalidomide; Gefitinib

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

Article ID: 1673-6273(2018)23-4474-04

前言

肺癌是常见的呼吸系统肿瘤,其发病率位居世界恶性肿瘤首位,并随着现代化、工业化发展的进程呈现出逐年递增的趋势,病因尚不清楚,但一般认为与吸烟、工业废气、电离辐射、既往慢性病感染等相关[1,2]。肺癌的临床表现较复杂,发生部位、病理类型、转移情况及并发症发生情况等均会影响患者症状有无及反应轻重,肿瘤在局部生长受到刺激或压迫组织时会引起局部症状,如咳嗽、声音嘶哑、咳血等,肺癌患者也会伴发发热、消瘦等全身症状[3-5]。

* 基金项目:陕西省教育厅科学研究计划项目(2013JK0799)

作者简介:王宏(1971-),男,本科,副主任医师,研究方向:肿瘤内科治疗,E-mail: wanghong_19711208@163.com

△ 通讯作者:王瑛(1978-),女,本科,主治医师,研究方向:肿瘤内科治疗,E-mail: wangying_1978@163.com

(收稿日期:2018-04-28 接受日期:2018-05-23)

非小细胞肺癌(non small cell lung cancer,NSCLC)在肺癌中占 80 %左右,是最常见的肺癌类型,包括鳞状细胞癌、腺癌、腺鳞癌等[6,7],与小细胞癌(small cell lung cancer,SCLC)相比其癌细胞生长分裂较慢、扩散转移较晚,但 75 %左右的 NSCLC 发现时已处于中晚期,且 5 年生存率很低[8,9]。目前治疗 NSCLC 的主要手段是放疗、化疗和手术治疗,而单纯手术或者常规化疗对患者的疗效不佳,提高 NSCLC 患者的临床疗效、延长生存期仍旧是肺癌临床研究的热点[10]。本研究使用沙利度胺联合吉非替尼靶向治疗非小细胞肺癌,取得较好疗效,现报道如下。

1 材料与方法

1.1 一般资料

选取 2014 年 1 月 -2016 年 12 月我院收治的非小细胞肺癌患者 79 例,按照治疗方法的不同,分为对照组 40 例、观察组 39 例。两组一般资料比较无显著差异(P>0.05),见表 1。本研究已通过我院伦理委员会审批。

表 1 两组一般资料比较(n, $\bar{x}\pm$ s)

Table 1 Comparison of the general information between two groups (n, $\bar{x}\pm$ s)

Groups	Age(yesrs)	Gender	TNM stages	Tumor types
		Male/female	II/III/IV	Squamous carcinoma/ adenocarcinoma/ adenosquamous carcinoma
Control group(n=40)	56.7± 8.6	26/14	8/27/5	16/20/4
Observation Group(n=39)	57.1± 9.4	24/15	7/28/4	17/19/3
P	0.844	0.750	0.912	0.911

1.2 纳入及排除标准

纳入标准:① 符合非小细胞肺癌诊断标准;② 对化疗药物、沙利度胺、吉非替尼药物耐受者;③ 预计生存期 >3 个月;④ 已签知情同意书。排除标准:① 合并重大器官功能缺陷或障碍者;② 无手术或化疗治疗指征。

1.3 方法

对照组患者直接进行手术治疗,行常规局部切除、肺叶切除手术并接受淋巴结清扫,1 个月后行常规化疗方案:50-70 mg/m^2 顺铂腹腔滴注 135-175 mg/m^2 紫杉醇静脉滴注进行化疗,21 d 为 1 个疗程,共进行 3 个疗程。观察组在术前给予沙利度胺联合吉非替尼靶向治疗,口服沙利度胺(常州制药厂有限公司, 国药准字:32026129, 规格:25 mg), 起始用量为 100 mg/d,若患者可耐受则 1 w 后加至 200 mg/d;口服吉非替尼(阿斯利康制药有限公司, 国药准字:20140142, 规格:0.25 g× 10 片),0.25 g/d,于早餐前温水送服;用药化疗 4 个周期,化疗期间肌肉注射维生素 B、口服地塞米松(遂成药业股份有限公司,国药准字:H41021038,规格:0.75 mg× 100 s)0.75 mg/ 次,2 次 /d;化疗后 4 w 实施常规治疗,方法同对照组。

1.4 观察指标

(1)临床疗效:按照实体瘤疗效标准(RECIST)进行评价[11],完全缓解(complete remission,CR),靶病灶全部消失,维持 4 w 以上;部分缓解(partial remission,PR),靶病灶最大直径之和减少≥ 50 %,无新病灶出现,维持 4 w 以上;疾病稳定(stable disease,SD),靶病灶最大直径之和 <50 %,无新病灶出现;疾病进展(progressive disease,PD),靶病灶最大直径之和至少增加 25 %,或出现新病灶。化疗缓解率 =(完全缓解例数 部分缓解例数) / 总例数× 100 %。(2)不良反应:观察并记录观察组患者治疗期间不良反应的发生情况。(3)生存率:随访至 2018 年 1 月,记录患者 6 个月、1 年生存率。

1.5 统计学分析

用 SPSS 20.0 软件对数据进行分析,计量资料用($\bar{x}\pm$ s)表示,进行 t 检验,计数资料以[n(%)]表示,组件比较进行 x^2 检验。P<0.05 表示有显著性差异。

2 结果

2.1 两组患者临床疗效的比较

观察组化疗的化疗缓解率(71.79 %)显著高于对照组(52.50 %)(P<0.05),见表 2。

表 2 两组患者临床疗效的比较(n,%)

Table 2 Comparison of clinical efficacy between two groups(n,%)

Group	CR	PR	SD	PD	Chemotherapy remission rate
Control group(n=40)	8(20.00)	13(32.50)	14(35.00)	5(12.50)	21(52.50)
Observation group(n=39)	13(33.33)	15(38.46)	8(20.51)	3(7.69)	28(71.79)
x^2					8.146
P					0.004

2.2 观察组不良反应的发生情况

观察组患者在治疗期间出现了不同程度的白细胞减少、、恶心呕吐、关节痛、脱发、肝功能损伤等不良反应,患者对以上症状均可耐受,给予对症治疗后均自行缓解。

2.3 两组患者生存率的比较

观察组患者 6 个月、1 年生存率均显著高于对照组(P<0.05),见表 4。

表 3 观察组患者不良反应的发生情况(n,%)

Table 3 The occurrence of adverse reactions of observation group(n,%)

Adverse reactions	Observation group(n=39)
Leucocyte reduction	16(41.03)
Hemoglobin reduction	12(30.77)
Platelet reduction	10(25.64)
Arthrodynia	14(35.90)
Nausea and vomit	13(33.33)
Skin rash	9(23.08)
Alopecia	7(17.95)
Hepatic Dysfunction	5(12.82)

表 4 两组患者生存率的比较(n,%)

Table 4 Comparison of survival rate between two groups(n,%)

Group	6 months	1 year
Control group(n=40)	33(82.50)	29(72.50)
Observation group(n=39)	37(94.87)	35(89.74)
P	0.004	0.001

3 讨论

目前,肺癌已是世界范围内发病率和死亡率增长最快的恶性肿瘤,我国肺癌的病死率居于肿瘤死亡率的第一位,对人类身心健康、生命安全构成极大危害[12,13]。从临床角度出发,结合生物学特性可以将肺癌分为 NSCLC 和 SCLC 两大类,SCLC 主要表现为神经内分泌特性、恶性程度高、生长快,较早出现淋巴转移和血行播散,对放疗、化疗敏感[14,15];大多数 NSCLC 缺乏神经内分泌特性,对放疗、化疗敏感性明显低于 SCLC[16,17]。临床中主要通过放疗、化疗和手术治疗 NSCLC,但并未使 NSCLC 的疗效获得突破性进展,随着分子生物学的不断发展与进步,靶向治疗已取得很大进展,为 NSCLC 的治疗提供新的方案和途径[18,19]。

肿瘤的转移、细胞的恶变与肿瘤细胞和血管内皮细胞的粘连、血管的生成有关[20,21]。沙利度胺是谷氨酸衍生物,能够抑制血管生成,通过减少血管内皮生长因子、纤维细胞生长因子等血管生成刺激剂的分泌,通过减少刺激信号的传导达到抑制血管生成的作用,还能够通过 COX-2 途径降低瘤内微血管密度,从而达到抗肿瘤增生的作用[22-24]。吉非替尼是一种表皮生长因子受体酪氨酸激酶(EGFR-TK)抑制剂,对 EGFR-TK 的抑制可阻碍肿瘤的生长、转移和血管生成,并增加肿瘤细胞的凋亡[25-27]。本研究结果显示,观察组的化疗缓解率(71.79 %)显著高于对照组(52.50 %),且观察组患者 6 个月、1 年生存率亦显著高于对照组,说明手术前对 NSCLC 患者进行沙利度胺联合吉非替尼靶向治疗的疗效较好,与 Wang J 等[28]研究结果基本一致。分析认为,相对于术后化疗来说,术前化疗具有一定的优势,新辅助化疗不仅可以有效杀伤均布淋巴结的转移肿瘤细胞,还能抑制肿瘤细胞活性、降低微转移灶再转移,对于增强手术治疗效果、增大生存率均有重要帮助[29,30]。

有研究[31]显示,对Ⅲ期的 NSCLC 患者仅实施单纯手术、术后放化疗是不能有效提高生存率,本研究中对观察组患者在手术前给予沙利度胺联合吉非替尼靶向治疗,结果显示 6 个月、1 年生存率均显著高于对照组,说明这种治疗方法能够显著提高 NSCLC 患者生存率,对于延长患者的生命具有重要意义。另外,观察组在不良反应的发生情况,本研究结果显示,观察组患者在治疗期间出现了不同程度的白细胞减少、、恶心呕吐、关节痛、脱发、肝功能损伤等不良反应,患者对以上症状均可耐受,给予对症治疗后均自行缓解。说明本研究中靶向药物对于患者产生了副作用,乏力、头晕是沙利度胺常见的副作用,绝大多数患者可以通过控制剂量耐受,胃肠道反应、皮疹、瘙痒是吉非替尼较为常见的副作用,程度较轻,停药或减少剂量后症状会减轻[32,33],以上结果说明沙利度胺联合吉非替尼的靶向治疗会出现不良反应,但患者可耐受。本研究中尚存在样本量不足、缺乏分子水平的检测指标等问题,还需要进行深入研究。

综上所述,沙利度胺联合吉非替尼靶向治疗 NSCLC 患者的疗效较好,能显著提高患者生存率,值得进一步深入研究。

参 考 文 献(References)

[1] Oya Y, Yoshida T, Kuroda H, et al. Clinical Efficacy of Alectinib in Patients with ALK-Rearranged Non-small Cell Lung Cancer After Ceritinib Failure[J]. Anticancer Research, 2017, 37(11): 6477-6480

[2] Wong W, Sun P, Mu Z, et al. Efficacy and Safety of Nab-Paclitaxel as Second-line Chemotherapy for Locally Advanced and Metastatic Non-small Cell Lung Cancer [J]. Anticancer Research, 2017, 37(8): 4687-4691

[3] Calpearmero P, Ferriolslisart R, Ferriolslisart F, et al. Effectiveness of Nivolumab versus Docetaxel as Second-Line Treatment in Non-Small Cell Lung Cancer Patients in Clinical Practice [J]. Chemotherapy, 2017, 62(6): 374-380

[4] Dya D, Kapoor V, Hoye K, et al. Antibody Targeting GRP78 Enhances the Efficacy of Radiation Therapy in Human Glioblastoma and Non-Small Cell Lung Cancer Cell Lines and Tumor Models[J]. Clinical Cancer Research, 2017, 23(10): 2556-2564

[5] Tassi E, Grazia G, Vegetti C, et al. Early Effector T Lymphocytes Co-express Multiple Inhibitory Receptors in Primary Non-Small Cell Lung Cancer[J]. Cancer Research, 2017, 77(4): 851-861

[6] Kawakami H, Tanizaki J, Tanaka K, et al. Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer [J]. Investigational New Drugs, 2017, 35 (4): 1-8

[7] Jia L, Lu X, Liu G, et al. Endostatin sensitizes p53-deficient non-small-cell lung cancer to genotoxic chemotherapy by targeting DNA-dependent protein kinase catalytic subunit[J]. Journal of Pathology, 2017, 243(2): 255

[8] Kanai O, Kim Y, Demura Y, et al. P2.07-013 Efficacy and Safety of Nivolumab in Non-Small Cell Lung Cancer with Preexisting Interstitial Lung Disease [J]. Journal of Thoracic Oncology, 2017, 12(11): S2420

[9] Sato K, Akamatsu H, Murakami E, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab [J]. Lung Cancer, 2018, 115(suppl_9): 71-74

[10] Kobayashi S, M.D, Ph. D, et al. Mutation and Resistance of

Non-Small-Cell Lung Cancer to Gefitinib[J]. New England Journal of Medicine, 2016, 352(8): 786-792

[11] 徐晓鸿, 陈家斌, 夏银稳,等. 沙利度胺联合吉非替尼新辅助化疗对非小细胞肺癌的临床价值 [J]. 昆明医科大学学报, 2016, 37(1): 65-68
Xu Xiao-hong, Chen Jia-bin, Xia Yin-wen, et al. Clinical Analysis of Preoperative Neoadjuvant Chemotherapy by Thalidomide Combined with Gefitinib for Non-small Cell Lung Cancer [J]. Journal of Kunming Medical University, 2016, 37(1): 65-68

[12] Yang Z, Hackshaw A, Feng Q, et al. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: A meta-analysis[J]. International Journal of Cancer, 2017, 140(12): 2805-2819

[13] Shou J, You L, Yao J, et al. Cyclosporine A sensitizes human non-small cell lung cancer cells to gefitinib through inhibition of STAT3[J]. Cancer Letters, 2016, 379(1): 124-133

[14] Wei L, Ning J, Li C, et al. Overexpression of Sphk2 is associated with gefitinib resistance in non-small cell lung cancer [J]. Tumor Biology, 2016, 37(5): 6331-6336

[15] Wekken A J V D, Kuiper J L, Saber A, et al. Overall survival in EGFR mutated non-small-cell lung cancer patients treated with afatinib after EGFR TKI and resistant mechanisms upon disease progression[J]. Plos One, 2017, 12(8): e0182885

[16] Hong D, Zhang G, Zhang X, et al. Pulmonary Toxicities of Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials [J]. Medicine, 2016, 95(9): e3008

[17] Schuler M, Yang J C, Park K, et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial [J]. Annals of Oncology, 2016, 27(3): 417-423

[18] Kazandjian D, Blumenthal G M, Yuan W, et al. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer [J]. Clinical Cancer Research, 2016, 22(6): 1307-1312

[19] Yang J J, Zhou Q, Yan H H, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations [J]. British Journal of Cancer, 2017, 116(5): 568-574

[20] Pazares L, Tan E H, O'Byrne K, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial[J]. Annals of Oncology, 2017, 28(2): 270-277

[21] Feng C, Liu X, Li X, et al. Zoledronic acid increases the antitumor effect of gefitinib treatment for non-small cell lung cancer with EGFR mutations[J]. Oncology Reports, 2016, 35(6): 3460-3470

[22] Kimura T, Taniguchi H, Watanabe N, et al. Phase II Study of Carboplatin and Pemetrexed in Advanced EGFR-wild-type Non-squamous Non-small Cell Lung Cancer: The Central Japan Lung Study Group Trial 0906[J]. Anticancer Research, 2016, 36(4): 1767-1771

[23] Li M X, He H, Ruan Z H, et al. Central nervous system progression in advanced non-small cell lung cancer patients with EGFR mutations in response to first-line treatment with two EGFR-TKIs, gefitinib and erlotinib: a comparative study[J]. Bmc Cancer, 2017, 17(1): 245

[24] Nishijima N, Seike M, Soeno C, et al. miR-200/ZEB axis regulates sensitivity to nintedanib in non-small cell lung cancer cells [J]. International Journal of Oncology, 2016, 48(3): 937-944

[25] Ninomiya T, Nogami N, Kozuki T, et al. A phase I trial of afatinib and bevacizumab in chemo-naïve patients with advanced non-small-cell lung cancer harboring EGFR mutations: Okayama Lung Cancer Study Group Trial 1404 [J]. Lung Cancer, 2018, 115: 103-108

[26] Zhao X M, Zhao J, Xing K L, et al. Prognostic and predictive value of serum carcinoembryonic antigen levels in advanced non-small cell lung cancer patients with epidermal growth factor receptor sensitive mutations and receiving tyrosine kinase inhibitors [J]. Oncotarget, 2017, 8(41): 70865-70873

[27] Forcella M, Oldani M, Epistolio S, et al. Non-small cell lung cancer (NSCLC), EGFR downstream pathway activation and TKI targeted therapies sensitivity: Effect of the plasma membrane-associated NEU3[J]. Plos One, 2017, 12(10): e0187289

[28] Wang J, Wu Y, Dong M, et al. Observation of hepatotoxicity during long-term gefitinib administration in patients with non-small-cell lung cancer[J]. Anti-cancer drugs, 2016, 27(3): 245-250

[29] Wang J, Bai H, Hong C, et al. Analyzing epidermal growth factor receptor mutation status changes in advanced non- small-cell lung cancer at different sampling time-points of blood within one day[J]. Thoracic Cancer, 2017, 8(4): 312-319

[30] Salih Z, Conway A M, Bayman N, et al. 76 Outcomes and tolerability of second line treatment for non small cell lung cancer (NSCLC)[J]. Lung Cancer, 2016, 91(1): S27-S28

[31] Yang J J, Zhou Q, Yan H H, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations [J]. British Journal of Cancer, 2017, 116(5): 568-574

[32] Yang Z, Hackshaw A, Feng Q, et al. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: A meta-analysis[J]. International Journal of Cancer, 2017, 140(12): 2805-2819

[33] Kazandjian D, Blumenthal G M, Yuan W, et al. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer [J]. Clinical Cancer Research, 2016, 22(6): 1307-1312