

doi: 10.13241/j.cnki.pmb.2019.24.021

顺铂联合立体定向体部放疗治疗晚期肺癌的疗效及对患者血清 CYFRA21-1、DR70 和肺功能的影响 *

刘 勋¹ 吴喜福² 陈 云¹ 迪拉拉·吐尔逊¹ 刘燕丽^{3Δ}(1 喀什地区第一人民医院 呼吸与危重症医学二科 新疆 喀什 844000; 2 中山大学附属第三医院 广东 广州 510630;
3 喀什地区第一人民医院 新生儿科 新疆 喀什 844000)

摘要 目的: 研究顺铂联合立体定向体部放疗治疗晚期肺癌的疗效及对患者血清角质蛋白 21-1(CYFRA21-1)、DR70 和肺功能的影响。方法: 选择 2016 年 2 月到 2018 年 2 月在我院诊治的晚期肺癌患者 110 例, 并根据随机数表法将其分为观察组(n=58)和对照组(n=52)。对照组使用常规化疗, 观察组采用顺铂联合立体定向体部放疗。比较两组治疗后的疗效、治疗前后血清 CYFRA21-1、DR70、第一秒最大呼气量(FEV1)、一秒用力呼气容积/用力肺活量(FEV1/FVC)、最大呼气流速峰值(PEF)及生活质量评分的变化。结果: 治疗后, 两组患者总有效率分别为 86.21%、59.62%, 观察组显著高于对照组($P<0.05$); 两组血清 CYFRA21-1、DR70 水平较治疗前均显著降低($P<0.05$), 且观察组以上指标明显低于对照组($P<0.05$); 两组 FEV1、FEV1/FVC、PEF 较治疗前均显著升高($P<0.05$), 且观察组以上指标均明显高于对照组($P<0.05$); 两组患者生活质量各项评分均较治疗前明显升高, 且观察组患者生活质量各项评分均显著高于对照组($P<0.05$)。结论: 顺铂联合立体定向体部放疗治疗晚期肺癌的临床疗效显著优于单用常规化疗, 其可有效改善患者血清 CYFRA21-1、DR70 水平和肺功能。

关键词: 顺铂; 立体定向体部放疗; 晚期肺癌; 角质蛋白 21-1; DR70; 肺功能

中图分类号: R734.2 **文献标识码:** A **文章编号:** 1673-6273(2019)24-4695-04

Curative Efficacy of Cisplatin Combined with Stereotactic Body Radiotherapy in the Treatment of Advanced Lung Cancer and Its Effects on the Serum CYFRA21-1, DR70 and Lung Function*

LIU Xun¹, WU Xi-fu², CHEN Yun¹, DI Lala·tu er xun¹, LIU Yan-li^{3Δ}

(1 Department of Respiratory and Critical Care Medicine, First People's Hospital of Kashgar, Kashgar, Xinjiang, 844000, China;

2 Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510630, China;

3 Department of Neonatology, First People's Hospital of Kashgar, Kashgar, Xinjiang, 844000, China)

ABSTRACT Objective: To study Curative efficacy of Cisplatin combined with stereotactic body radiotherapy Advanced lung cancer and its effects on serum Keratin 21-1 (cyfra21-1), DR70 and lung function. **Methods:** 110 patients with advanced lung cancer who were treated in our hospital from February 2016 to February 2018 were selected and divided into the observation group (n=58) and the control group (n=52) according to the random number table. The control group received conventional chemotherapy, while the observation group received cisplatin combined with stereotactic body radiotherapy. The changes in serum cyfra21-1, DR70, first-second maximum expiratory volume (FEV1), 1-second forced expiratory volume/forced vital capacity (FEV1 /FVC), maximum expiratory velocity peak (PEF), and quality of life score were compared between the two groups after treatment. **Results:** After treatment, the total effective rate of patients in the two groups was 86.21% and 59.62%, respectively, which was significantly higher in the observation group than in the control group ($P<0.05$). Serum levels of cyfra21-1 and DR70 in both groups were significantly lower than those before treatment ($P<0.05$), and the above indicators in the observation group were significantly lower than those in the control group ($P<0.05$). FEV1, FEV1/FVC and PEF in the two groups were significantly higher than those before treatment ($P<0.05$), and the above indicators, FEV1/FVC and PEF in the observation group were significantly higher than those in the control group ($P<0.05$). The scores of quality of life in the two groups were significantly higher than those before treatment, and the scores of quality of life in the observation group were significantly higher than those in the control group ($P<0.05$). **Conclusion:** Cisplatin combined with stereotactic body radiotherapy is significantly better than conventional chemotherapy alone in the treatment of advanced lung cancer, and can effectively improve serum cyfra21-1, DR70 levels and lung function in patients.

Key words: Cisplatin; Stereotactic body radiotherapy; Advanced lung cancer; Keratin 21-1; DR70; Lung function

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

Article ID: 1673-6273(2019)24-4695-04

* 基金项目: 新疆维吾尔自治区自然科学基金面上项目(2011211A065)

作者简介: 刘勋(1984-), 男, 本科, 主治医师, 研究方向: 呼吸专业方向、肺结核以及肺癌, 电话: 15209063228, E-mail: fengjunyisheng@163.com

Δ 通讯作者: 刘燕丽(1986-), 女, 主治医师, 研究方向: 儿科专业方向

(收稿日期: 2019-07-11 接受日期: 2019-08-05)

前言

肺癌是发生于各级支气管上皮细胞及支气管肺泡上皮细胞的肿瘤,致病原因包括吸烟、职业原因、大气污染、电离辐射等^[1,2]。研究表明长期大量吸烟与肺癌的发生有密切关系,其发生风险是不吸烟患者的 10~20 倍^[3]。肺癌的临床表现较为复杂,早期基本无明显症状,确诊时多属晚期。近 20 年来,肺癌常规放疗疗效无明显提高,患者 5 年生存率较低,大多与肿瘤局部复发和转移有关^[4,5]。立体定向体部是采用短疗程、大剂量、共面实现对病灶组织的聚焦式照射,能使高剂量放射线的分布形态与病灶组织一致,同时给予远高于常规分割剂量的总剂量或分次剂量杀死癌细胞^[9,10]。顺铂属于细胞周期的非特异性药物,具有抗癌谱广、乏氧细胞有效、作用性强等优点,可抑制癌细胞 DNA 复制过程^[7,8]。研究表明立体定向体部联合放疗药物可提高晚期肺癌的生存率^[6]。因此,本研究主要对顺铂联合立体定向体部放疗治疗晚期肺癌进行研究,观察其对血清 CYFRA21-1、DR70 及肺功能的影响。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月-2018 年 1 月我院收治的 110 例晚期肺癌进行研究。其中,观察组男 37 例,女 21 例;年龄 45~68 岁,平均(57.62± 5.69)岁;对照组男 25 例,女 27 例;年龄 46~67 岁,平均(57.59± 5.71)岁。两组基线资料无差异($P>0.05$),可比较。纳入标准:(1)预计生存期 ≥ 3 个月;(2)经支气管镜活检或胸膜

活检等确诊;(3)认知功能正常。排除标准:(1)重要器官功能不全者;(2)沟通障碍者;(3)意识不清楚者。

1.2 治疗方法

对照组采用常规放疗,剂量 1.5~2.5 Gy 每次,一次 1 天。总剂量不超过 75 Gy。观察组患者采用立体定向体部放疗,剂量为 4.5~6 Gy 每次,总剂量不超过 60 Gy。再加用顺铂(规格 100 mL,厂家:济南三九益民制药有限责任公司,国药准字 H20050269)治疗,500 mL 生理盐水中加入 80~100 mg/m² 的顺铂,通过静脉输注。

1.3 疗效评定

采集治疗前、后肘静脉血 4 mL,3500 r·min⁻¹ 离心 10 min,提取血清,采用双抗体夹心酶联免疫吸附法(ELISA)测定 CYFRA21-1、DR70;FEV1、FEV1/FVC、PEF 水平采用 HI-101 肺功能检测仪测定。

疗效评价标准:(1)显效:影像检查肿瘤消失,无残留;(2)有效:体内肿瘤缩小 50%以上;(3)无效:肿瘤增大 25%以上

1.4 统计学分析

以 spss18.0 软件包处理,符合正态分布计量资料用均数±标准差($\bar{x} \pm s$)表示,组间比较使用独立样本 t 检验,计数资料以率表示, χ^2 检验, $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组疗效的比较

两组总有效率为 86.21%、59.62%,观察组显著高于对照组($P<0.05$),见表 1。

表 1 两组临床疗效比较[例(%)]

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

Groups	n	Effective	Valid	Invalid	Total effective rate
Observation group	58	34(58.62)	16(27.59)	8(13.79)	50(86.21)
Control group	52	18(34.62)	13(25.00)	21(40.38)	31(59.62)
χ^2 value					9.987
P value					0.002

2.2 两组 CYFRA21-1、DR70 水平的比较

治疗后,两组 CYFRA21-1、DR70 水平显著降低($P<0.05$),

且观察组低于对照组($P<0.05$),见表 2。

表 2 两组血清 CYFRA21-1、DR70 水平的比较($\bar{x} \pm s$)

Table 2 Comparison of the serum cyfra21-1 and DR70 levels between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	CYFRA21-1(ng/mL)		DR70(mg/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	58	7.02± 5.04	3.20± 2.14	12.05± 5.71	4.71± 1.25
Control group	52	7.03± 5.06	5.45± 3.21	12.07± 5.65	7.53± 1.34
t value		0.010	4.366	0.018	11.418
P value		0.992	0.000	0.985	0.000

2.3 两组肺功能的比较

两组治疗后 FEV1、FEV1/FVC、PEF 较治疗前均显著升高

($P<0.05$),且观察组以上指标均明显高于对照组($P<0.05$),见表 3。

表 3 两组肺功能的比较($\bar{x} \pm s$)Table 3 Comparison of the lung function before and after treatment between the two groups($\bar{x} \pm s$)

Groups	n	FEV1(L)		FEV1 /FVC(%)		PEF(L/s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	58	1.59± 0.26	1.93± 0.59	52.15± 5.33	65.85± 6.13	2.69± 0.57	3.97± 0.42
Control group	52	1.57± 0.23	1.64± 0.61	51.87± 4.75	56.12± 5.24	2.68± 0.53	3.04± 0.43
<i>t</i> value		0.425	2.533	0.290	8.896	0.095	11.465
<i>P</i> value		0.672	0.013	0.773	0.000	0.925	0.000

2.4 两组治疗前后生活质量的比较

组高于对照组($P < 0.05$),见表 4。

治疗后,两组生活质量评分均较治疗前明显改善,且观察

表 4 两组治疗前后生活质量评分的比较($\bar{x} \pm s$,分)Table 4 Comparison of the quality of life scores before and after treatment between the two groups($\bar{x} \pm s$, points)

Groups	n	Body function		Role functions		Emotional function		Social function		Cognitive function	
		Before	After	Before	After	Before	After	Before	After	Before	After
		treatment	treatment	treatment	treatment	treatment	treatment	treatment	treatment	treatment	treatment
Observa- tion group	58	8.13±	12.99±	3.98±	7.16±	6.19±	8.07±	4.23±	5.98±	4.13±	5.99±
		1.05	1.55	1.02	2.01	1.19	0.83	0.64	0.73	0.58	0.69
Control group	52	8.14±	10.74±	4.02±	5.79±	6.22±	6.88±	4.22±	5.03±	4.14±	5.01±
		1.06	1.89	0.94	1.64	1.11	0.94	0.65	0.75	0.59	0.73
<i>t</i> value		0.050	6.854	0.213	3.889	0.136	7.052	0.081	6.727	0.090	7.236
<i>P</i> value		0.960	0.000	0.832	0.000	0.892	0.000	0.935	0.000	0.929	0.000

3 讨论

肺癌已成为目前人类死亡的主要原因之一^[11,12],其发病原因尚不完全明确,研究表明长期大量吸烟与肺癌的发生密切相关^[13,14],临床上通常使用常规放疗,但疗效不尽如人意,且不良反应较多^[15,16]。立体定向体部放疗是工程学和物理学研究发展的产物,能提高肿瘤控制率^[17-19]。有研究显示立体定向体部放疗可用于治疗边界清晰、直径可达 5~7 cm 的可见肿瘤^[20]。顺铂属常见铂类金属化合物,有较强的广谱抗癌作用,可损伤肿瘤细胞膜,造成 DNA 损伤,破坏 DNA 复制和转录^[21-23]。

本研究结果显示顺铂联合立体定向体部放疗的患者总有效率高达 86.21%,明显高于使用常规放疗的患者,与 Hardin C^[24]等研究结果相似,提示顺铂联合立体定向体部放疗可明显提高肺癌患者的临床疗效。Shen Q^[25]等研究表明立体定向体部联合顺铂治疗晚期肺癌可明显提高患者情绪功能、社会功能。本研究结果与上述观点基本一致。

CYFRA21-1 由 KRT19 基因编码,主要分布于单层上皮细胞中,是上皮细胞内细胞骨架的组分之一,较多研究显示其在肺癌中具有较高的敏感性,是诊断肿瘤的标志物^[26,27]。DR70 是一种新的肿瘤标志物,是肿瘤细胞分泌的一类蛋白水解酶,其在肺癌中有较高的表达^[28,29]。本研究结果显示联合治疗的血清 CYFRA21-1、DR70 水平明显低于使用常规放疗的患者,提示顺铂联合立体定向体部放疗可有效降低患者血清肿瘤标志物水平。分析是因为顺铂作为细胞周期的非特异性药物,能够通过铂和 DNA 双链的交叉结合而抑制癌细胞的复制,使癌细胞

凋亡;而立体定向体部则可有效监测和控制病灶靶区周边剂量的阶梯变化,提高病灶的照射量,减少周围正常器官的剂量,从而增强其照射强度及剂量,两者联合治疗最终改善患者的肿瘤标志物水平。

Lee S^[30]等研究认为顺铂联合立体定向体部放疗可有效缓解患者病情,改善患者肺功能。本研究结果显示顺铂联合立体定向体部放疗患者 FEV1、FEV1 /FVC、PEF 水平均明显高于使用常规放疗的患者,提示顺铂联合立体定向体部放疗可有效改善患者肺功能。分析原因是因为顺铂是肺癌一线化疗药物,能够以 DNA 为作用靶点,引起链内与链间的交联,抑制 DNA 复制及肿瘤细胞的修复并引发细胞凋亡;立体定向体部则是利用计算机技术形成照射,使照射高剂量区在三维方向上与肿瘤靶区高度一致,以最大限度保护重要器官,两者联合治疗以缓解患者病情,改善患者肺功能。

综上所述,顺铂联合立体定向体部放疗治疗晚期肺癌的临床疗效显著优于单用常规化疗,其可有效改善患者血清 CYFRA21-1、DR70 水平和肺功能。

参考文献(References)

- [1] Yoh K, Seto T, Satouchi M, et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial [J]. Lancet Respir Med, 2017, 5(1): 42-50
- [2] Paz-Ares 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
- [3] Lin G N, Peng J W, Liu P P, et al. Elevated neutrophil-to-lymphocyte ratio predicts poor outcome in patients with advanced non-small-cell lung cancer receiving first-line gefitinib or erlotinib treatment[J]. Asia-Pacific Journal of Clinical Oncology, 2017, 13(5): 2696-2703
- [4] Jenkins S, Yang C H, Ramalingam S S, et al. Plasma ctDNA Analysis for Detection of the EGFR T790M Mutation in Patients with Advanced Non-Small Cell Lung Cancer[J]. Journal of Thoracic Oncology Official Publication of the International Association for the Study of Lung Cancer, 2017, 12(7): 1061-1070
- [5] Rosell R, Dafni U, Felip E, et al. Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial [J]. Lancet Respir Med, 2017, 5(5): 435-444
- [6] Reck M, Rabe K F. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer [J]. N Engl J Med, 2017, 377 (9): 849-861
- [7] Hui R, Garon E B, Goldman J W, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial[J]. Annals of Oncology Official Journal of the European Society for Medical Oncology, 2017, 28(4): 874-881
- [8] Nan X, Xie C, Yu X, et al. EGFR TKI as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer [J]. Oncotarget, 2017, 8(43): 75712-75726
- [9] Berardi R, Santoni M, Newsom-Davis T, et al. Hyponatremia normalization as an independent prognostic factor in patients with advanced non-small cell lung cancer treated with first-line therapy[J]. Oncotarget, 2017, 8(14): 23871-23879
- [10] Fan G, Zhang K, Ding J, et al. Prognostic value of EGFR and KRAS in circulating tumor DNA in patients with advanced non-small cell lung cancer: a systematic review and meta-analysis [J]. Oncotarget, 2017, 8 (20): 33922-33932
- [11] Ilie M, Szaferglusman E, Hofman V, et al. Expression of MET in circulating tumor cells correlates with expression in tumor tissue from advanced-stage lung cancer patients [J]. Oncotarget, 2017, 8 (16): 26112-26121
- [12] Sgambato A, Casaluze F, Gridelli C. The role of checkpoint inhibitors immunotherapy in advanced non-small cell lung cancer in the elderly[J]. Expert Opin Biol Ther, 2017, 17(5): 565-571
- [13] Lamb Y N, Scott L J. Osimertinib: A Review in T790M-Positive Advanced Non-Small Cell Lung Cancer[J]. Targeted Oncology, 2017, 12 (4): 555-562
- [14] Kashiwabara, Kosuke, Semba, et al. Outcome in advanced non-small cell lung cancer patients with successful rechallenge after recovery from epidermal growth factor receptor tyrosine kinase inhibitor-induced interstitial lung disease [J]. Cancer Chemother Pharmacol, 2017, 79(4): 705-710
- [15] Pakkala S, Ramalingam S S. Epidermal Growth Factor Receptor Mutated Advanced Non-Small Cell Lung Cancer: A Changing Treatment Paradigm[J]. Hematol Oncol Clin North Am, 2017, 31(1): 83-99
- [16] Wei Z, Ye X, Yang X, et al. Advanced non small cell lung cancer: response to microwave ablation and EGFR Status[J]. European Radiology, 2017, 27(4): 1685-1694
- [17] Zhong W Z, Zhou Q, Wu Y L. The resistance mechanisms and treatment strategies for EGFR-mutant advanced non-small-cell lung cancer [J]. Oncotarget, 2017, 8(41): 71358-71370
- [18] Wu C Y, Cherng J Y, Yang Y H, et al. Danshen improves survival of patients with advanced lung cancer and targeting the relationship between macrophages and lung cancer cells [J]. Oncotarget, 2017, 8 (53): 90925-90947
- [19] Iliä© M, Szafer-Glusman E, Hofman V, et al. Detection of PD-L1 in circulating tumor cells and white blood cells from patients with advanced non-small-cell lung cancer [J]. Annals of Oncology, 2018, 29 (1): 193-199
- [20] Takeuchi A, Oguri T, Sone K, et al. Predictive and Prognostic Value of CYFRA 21-1 for Advanced Non-small Cell Lung Cancer Treated with EGFR-TKIs [J]. Anticancer Research, 2017, 37(10): 5771-5776
- [21] Edelman M J, Wang X, Hodgson L, et al. Final Results of a Phase 3 Trial of Celecoxib (C) in Addition to Standard Chemotherapy for Advanced Non-Small Cell Lung Cancer With COX- 2 Overexpression: CALGB 30801 (Alliance)[J]. Int J Radiat Oncol Biol Phys, 2017, 98 (1): 220-221
- [22] Wang H, Zhang M, Li P, et al. Retrospective Analysis of Different Treatment Schemes After Gefitinib Resistance in Advanced Non-Small Cell Lung Cancer [J]. Clinical Therapeutics, 2017, 39(3): 610-619
- [23] Bradley C J, Yabroff K R, Mariotto A B, et al. Antineoplastic Treatment of Advanced-Stage Non-Small-Cell Lung Cancer: Treatment, Survival, and Spending (2000 to 2011)[J]. Journal of Clinical Oncology, 2017, 35(5): 529-535
- [24] Hardin C, Shum E, Singh A P, et al. Emerging Treatment using Tubulin Inhibitors in Advanced Non-Small Cell Lung Cancer [J]. Expert Opinion on Pharmacotherapy, 2017, 18(7): 701-716
- [25] Shen Q, Dong X, Tang X, et al. Risk factors and prognosis value of venous thromboembolism in patients with advanced non-small cell lung cancer: a case-control study [J]. J Thorac Dis, 2017, 9 (12): 5068-5074
- [26] Yang Y, Wen G, Xi D, et al. Variations within 3'-UTR of MDM4 gene contribute to clinical outcomes of advanced non-small cell lung cancer patients following platinum-based chemotherapy [J]. Oncotarget, 2017, 8(10): 16313-16324
- [27] Meriggi F, Codignola C, Beretta G D, et al. Significance of neutrophil-to-lymphocyte ratio in Western advanced EGFR-mutated non-small cell lung cancer receiving a targeted therapy [J]. Tumori, 2017, 103(5): 443-448
- [28] Brown J, Cook K, Adamski K, et al. Utility values associated with advanced or metastatic non-small cell lung cancer: data needs for economic modeling [J]. Expert Review of Pharmacoeconomics & Outcomes Research, 2017, 17(2): 153-164
- [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, 8,4(2017-04-24), 2017, 8(4): 312-319
- [30] Lee S, Eo W, Jeon H, et al. Prognostic Significance of Host-related Biomarkers for Survival in Patients with Advanced Non-Small Cell Lung Cancer[J]. Journal of Cancer, 2017, 8(15): 2974-2983