

doi: 10.13241/j.cnki.pmb.2017.19.035

埃克替尼治疗晚期非小细胞肺癌的疗效及对患者血清相关指标水平的影响*

汪建¹ 王兴远¹ 周伟¹ 陈朝辉² 江波¹

(1 四川大学华西广安医院 肿瘤科 四川 广安 638000; 2 川北医学院附属医院 麻醉科 四川 南充 637000)

摘要 目的:分析埃克替尼对晚期非小细胞肺癌的治疗效果及对血清指标的影响。**方法:**将 86 例晚期非小细胞肺癌患者按抽签法分成对照组与观察组,各 43 例。对照组采用多西他赛治疗,观察组采用埃克替尼治疗。观察并比较两组患者治疗前后血清细胞角蛋白 21-1(Cyfr21-1)、鳞状细胞癌抗原(SCCA)、血管内皮生长因子(VEGF)、自然杀伤(NK)细胞、CD4⁺、CD8⁺、CD4⁺/CD8⁺、白细胞介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)、基质金属蛋白酶-2(MMP-2)及基质金属蛋白酶-9(MMP-9)水平、临床疗效以及安全性。**结果:**观察组疾病控制率高于对照组,差异具有统计学意义($P<0.05$)。治疗后,两组患者血清 Cyfr21-1、SCCA、CD8⁺、LI-8、TNF- α 、MMP-2 及 MMP-9 均低于治疗前,且观察组低于对照组,差异具有统计学意义($P<0.05$);治疗后,两组患者血清 VEGF 水平均降低,且观察组低于对照组,差异具有统计学意义($P<0.05$);治疗后,两组患者血清 NK、CD4⁺ 及 CD4⁺/CD8⁺ 均高于治疗前,且观察组高于对照组,差异具有统计学意义($P<0.05$);观察组不良反应发生率低于对照组,差异具有统计学意义($P<0.05$)。**结论:**埃克替尼对晚期非小细胞肺癌的临床效果肯定,可下调血清 VEGF 表达。

关键词:晚期非小细胞肺癌;埃克替尼;细胞角蛋白 21-1;鳞状细胞癌抗原;血管内皮生长因子

中图分类号:R734.2 **文献标识码:**A **文章编号:**1673-6273(2017)19-3738-04

Effects of Icotinib on Treatment of Advanced Non-small Cell Lung Cancer and Serum Levels of Related Indexes*

WANG Jian¹, WANG Xing-yuan¹, ZHOU Wei¹, CHEN Zhao-hui², JIANG Bo¹

(1 Department of oncology Guang'an Huaxi Hospital of Sichuan University, Guang'an, Sichuan, 638000, China;

2 Department of oncology, Affiliated Hospital of Chuanbei Medical College, Nanchong, Sichuan, 637000, China)

ABSTRACT Objective: To analyze the clinical effect of icotinib on treatment of advanced non-small cell lung cancer and serum index levels. **Methods:** 86 patients with advanced non-small cell lung cancer were selected and randomly divided into the control group and the observation group with 43 cases in each group. The patients in the control group were treated with docetaxel, while the patients in the observation group were treated with icotinib. Then the serum levels of cytokeratin 21-1 (Cyfr21-1), squamous cell carcinoma antigen (SCCA), natural killer (NK) cells, CD4⁺, CD8⁺, CD4⁺/CD8⁺, interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinases-9 (MMP-9) of patients and the clinical efficacy and security. **Results:** The disease control rate of observation group was higher than that of the control group, and the difference was statistically significant ($P<0.05$). After treatment, the serum levels of SCCA, Cyfr21-1, CD8⁺, LI-8, TNF- α , MMP-2 and MMP-9 in the two groups decreased, and the observation group was lower than that of the control group, and the differences were statistically significant ($P<0.05$); After treatment, the serum levels of VEGF in the two groups decreased, and the observation group was lower than that of the control group, and the differences were statistically significant ($P<0.05$); After treatment, the serum levels of NK, CD4⁺ and CD4⁺/CD8⁺ in the two groups increased, and the observation group was higher than that of the control group, and the differences were statistically significant ($P<0.05$). The adverse reactions of the observation group was lower than that of the control group, and the difference was statistically significant ($P<0.05$). **Conclusion:** The clinical efficacy of icotinib in the treatment of advanced non-small cell lung cancer can reduce the serum levels of SCCA, Cyfr21-1, CD8⁺, LI-8, TNF- α , MMP-2 and MMP-9 and increase the NK, CD4⁺ and CD4⁺/CD8⁺ of patients.

Key words: Advanced non-small cell lung cancer; Icotinib; Cyfr21-1; SCCA; VEGF

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

Article ID: 1673-6273(2017)19-3738-04

前言

药物化疗是晚期非小细胞肺癌患者延长生存时间的关键,

但疗效多已到达平台期^[1]。近年来有关研究指出肺癌进展与表皮生长因子受体(EGFR)联系密切,通过靶向作用于 EGFR 可取得不错的效果^[2]。埃非替尼作为一种选择性 EGFR 酪氨酸激

* 基金项目:四川省卫生厅科研项目(050246)

作者简介:汪建(1983-),男,本科,研究方向:肺部肿瘤的治疗,电话:13982658608

(收稿日期:2016-12-19 接受日期:2016-12-30)

酶的抑制剂,其分子作用原理、化学结构及疗效等与吉非替尼相似,但安全性更高,现已广泛用于晚期非小细胞肺癌治疗^[3]。肿瘤生长需依靠新生血管,血管内皮生长因子(VEGF)是肿瘤血管形成的关键因子^[4]。本研究就分析埃克替尼对晚期非小细胞肺癌的治疗效果及对血清 VEGF 水平的影响。

1 资料与方法

1.1 一般资料

选择我院 2014 年 2 月~2015 年 8 月收治的 86 例晚期非小细胞肺癌患者,均与非小细胞肺癌诊断标准相吻合^[5],同时经过组织病理及细胞学等检查明确诊断,本研究已得到医院伦理委员会许可,且签署家属和患者知情同意书,按抽签法进行分组。对照组有 29 例男性,有 14 例女性;年龄 35~67 岁,平均(53.24±3.68)岁;病灶直径 2~5 cm,平均(3.51±0.39)cm;TNM 分期:有 11 例Ⅲa 期,有 14 例Ⅲb 期,有 18 例Ⅳ期;病理类型:有 26 例鳞癌,有 13 例腺癌,有 4 例大细胞癌;EHFR 突变:有 20 例 EGFR19 位突变,有 23 例 EGFR21 位突变。观察组有 32 例男性,有 11 例女性;年龄 33~69 岁,平均(52.68±3.84)岁;病灶直径 2~5cm,平均(3.24±0.42)cm;TNM 分期:有 10 例Ⅲa 期,有 16 例Ⅲb 期,有 17 例Ⅳ期;病理类型:有 26 例鳞癌,有 11 例腺癌,有 6 例大细胞癌;EHFR 突变:有 22 例 EGFR19 位突变,有 21 例 EGFR21 位突变。比较两组一般资料无差异(P>0.05),有比较性。

1.2 纳入与排除标准

纳入明确 EGFR19 位或者 21 位外显子突变;TNM 分期在Ⅲa~Ⅳ期;无手术指征;经标准一线化疗无效;预计生存时间超过 3 个月;体能状态评分低于 2 分;一线化疗至二线化疗间隔时间在 4 周以上;可测量病灶超过 1 个。排除心肝肾等功能不全;化疗禁忌症;近期伴手术史或者外伤史;合并其他肿瘤;妊娠或者哺乳期。

1.3 方法

对照组采用多西他赛治疗,于每周期的第 1 天予以 75

mg/m² 多西他赛(重庆新原兴药业有限公司,0.5 mL: 20 mg, 20140124)静脉滴注,1 个周期为 21 天,连续治疗 4 个周期,于用药前 1 天及用药后 3 天(包含当天)口服 4 mg 地塞米松(江西金钥药业有限公司,0.75 mg/片,20140113)行预处理,每天 2 次。实验组采用埃克替尼治疗,每次口服 125 mg 埃克替尼(安徽辉克药业有限公司,125 mg/片,20140117),早中晚各 1 次,待患者无法耐受药物毒性或者肿瘤进展时停药。

1.4 观察指标

1.4.1 临床疗效评估 完全缓解(CR):病灶全部消失,同时维持时间在 1 个月以上;部分缓解(PR):病灶最长直径减小超过 30%,同时维持时间在 1 个月以上;疾病稳定(SD):于部分缓解与疾病进展之间;疾病进展(PD):病灶最长直径增大在 20%以上,CR+PR+SD= 疾病控制。

1.4.2 指标检测 于治疗前及治疗结束时抽取患者空腹静脉血 2 mL,抗凝后分离血清,保存待检。采用酶联免疫法检测 VEGF 水平。采用化学发光法检测人细胞角蛋白 21-1(Cyfr21-1)、鳞状细胞癌抗原(SCCA)。采用流式细胞术检测自然杀伤(NK)细胞、CD4⁺、CD8⁺。采用免疫比浊法检测白细胞介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)。采用免疫放射法检测基质金属蛋白酶-2(MMP-2)、MMP-9。

1.4.3 安全性评估 用药期间对血常规、肝肾功能等进行定期检查,并依据世界卫生组织拟定的不良反应评价标准评估毒副反应。

1.5 统计学分析

选择 SPSS18.0 行数据统计,用均数±标准差($\bar{x} \pm s$)表示计量资料,组间比较 t 检验,用[(n)%]表示计数资料,用 χ^2 检验比较,等级资料用秩和检验,P<0.05 则有统计学意义。

2 结果

2.1 两组患者临床疗效比较

观察组疾病控制率高于对照组,比较有统计学差异(P<0.05),见表 1。

表 1 两组患者临床疗效比较[(n)%]

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

Groups	CR	PR	SD	PD	Disease control rate
Control group(n=43)	0	7	22	14	29(67.44)
Observation group(n=43)	2	15	20	6	37(86.04) [#]

Note: compared with control group, [#]P<0.05.

2.2 两组患者治疗前后血清 VEGF 水平比较

治疗前,比较两组 VEGF 水平无统计学差异(P>0.05);治

疗后,两组 VEGF 水平均降低,观察组低于对照组,比较有统计学差异(P<0.05),见表 2。

表 2 两组患者治疗前后血清 VEGF 水平比较($\bar{x} \pm s$)

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

Groups	Time	VEGF(ng/L)
Control group(n=43)	Before treatment	544.76±77.71
	After treatment	492.38±71.28*
Observation group(n=43)	Before treatment	547.93±78.14
	After treatment	475.60±67.83 [#]

Note: compared with control group after treatment, [#]P<0.05; compared with before treatment, * P<0.05.

2.3 两组患者治疗前后肿瘤标志物水平比较 (P>0.05); 治疗后, 两组 Cyfr21-1、SCCA 水平均降低, 观察组治疗前, 比较两组 Cyfr21-1、SCCA 水平无统计学差异 低于对照组, 差异具有统计学意义(P<0.05), 见表 3。

表 3 两组患者治疗前后肿瘤标志物水平比较($\bar{x} \pm s$)

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

Groups	Time	Cyfr21-1($\mu\text{g/L}$)	SCCA(ng/L)
Control group(n=43)	Before treatment	18.77 $\pm$ 2.23	5.97 $\pm$ 0.74
	After treatment	7.42 $\pm$ 0.87 [*]	3.69 $\pm$ 0.46 [*]
Observation group(n=43)	Before treatment	17.96 $\pm$ 2.12	5.85 $\pm$ 0.71
	After treatment	5.68 $\pm$ 0.70 [#]	2.84 $\pm$ 0.35 [#]

Note: compared with control group after treatment, [#]P<0.05; compared with before treatment, ^{*}P<0.05.

2.4 两组患者治疗前后免疫功能比较 组 CD8⁺ 均降低, 观察组低于对照组, 差异具有统计学意义
治疗前, 比较两组免疫功能无统计学差异(P>0.05); 治疗 (P<0.05), 见表 4。
后, 两组 NK、CD4⁺、CD4⁺/CD8⁺ 均上升, 观察组高于对照组, 两

表 4 两组患者治疗前后免疫功能比较($\bar{x} \pm s$)

Table 4 Comparison of immune functions between two groups before and after the treatment ($\bar{x} \pm s$)

Groups	Time	NK(%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺ (%)
Control group(n=43)	Before treatment	14.97 $\pm$ 1.73	32.20 $\pm$ 4.11	30.55 $\pm$ 3.69	1.10 $\pm$ 0.13
	After treatment	16.55 $\pm$ 2.21 [*]	35.80 $\pm$ 4.36 [*]	27.64 $\pm$ 3.36 [*]	1.23 $\pm$ 0.15 [*]
Observation group (n=43)	Before treatment	14.85 $\pm$ 1.63	31.76 $\pm$ 3.87	29.74 $\pm$ 3.60	1.03 $\pm$ 0.12
	After treatment	18.79 $\pm$ 2.26 [#]	38.44 $\pm$ 0.86 [#]	25.45 $\pm$ 3.11 [#]	1.48 $\pm$ 0.19 [#]

Note: compared with control group after treatment, [#]P<0.05; compared with before treatment, ^{*}P<0.05.

2.5 两组患者治疗前后炎症因子水平比较 05); 治疗后, 两组 IL-8、TNF- α 水平均降低, 观察组低于对照
治疗前, 比较两组 IL-8、TNF- α 水平无统计学差异(P>0. 组, 比较有统计学差异(P<0.05), 见表 5。

表 5 两组患者治疗前后炎症因子比较($\bar{x} \pm s$)

Table 5 Comparison of inflammatory factors between two groups before and after the treatment ($\bar{x} \pm s$)

Groups	Time	IL-8($\mu\text{g/L}$)	TNF- α (ng/L)
Control group(n=43)	Before treatment	45.51 $\pm$ 5.61	42.87 $\pm$ 5.11
	After treatment	34.20 $\pm$ 4.18 [*]	37.23 $\pm$ 4.63 [*]
Observation group(n=43)	Before treatment	44.32 $\pm$ 5.47	41.60 $\pm$ 5.10
	After treatment	29.75 $\pm$ 3.61 [#]	31.58 $\pm$ 3.89 [#]

Note: compared with control group after treatment, [#]P<0.05; compared with before treatment, ^{*}P<0.05.

2.6 两组患者治疗前后 MMP-2、MMP-9 水平比较 (P>0.05); 治疗后, 两组 MMP-2、MMP-9 水平均降低, 观察组下
治疗前, 比较两组 MMP-2、MMP-8 水平无统计学差异 降更明显, 比较有统计学差异(P<0.05), 见表 6。

表 6 两组患者治疗前后 MMP-2、MMP-9 水平比较($\bar{x} \pm s$)

Table 6 Comparison of serum levels of MMP-2 and MMP-9 between two groups before and after the treatment ($\bar{x} \pm s$)

Groups	Time	MMP-2($\mu\text{g/L}$)	MMP-9(ng/L)
Control group(n=43)	Before treatment	451.76 $\pm$ 56.32	102.52 $\pm$ 14.57
	After treatment	400.63 $\pm$ 57.42 [*]	77.81 $\pm$ 11.20 [*]
Observation group n=43)	Before treatment	448.80 $\pm$ 64.39	105.78 $\pm$ 15.69
	After treatment	375.62 $\pm$ 53.26 [#]	65.42 $\pm$ 9.28 [#]

Note: compared with control group after treatment, [#]P<0.05; compared with before treatment, ^{*}P<0.05.

2.7 比较两组患者安全性 泻, 有 2 例恶心, 1 例肝功能损伤, 5 例皮疹, 比较有统计学差异
对照组有 22 例 III 度不良反应: 4 例肝功能受损, 8 例血液 (P<0.05)。
毒性, 10 例胃肠反应; 观察组有 11 例 I~II 度不良反应: 3 例腹

3 讨论

肺癌是一种发病率最高的肺部恶性肿瘤,其中非小细胞肺癌约为肺癌的 80%,其早期缺乏特异性症状,以至于大部分患者确诊时已进展至晚期,错过了手术救治机会^[8]。晚期非小细胞肺癌一线治疗后容易复发,为延长患者生存期,改善生活质量,大部分患者需行二线治疗^[9]。多西他赛是晚期非小细胞肺癌常用二线化疗方案,作为半合成紫杉类的抗癌药,其抗癌谱优于紫杉醇,且抗癌活性高出紫杉醇 2 倍,能够于肿瘤细胞内滞留更长时间,其可阻止细胞的有丝分裂、增殖^[10]。

近年来,肿瘤治疗已倾向于靶向治疗方式,分子靶向治疗是将 EGFR 选作靶点,导致分子靶向药物直接于靶点处发挥作用,从而起到杀灭肿瘤细胞的效果,针对性比较强^[11]。EGFR 是一种糖蛋白,可与络氨酸蛋白激酶作用后促进肿瘤细胞的分化、增殖、侵袭等^[12]。埃克替尼是目前研发的小分子靶向药物,可诱导异常酪氨酸激酶的信号传导产生阻断,从而抑制肿瘤的生长及转移,促进肿瘤细胞产生凋亡^[13]。有研究报道,晚期非小细胞肺癌患者采用埃克替尼二线治疗的疾病控制率较高,本结果与研究报道一致,证实埃克替尼治疗晚期非小细胞肺癌的疗效确切,可行性高^[14]。肿瘤的发生、发展期间可有多数新生血管形成,从而提供丰富的营养,利于肿瘤细胞的生长发育,VEGF 作为一种促血管生成因子,可诱导血管新生,特异性高^[15]。本结果显示,埃克替尼治疗后 VEGF 水平显著降低,表明其可阻断肿瘤血供,从而促进瘤体萎缩、坏死。

国外学者研究发现肿瘤标志物可客观评估病情进展,机体正常状态下 Cyera21-1 的浓度很低,恶性肿瘤细胞可导致细胞角蛋白 19 的降解加快,从而引起 Cyera21-1 水平上升,其水平可提示机体上皮细胞的分化程度;SCCA 作为一种糖蛋白,其水平升高与肿瘤的恶性程度、分化程度等密切相关^[16]。本结果显示,埃克替尼治疗后 Cyera21-1 及 SCCA 水平显著降低,表明埃克替尼可有效控制肿瘤进展,从而使肿瘤标志物水平降低。Soria JC 等学者发现恶性肿瘤发病与免疫功能低下密切相关,其中 T 淋巴细胞可起到关键作用,主要是增加 CD4⁺ 活性,抑制 CD8⁺ 增多,保持 CD4⁺/CD8⁺ 动态平衡^[17,18]。NK 细胞是机体重要的免疫细胞,对靶细胞有识别作用,可杀伤肿瘤细胞。本结果显示,埃克替尼治疗后 CD4⁺、CD4⁺/CD8⁺、NK 水平显著上升,表明埃克替尼促进机体免疫微环境的改善,缓解免疫功能的抑制状态,增强 NK 细胞的杀伤能力。有学者表示,肺部的炎症性疾病与肺癌有着紧密联系,可诱导肿瘤微环境产生变化,IL-8 可经自分泌与旁分泌方式,促进肿瘤生长;TNF- α 可利于肿瘤细胞的侵袭,其水平升高多提示预后不良^[18,19]。本结果显示,埃克替尼治疗后 IL-8、TNF- α 水平显著降低,表明其可缓解机体的炎症状态,延缓肿瘤进展,避免进一步损伤。相关研究指出,基质金属蛋白酶能够导致血管基底膜及细胞外基质产生降解,MMP-2 可破坏细胞组织成分,诱导新生血管形成;MMP-9 可诱导肿瘤细胞透过正常组织,甚至穿透淋巴管、血管,引起肿瘤转移^[20,21]。本结果显示,埃克替尼治疗后 MMP-2 及 MMP-9 水平明显低于多西他赛组,表明埃克替尼可抑制肿瘤的侵袭及转移,从而控制肿瘤的进展。

综上所述,多西他赛治疗后不良反应程度比较重,多为 III 度不良反应,埃克替尼主要为 I~II 度不良反应,且其不良反应

率明显低于多西他赛组,说明埃克替尼的安全性比较可靠,对晚期非小细胞肺癌的临床效果肯定,可下调血清 VEGF 表达。

参考文献(References)

- [1] Kuribayashi K, Funaguchi N, Nakano T. Chemotherapy for advanced non-small cell lung cancer with a focus on squamous cell carcinoma [J]. J Cancer Res Ther, 2016, 12(2): 528-534
- [2] Zhang Q, Zhang X, Yan H, et al. Effects of epidermal growth factor receptor-tyrosine kinase inhibitors alone on EGFR-mutant non-small cell lung cancer with brain metastasis [J]. Thorac Cancer, 2016, 7(6): 648-654
- [3] Huang A, Li R, Zhao J, et al. Epidermal growth factor receptor (EGFR) -tyrosine kinase inhibitors combined with chemotherapy in first-line treatment in an advanced non-small cell lung cancer patient with EGFR sensitive mutation[J]. Thorac Cancer, 2016, 7(5): 614-618
- [4] Horinouchi H. Anti-vascular endothelial growth factor therapies at the crossroads: linifanib for non-small cell lung cancer [J]. Transl Lung Cancer Res, 2016, 5(1): 78-81
- [5] Shi Y, Sun Y, Ding C, et al. China Experts Consensus on Icotinib for Non-small Cell Lung Cancer Treatment?(2016 version) [J]. Chinese Journal of Lung Cancer, 2016, 19(7): 489-494
- [6] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)[J]. Eur J Cancer, 2009, 45(2): 228-247
- [7] 任保瑞, 朱彦君, 王桂洪, 等. I-III 期非小细胞肺癌 KRAS 基因突变与 ERCC1、TYMS mRNA 表达水平的相关研究 [J]. 现代生物医学进展, 2016, 16(10): 1833-1837
- [8] Ren Bao-rui, Zhu Yan-jun, Wang Gui-hong, et al. Correlation of KRAS Mutations with the mRNA Expression Levels of ERCC 1 and TYMS in Stage I to IIIA Non-small Cell Lung Cancer [J]. Progress in Modern Biomedicine, 2016, 16(10): 1833-1837
- [9] Semiha EU, Birsan Y, Eda E, et al. Prognostic Factors in Stage III Non-Small-Cell Lung Cancer Patients [J]. Asian Pac J Cancer Prev, 2016, 17(10): 4693-4697
- [10] Espinosa Bosch M, Asensi Diez R, Garcí a Agudo S, et al. Nintedanib in combination with docetaxel for second-line treatment of advanced non-small-cell lung cancer; GENESIS-SEFH drug evaluation report [J]. Farm Hosp, 2016, 40(4): 316-327
- [11] Kotsakis A, Matikas A, Koinis F, et al. A multicentre phase II trial of cabazitaxel in patients with advanced non-small-cell lung cancer progressing after docetaxel-based chemotherapy [J]. Br J Cancer, 2016, 115(7): 784-788
- [12] Felizardo M, Matos CP, Furtado ST, et al. P1.26: A Case of Non Small Cell Lung Cancer EGFR Mutation EXON 18 Positive with Poor Response to Targeted Therapy: Track: Advanced NSCLC [J]. J Thorac Oncol, 2016, 11(10): S198
- [13] Xue ZX, Wen WX, Zhuang Y, et al. Comparison of the efficacy of icotinib in patients with non-small-cell lung cancer according to the type of epidermal growth factor receptor mutation[J]. Mol Clin Oncol, 2016, 5(3): 265-268
- [14] Li X, Qin N, Wang J, et al. Clinical Observation of Icotinib Hydrochloride for Advanced Non-small Cell Lung Cancer Patients with EGFR Status Identified[J]. Chinese Journal of Lung Cancer, 2015, 18(12): 734-739

(下转第 3779 页)

- [11] 庄玲玲. 夏枯草药理作用研究进展[J]. 中国中医药信息杂志, 2009, 16(Z1): 94-96
Zhuang Ling-ling. Advances in pharmacological effects of *Prunella vulgaris* [J]. Chinese Journal of Information on Traditional Chinese Medicine, 2009, 16(Z1): 94-96
- [12] 崔鹏, 高天舒. 常用软坚散结中药及复方碘含量的测定[J]. 中华中医药学刊, 2007, 25(7): 1396-1398
Cui Peng, Gao Tian-shu. To Mensurate the Content of Iodine in Herbal Medicine and Compound Prescription Used in Softening Hard Mass and Disintegrating Masses [J]. Chinese Archives of Traditional Chinese Medicine, 2007, 25(7): 1396-1398
- [13] 王庆浩, 陈如泉, 张胜兰. 抗甲状腺中药的筛选实验 [J]. 辽宁中医杂志, 2003, 30(7): 519-520
Wang Qing-hao, Chen Ru-quan, Zhang Sheng-lan. Screening experiment of antithyroid drugs [J]. Liaoning Journal of traditional Chinese Medicine, 2003, 30(7): 519-520
- [14] 周强, 甄仲, 刘超, 等. 单味中药治疗甲状腺功能亢进的机制研究概况[J]. 辽宁中医杂志, 2010, 37(S1): 343-345
Zhou Qiang, Zhong Zhen, Liu Chao, et al. Study on the mechanism of single herb in the treatment of hyperthyroidism [J]. Liaoning Journal of traditional Chinese Medicine, 2010, 37(S1): 343-345
- [15] 倪青. 甲状腺功能亢进症中医治疗述评 [J]. 北京中医药, 2016, 36(6): 517-520
Ni Qing. Review on treatment of hyperthyroidism with traditional Chinese Medicine[J]. Beijing Journal of traditional Chinese Medicine, 2016, 36(6): 517-520
- [16] 秦龙, 胡雪剑, 任建功, 等. 薯蓣皂苷元的制备及其抗甲亢活性研究[J]. 中国现代应用药学, 2015, 32(6): 692-695
Qin Long, Hu Xue-jian, Ren Jian-gong, et al. Preparation and Study on Anti-hyperthyroidism Activities of Diosgenin [J]. Chinese Journal of Modern Applied Pharmacy, 2015, 32 (6): 692-695
- [17] 王芙蓉, 赵元, 杨莹. 薯蓣皂苷元对甲状腺功能亢进大鼠肝功能和氧化应激状态的影响[J]. 中药药理与临床, 2016, 32(5): 39-41
Wang Fu-rong, Zhao Yuan, Yang Ying. Effects of diosgenin on hepatic function and states of oxidative stress in hyperthyroidism rats[J]. Pharmacology and Clinics of Chinese Materia Medica, 2016, 32(5): 39-41
- [18] 赵子剑, 胡晓娟, 张恩户, 等. 知母药理作用的文献再评价[J]. 中成药, 2012, 34(7): 1350-1353
Zhao Zi-jian, Hu Xiao-juan, Zhang En-hu, et al. Re-evaluation the literature about pharmacological effects of *Anemarrhena* [J]. Chinese Traditional Patent Medicine, 2012, 34(7): 1350-1353
- [9] 佟连琨, 高慧, 姜永粮, 等. 知母与盐知母对甲亢阴虚大鼠红细胞膜 $\text{Na}^+\text{-K}^+\text{-ATP}$ 酶影响的比较研究[J]. 中国实验方剂学杂志, 2011, 17(9): 184-186
Tong Lian-kun, Gao Hui, Jiang Yong-liang, et al. Effects of *Anemarrhena* and salt *Anemarrhena* on erythrocyte membrane $\text{Na}^+\text{-K}^+\text{-ATP}$ Pase in Hyperthyroid rats with Yin deficiency [J]. Chinese Journal of Experimental Traditional Medical Formulas, 2011, 17(9): 184-186
- [20] 田焕云, 田鲁. 黄连素联合抗甲状腺药物治疗甲状腺机能亢进疗效观察[J]. 中国中西医结合杂志, 2003, 23(5): 385-385
Tian Huan-yun, Tian Lu. Clinical observation of berberine combined with antithyroid drugs in the treatment of hyperthyroidism[J]. Chinese Journal of Integrated Traditional and Western Medicine, 2003, 23(5): 385-385
- [21] 肖航, 谭成, 窦德强. 3种寒性中药对优甲乐所致甲亢模型动物的影响[J]. 中华中医药学刊, 2016(9): 2122-2125
Xiao Hang, Tan Cheng, Dou De-qiang. Effects of 3 Chinese Drugs with Cold Property on Hyperthyroidism Rats Induced by Euthyrox [J]. Chinese Archives of Traditional Chinese Medicine, 2016 (9): 2122-2125
- [22] 许馨予, 徐坦, 许公平. 许公平老中医治疗甲状腺功能亢进症经验 [J]. 四川中医, 2016, (9): 12-14
Xu Xin-yu, Xu Tan, Xu Gong-ping. Xu Gong-ping's experience in treating hyperthyroidism by traditional Chinese Medicine[J]. Sichuan Journal of traditional Chinese Medicine, 2016, (9): 12-14
- [23] 卞子瑶. 余江毅治疗甲状腺功能亢进症经验 [J]. 河南中医, 2016, 36(7): 1142-1143
Bian Zi-yao. Yu Jiang-yi's experience in the treatment of hyperthyroidism[J]. Henan Traditional Chinese Medicine, 2016, 36(7): 1142-1143
- [24] 郭强, 赵欢, 雷星星, 等. 基于因子分析的张发荣教授治疗甲状腺功能亢进症用药特点研究[J]. 中华中医药学刊, 2016(8): 1849-1851
Guo Qiang, Zhao Huan, Lei Xing-xing, et al. Medication Characteristics of ZHANG Fa-rong in Treating Hyperthyroidism [J]. Chinese Archives of Traditional Chinese Medicine, 2016(8): 1849-1851

(上接第 3741 页)

- [14] Jiang X, Wang W, Zhang Y. Clinical Analysis of Icotinib on Beneficiary of Advanced Non-small Cell Lung Cancer with EGFR Common Mutation[J]. Chinese Journal of Lung Cancer, 2016, 19(4): 200-206
- [15] Holzer TR, Fulford AD, Reising LO, et al. Profiling of Vascular Endothelial Growth Factor Receptor Heterogeneity Identifies Protein Expression-defined Subclasses of Human Non-small Cell Lung Carcinoma[J]. Anticancer Res, 2016, 36(7): 3277-3288
- [16] Essink A, Korse T, van den Heuvel M. 157P: Serum tumor markers and the response to immunotherapy in advanced non-small cell lung carcinoma[J]. J Thorac Oncol, 2016, 11(4): S126
- [17] Soria JC, Marabelle A, Brahmer JR, et al. Immune checkpoint modulation for non-small cell lung cancer [J]. Clin Cancer Res, 2015, 21(10): 2256-2262
- [18] Badovinac S, Korsic M, Mursic D, et al. Cancer-related inflammation as predicting tool for treatment outcome in locally advanced and metastatic non-small cell lung cancer [J]. J Thorac Dis, 2016, 8(7): 1497-1503
- [19] Tang H, Ma H, Peng F, et al. Prognostic performance of inflammation-based prognostic indices in locally advanced non-small-lung cancer treated with endostar and concurrent chemoradiotherapy [J]. Mol Clin Oncol, 2016, 4(5): 801-806
- [20] Wang G, Tian W, Liu Y, et al. Visfatin Triggers the Cell Motility of Non-Small Cell Lung Cancer via Up-Regulation of Matrix Metalloproteinases[J]. Basic Clin Pharmacol Toxicol, 2016, 119(6): 548-554
- [21] Jiang LY, Bi R, Ding FB, et al. Prognostic significance of overexpressed matrix metalloproteinase-2, mouse-double minute: 2 homolog and epidermal growth factor receptor in non-small cell lung cancer[J]. J BUON, 2016, 21(2): 341-348