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Original Article

Clinical effect of anlotinib in combination with docetaxel in treating advanced non-small cell lung cancer

Guibin Weng, Weimin Fang, Yijin Lin, Lin Chen, Weikun Su*

Department of Thoracic Oncology Surgery, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian 350014, China

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Abstract

This study aimed to explore the clinical performance of anlotinib in combination with docetaxel in treating advanced non-small cell lung cancer (NSCLC). One hundred advanced NSCLC patients admitted to our hospital from January 2019 to December 2022 were retrospectively chosen to be the study objects, and separated into observation group (OG, n=50) and control group (CG, n=50) based on the different drugs used. The CG was given docetaxel injection. The OG was treated with anlotinib hydrochloride capsule combined with docetaxel injection. The clinical effective rate, levels of serum tumor markers, quality of life and occurrence of adverse reactions in both groups were compared. The total clinical effective rate in the OG presented elevated relative to the CG (P<0.01). After treatment, CEA, CA125, SCC and CYFRA21-1 levels in both groups were decreased in both groups, and those in the OG presented lower relative to the CG (P<0.05). After treatment, KPS score in both groups was increased in both groups and that in the OG presented higher relative to the CG (P<0.05). No difference was seen in the occurrence of adverse reactions between 2 groups (P=0.35). In treating advanced NSCLC patients, anlotinib combined with docetaxel can promote efficacy to a certain extent, effectively regulate the level of serum tumor markers, promote the quality of life of patients, and will not significantly affect clinical safety.

Keywords: Advanced non-small cell lung cancer, Anlotinib, Docetaxel, Chemotherapy.

1. Introduction

Lung cancer belongs to the most common clinical malignant tumor, and non-small cell lung cancer (NSCLC) takes up 80% to 85% of lung cancer [1]. Because patients with early NSCLC often have no typical symptoms, many patients have entered the middle and late stage of the disease at the time of diagnosis, missed the opportunity for surgical treatment, and even some tumors metastasized, and can only alleviate symptoms through radiotherapy and chemotherapy to prolong survival [2]. Platinum-containing double-drug chemotherapy is the current first-line chemotherapy regimen for the clinical treatment of advanced NSCLC patients, which can relieve the symptoms of patients to a certain extent [3]. However, some patients have poor chemotherapy effects or even chemotherapy failure due to drug resistance during treatment, so second-line or third-line chemotherapy regimen should be used for treatment [4].

Docetaxel is a plant chemotherapeutic agent that can accelerate the apoptosis process of cancer cells by inhibiting microtubule depolymerization and normal recombination [5], and docetaxel alone is currently the second-line standard chemotherapy regimen for the clinical treatment of advanced NSCLC [6]. Since long-term application of docetaxel can easily result in drug resistance in patients, and then adversely affect the subsequent tumor inhibition effect, it is necessary to combine it with less dose-dependent drugs to improve the tumor inhibition effect [7]. Hence, it is essential to explore a safe as well as efficient chemotherapy regimen for advanced NSCLC patients who have failed second-line chemotherapy.

Anlotinib is a novel multi-target tyrosine kinase inhibitor independently developed in China, which has anti-tumor angiogenesis effect and low incidence of adverse reactions [8]. Relevant studies have reported that anlotinib can demonstrate good efficacy in various malignant tumors such as NSCLC and cervical cancer [9, 10].

Therefore, our study explored the clinical performance of anlotinib combined with docetaxel in treating advanced NSCLC, aiming to provide reference for patients to develop multi-line chemotherapy regimens.

2. Materials and Methods

2.1. General data

One hundred patients with advanced NSCLC admitted to our hospital from January 2019 to December 2022 were retrospectively chosen to be the study objects, and separated into observation group (OG, n=50) and control group

* Corresponding author.
E-mail address: suwk163@163.com (W. Su).
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(CG, n=50) based on the different drugs used. No significant difference was discovered in clinical data containing gender, age, type of NSCLC and TNM stage between 2 groups (P>0.05), indicating comparability (Table 1).

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Met the diagnostic criteria of NSCLC; (2) Estimated survival time >3 months; (3) TNM stages ranged from IIIb to IV; (4) Could tolerate chemotherapy; (5) Good compliance; (6) Progression of the disease after first-line chemotherapy; (6) All patients sign informed consent forms.

Exclusion criteria: (1) There are other types of malignant tumors; (2) Acute blood disease; (3) Persons with conscious or mental disorders; (4) Allergic reactions to investigational drugs; (5) Patients who could not insist on completing chemotherapy due to serious adverse reactions.

2.3. Methods

The CG was given docetaxel injection (Qilu Pharmaceutical Co., LTD., specification: 4 ml vs. 80 mg)75 mg/m^2 mixed with 250 ml normal saline for treatment, 21 days for 1 treatment cycle. The drug was stopped for 20 days after intravenous infusion on day 1 of each treatment cycle.

The OG was treated with anlotinib hydrochloride capsule (Zhengda Tianqing Pharmaceutical Group Co., LTD., specification: 12 mg) combined with docetaxel injection. Oral antirotinib hydrochloride capsule 12 mg once a day. After 14 days of treatment, the drug was stopped for 7 days, and 21 days was 1 cycle. Both groups were treated for 4 cycles.

2.4. Observation index and evaluation criteria

(1) Clinical effective rate: On the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [11], complete remission (CR) meant the target lesion disappeared completely after treatment. Partial response (PR) meant the target lesion volume decreased by >50% after treatment. Stable disease (SD) meant the volume of target lesion decreased by less than 50% after treatment. Progressive disease (PD) meant the target lesion volume increased by >25% or new lesions appeared after treatment. Total clinical effective rate = (CR+PR)/total cases ×100%.

(2) Serum tumor markers: Carcinoembryonic antigen (CEA), glycoprotein antigen 125 (CA125), squamous cell carcinoma antigen (SCC) as well as Cytokeratin fragment antigen 21-1 (CYFRA21-1) were detected by ELISA.

(3) Quality of life: The Karnofsky Performance Status (KPS) was compared between 2 groups. This scale comprehensively evaluated the quality of life of tumor patients from the dimensions of self-care ability and symptom severity. The full score was 100, and the higher the score was, the better the quality of life was.

(4) The occurrence of hematotoxic reactions (platelet count decrease, white blood cell count decrease, as well as granulocyte count decrease) and non-hematotoxic reactions (hypertension, fatigue and proteinuria) were compared between the two groups.

2.5. Statistical analysis

The data were processed by SPSS 23.0 statistical software. Measurement data were exhibited as (x±s) and t-test was adopted for comparison. The statistical data were represented by [n (%)] and χ^2 test was performed for comparison. P<0.05 meant the difference was statistically significant.

3. Results

3.1. Clinical effects in both groups

Table 2 displayed that the total clinical effective rate in the OG was 52.22%, presented elevated relative to that of 24.00% in the CG (P<0.01).

3.2. Serum tumor markers in both groups

Figure 1 displayed no difference in levels of serum tu-

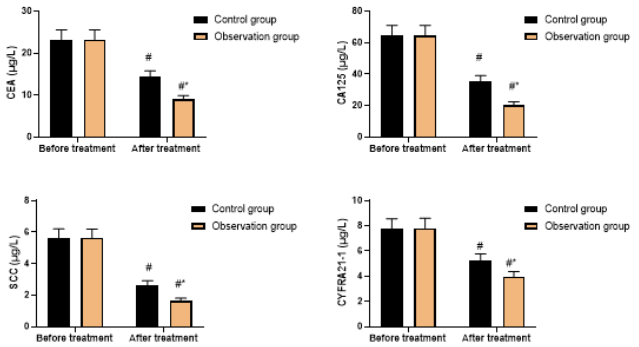

Fig. 1. Serum tumor markers in both groups. #P<0.05, compared with before therapy. *P<0.05, compared with CG.

Table 1. General data of patients in both groups.

Index		Control group (n=50)	Observation group (n=50)	P
Gender (male/female)		25/25	26/24	>0.05
Average age (years)		48.42±5.73	48.36±5.70	>0.05
Type of NSCLC	Adenocarcinoma	30	29	>0.05
	Squamous cell carcinoma	20	21	
TNM stage	Stage IIIb	19	20	>0.05
	Stage IV	31	30	

Table 2. Clinical effects in both groups [n (%)].

Groups	N	CR	PR	SD	PR	Total clinical effective rate
Control group	50	2	10	25	13	12 (24.00%)
Observation group	50	5	21	21	3	26 (52.22%)
χ^2						8.319
P						<0.01

mor markers between 2 groups before therapy (P>0.05). After therapy, CEA, CA125, SCC and CYFRA21-1 levels in both groups were decreased in both groups, and those in the OG presented reduced relative to the CG (P<0.05).

3.3. Quality of life in both groups

Figure 2 displayed no difference in KPS score between 2 groups previous to therapy (P>0.05). After treatment, KPS score in both groups was elevated in both groups and that in the OG presented higher relative to the CG (P<0.05).

3.4. Occurrence of adverse reactions in both groups

Table 3 revealed no difference in the occurrence of adverse reactions between 2 groups (P=0.35).

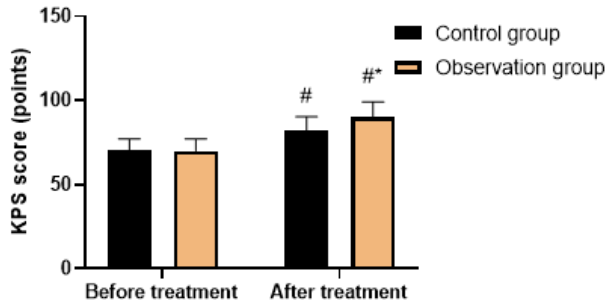

Fig. 2. Quality of life in both groups. #P<0.05, compared with before therapy. *P<0.05, compared with CG.

4. Discussion

Since surgery cannot play a good role in treating advanced NSCLC, chemotherapy has become the current clinical treatment of this disease, which is of great importance in controlling the proliferation and metastasis of tumor cells as well as prolonging the survival of patients [12]. For the past few years, with the gradual deepening of clinical research on the treatment of advanced NSCLC, it has been found that more chemotherapy drugs can be used for this disease [13]. However, affected by many adverse factors, some patients cannot achieve the expected effect after first-line chemotherapy, and some patients also have problems such as short duration of efficacy and high drug toxicity when receiving second-line chemotherapy [14]. Therefore, the safe and efficient multi-line chemotherapy regimen for patients with advanced NSCLC has become a major direction of clinical research.

Docetaxel is a novel anti-microtubule drug, belonging to semi-synthetic derivatives, which can control the synthesis of tumor DNA, RNA and protein, enhance the assembly of microtubule dimers into microtubules on the basis of acting on microtubules, disturb the process of depolymerization, as well as maintain stability [15]. At present, many clinical reports have pointed out that docetaxel is an effective supportive chemotherapy drug for a variety of advanced malignant tumors and has a certain prolonging effect on the survival of patients [16]. However, it has also been reported that docetaxel alone has limited remission effect on patients with advanced malignant tumors, and continuous use of docetaxel has obvious side effects, and some patients may suffer from interruption or failure of chemotherapy due to their inability to tolerate chemotherapy [17].

As a targeted anti-angiogenesis drug, anlotinib can strengthen the inhibition of enzymes related to tumor cell proliferation, thus blocking downstream signal transduction along with repressing tumor growth [18]. Anlotinib is well absorbed orally, can promote the overall therapeutic effect, and is widely applied in the therapy of NSCLC, gastric cancer along with other tumor diseases [19, 20].

In our study, the outcomes revealed that after therapy, the total clinical effective rate in the OG was 52.22%, presented elevated relative to that of 24.00% in the CG, and CEA, CA125, SCC as well as CYFRA21-1 levels in the OG presented lower relative to the CG, suggesting that this combination chemotherapy regimen could improve the chemotherapy effect and inhibit the expression of serum tumor markers in treating advanced NSCLC to a certain extent. Consistently, Ji et al. have indicated that the total effective rate of anlotinib in combination with docetaxel in treating lung cancer is 57.14%, and can improve the long-term survival rate [21]. Moreover, a previous study has proved that the serum levels of tumor markers including VEGF, CEA, as well as SCC-AG in the anlotinib in combination with immune checkpoint inhibitors group present lower relative to the immune checkpoint inhibitors group alone [22].

Besides, our study indicated that after treatment, KPS score in the OG presented elevated relative to the CG, implying that anlotinib combined with docetaxel could promote the quality of life of advanced NSCLC patients. At the same time, no difference was seen in the occurrence of adverse reactions between 2 groups, confirming that anlotinib in combination with docetaxel in treating advanced NSCLC has no significant impact on clinical safety compared with docetaxel alone. In line with our finding, it has been reported that anlotinib in combination with docetaxel has been reported to show good efficacy and manageable toxicity in second-line therapy of metastatic osteosarcoma

Table 3. Occurrence of adverse reactions in both groups [n (%)].

Groups	N	Hematotoxic reactions			non-hematotoxic reactions			Total incidence rate
		Platelet count decrease	White blood cell count decrease	Granulocyte count decrease	Hypertension	Fatigue	Proteinuria	
Control group	50	2	1	2	2	2	1	10 (20.00%)
Observation group	50	2	2	2	3	3	2	14 (28.00%)
χ^2								0.877
P								0.35

compared to docetaxel [23]. Additionally, Si et al. have proposed that anlotinib can enhance the quality of life compared to placebo in advanced NSCLC patients who have accepted more than two chemotherapy treatments [24-27].

5. Conclusion

In conclusion, in treating advanced NSCLC patients, anlotinib combined with docetaxel can promote efficacy to a certain extent, effectively regulate the level of serum tumor markers, promote the quality of life of patients, and will not significantly affect clinical safety.

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Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

WG conducted the experiments and wrote the paper; FW, LY and CL analyzed and organized the data; SW conceived, designed the study and revised the manuscript.

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References

1. Bade BC, Dela Cruz CS (2020) Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med 41 (1): 1-24. doi: 10.1016/j.ccm.2019.10.001
2. Mithoowani H, Febbraro M (2022) Non-Small-Cell Lung Cancer in 2022: A Review for General Practitioners in Oncology. Curr Oncol 29 (3): 1828-1839. doi: 10.3390/curroncol29030150
3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, Hui R, Hochmair MJ, Clingan P, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Garon EB, Novello S, Rubio-Viqueira B, Boyer M, Kurata T, Gray JE, Yang J, Bas T, Pietanza MC, Garassino MC (2020) Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 38 (14): 1505-1517. doi: 10.1200/jco.19.03136
4. Durm G, Hanna N (2017) Second-Line Chemotherapy and Beyond for Non-Small Cell Lung Cancer. Hematol Oncol Clin North Am 31 (1): 71-81. doi: 10.1016/j.hoc.2016.08.002
5. Ma Z, Zhang W, Dong B, Xin Z, Ji Y, Su R, Shen K, Pan J, Wang Q, Xue W (2022) Docetaxel remodels prostate cancer immune microenvironment and enhances checkpoint inhibitor-based immunotherapy. Theranostics 12 (11): 4965-4979. doi: 10.7150/thno.73152
6. Shi Y, Wu L, Yu X, Xing P, Wang Y, Zhou J, Wang A, Shi J, Hu Y, Wang Z, An G, Fang Y, Sun S, Zhou C, Wang C, Ye F, Li X, Wang J, Wang M, Liu Y, Zhao Y, Yuan Y, Feng J, Chen Z, Shi J, Sun T, Wu G, Shu Y, Guo Q, Zhang Y, Song Y, Zhang S, Chen Y, Li W, Niu H, Hu W, Wang L, Huang J, Zhang Y, Cheng Y, Wu Z, Peng B, Sun J, Mancao C, Wang Y, Sun L (2022) Sintilimab versus docetaxel as second-line treatment in advanced or metastatic squamous non-small-cell lung cancer: an open-label, randomized controlled phase 3 trial (ORIENT-3). Cancer Commun (Lond) 42 (12): 1314-1330. doi: 10.1002/cac2.12385
7. Wang Y, Nie J, Dai L, Hu W, Zhang J, Chen X, Ma X, Tian G, Han J, Han S, Wu D, Long J, Zhang Z, Fang J (2022) Evaluation of efficacy and toxicity of nivolumab combined with or without docetaxel in patients with advanced NSCLC. Cancer Immunol Immunother 71 (2): 267-276. doi: 10.1007/s00262-021-02964-x
8. Shen G, Zheng F, Ren D, Du F, Dong Q, Wang Z, Zhao F, Ahmad R, Zhao J (2018) Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol 11 (1): 120. doi: 10.1186/s13045-018-0664-7
9. Lei T, Xu T, Zhang N, Zou X, Kong Z, Wei C, Wang Z (2023) Anlotinib combined with osimertinib reverses acquired osimertinib resistance in NSCLC by targeting the c-MET/MYC/AXL axis. Pharmacol Res 188: 106668. doi: 10.1016/j.phrs.2023.106668
10. Xu Q, Wang J, Sun Y, Lin Y, Liu J, Zhuo Y, Huang Z, Huang S, Chen Y, Chen L, Ke M, Li L, Li Z, Pan J, Song Y, Liu R, Chen C (2022) Efficacy and Safety of Sintilimab Plus Anlotinib for PD-L1-Positive Recurrent or Metastatic Cervical Cancer: A Multicenter, Single-Arm, Prospective Phase II Trial. J Clin Oncol 40 (16): 1795-1805. doi: 10.1200/jco.21.02091
11. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE (2017) iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18 (3): e143-e152. doi: 10.1016/s1470-2045(17)30074-8
12. Miller M, Hanna N (2021) Advances in systemic therapy for non-small cell lung cancer. Bmj 375: n2363. doi: 10.1136/bmj.n2363
13. Duma N, Santana-Davila R, Molina JR (2019) Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clin Proc 94 (8): 1623-1640. doi: 10.1016/j.mayocp.2019.01.013
14. Jiang T, Wang P, Zhang J, Zhao Y, Zhou J, Fan Y, Shu Y, Liu X, Zhang H, He J, Gao G, Mu X, Bao Z, Xu Y, Guo R, Wang H, Deng L, Ma N, Zhang Y, Feng H, Yao S, Wu J, Chen L, Zhou C, Ren S (2021) Toripalimab plus chemotherapy as second-line treatment in previously EGFR-TKI treated patients with EGFR-mutant-advanced NSCLC: a multicenter phase-II trial. Signal Transduct Target Ther 6 (1): 355. doi: 10.1038/s41392-021-00751-9
15. Zhou C, Huang D, Fan Y, Yu X, Liu Y, Shu Y, Ma Z, Wang Z, Cheng Y, Wang J, Hu S, Liu Z, Poddubskaya E, Disel U, Akopov A, Dvorkin M, Zheng W, Ma Y, Wang Y, Li S, Yu C, Rivalland G (2023) Tislelizumab Versus Docetaxel in Patients With Previously Treated Advanced NSCLC (RATIONALE-303): A Phase 3, Open-Label, Randomized Controlled Trial. J Thorac Oncol 18 (1): 93-105. doi: 10.1016/j.jtho.2022.09.217
16. Maiorano BA, De Giorgi U, Roviello G, Messina C, Altavilla A, Cattrini C, Mennitto A, Maiello E, Di Maio M (2022) Addition of androgen receptor-targeted agents to androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. ESMO Open 7 (5): 100575. doi: 10.1016/j.esmoop.2022.100575
17. Taniguchi Y, Shimokawa T, Takiguchi Y, Misumi T, Nakamura Y, Kawashima Y, Furuya N, Shiraishi Y, Harada T, Tanaka H, Miura S, Uchiyama A, Nakahara Y, Tokito T, Naoki K, Bessho A, Goto Y, Seike M, Okamoto H (2022) A Randomized Comparison of Nivolumab versus Nivolumab + Docetaxel for Previously Treated Advanced or Recurrent ICI-Naïve Non-Small Cell Lung

Cancer: TORG1630. Clin Cancer Res 28 (20): 4402-4409. doi: 10.1158/1078-0432.Ccr-22-1687

18. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, Cheng Y, He J, Shi Y, Zhao Y, Yu H, Zhao Y, Chen W, Luo Y, Wu L, Wang X, Pirker R, Nan K, Jin F, Dong J, Li B, Sun Y (2018) Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients With Advanced Non-Small Cell Lung Cancer: The ALTER 0303 Phase 3 Randomized Clinical Trial. JAMA Oncol 4 (11): 1569-1575. doi: 10.1001/jamaoncol.2018.3039
19. Gu G, Hu C, Hui K, Zhang H, Chen T, Zhang X, Jiang X (2021) Exosomal miR-136-5p Derived from Anlotinib-Resistant NSCLC Cells Confers Anlotinib Resistance in Non-Small Cell Lung Cancer Through Targeting PPP2R2A. Int J Nanomedicine 16: 6329-6343. doi: 10.2147/ijn.S321720
20. Yuan M, Guo XL, Chen JH, He Y, Liu ZQ, Zhang HP, Ren J, Xu Q (2022) Anlotinib suppresses proliferation, migration, and immune escape of gastric cancer cells by activating the cGAS-STING/IFN-β pathway. Neoplasma 69 (4): 807-819. doi: 10.4149/neo_2022_211012N1441
21. Ji X, Jing X, Liu Y, Huang J, Yang S, Yun Y (2022) Clinical Application of Anlotinib Combined with Docetaxel: Safe and Effective Treatment for Lung Carcinoma. Dis Markers 2022: 2483816. doi: 10.1155/2022/2483816
22. He L, Chen X, Ding L, Zhang X (2022) Clinical Efficacy of Anti-anlotinib Combined with Immune Checkpoint Inhibitors in the Treatment of Advanced Non-Small-Cell Lung Cancer and Its Effect on Serum VEGF, CEA, and SCC-Ag. J Oncol 2022: 1530875. doi: 10.1155/2022/1530875
23. Wang T, Lin F, Huang Y, Qian G, Yu W, Hu H, Ji T, Tang L, Yao Y (2022) The Combination of Anlotinib and Gemcitabine/Docetaxel in Patients with Metastatic Osteosarcoma Who Have Failed Standard Chemotherapy. Cancer Manag Res 14: 2945-2952. doi: 10.2147/cmar.S378264
24. Ismaili A, Yari K, Moradi MT, Sohrabi M, Kahrizi D, Kazemi E, Souri Z. (2015). IL-1B (C+3954T) gene polymorphism and susceptibility to gastric cancer in the Iranian population. Asian Pac J Cancer Prev 16(2):841-4. doi: 10.7314/apjcp.2015.16.2.841. PMID: 25684535.
25. Kazemi E, Kahrizi D, Moradi MT, Sohrabi M, Yari K. (2016). Gastric Cancer and Helicobacter pylori: Impact of hopQII Gene. Cell Mol Biol (Noisy-le-grand). 62(2):107-10. PMID: 26950460.
26. Kazemi E, Kahrizi D, Moradi MT, Sohrabi M, Amini S, Mousavi SA, Yari K. (2016). Association between Helicobacter pylori hopQI genotypes and human gastric cancer risk. Cell Mol Biol (Noisy-le-grand). 62(1):6-9. PMID: 26828979.
27. Si X, Zhang L, Wang H, Zhang X, Wang M, Han B, Li K, Wang Q, Shi J, Wang Z, Cheng Y, He J, Shi Y, Chen W, Wang X, Luo Y, Nan K, Jin F, Li B, Chen Y, Zhou J, Wang D (2018) Quality of life results from a randomized, double-blinded, placebo-controlled, multi-center phase III trial of anlotinib in patients with advanced non-small cell lung cancer. Lung Cancer 122: 32-37. doi: 10.1016/j.lungcan.2018.05.013