Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Management of anlotinib-related adverse events in patients with advanced non-small cell lung cancer: Experiences in ALTER-0303

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Keywords
Adverse event; anlotinib; multi-target tyrosine kinase inhibitor; non-small cell lung cancer.

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Received: 1 October 2018;
Accepted: 24 December 2018.

doi: 10.1111/1759-7714.12977

Thoracic Cancer **10** (2019) 551–556

Abstract

Background: Anlotinib is an oral tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor, fibroblast growth factor receptor, platelet-derived growth factor receptor, and stem cell factor receptor (c-Kit). In the phase III ALTER-0303 trial (Clinical Trial Registry ID: NCT 02388919), anlotinib significantly improved overall survival versus placebo in advanced non-small cell lung cancer patients who had received at least two previous chemotherapy and epidermal growth factor receptor/anaplastic lymphoma kinase targeted therapy regimens. This study summarized adverse event management in this trial.

Methods: Patients were randomized (2:1) to anlotinib or placebo up to progression or intolerable toxicity. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 and managed by investigators. Key strategies for preventing and managing the most common adverse events included patient education, supportive care, and dose modification.

Results: Between February 2015 and August 2016, 294 patients received anlotinib. A total of 170 (57.8%) patients received antihypertensive medications for hypertension, 53 (18.0%) patients received levothyroxine for hypothyroidism, 24 (8.2%) patients received fibrates for hypertriglyceridemia, 11 (3.7%) patients took cortisone cream for hand-foot syndrome, and 38 (12.9%) patients received anti-diarrheal medications for diarrhea. Dose reduction and drug discontinuation were required in 24 (8.16%) and 31 (10.54%) patients in the anlotinib group, respectively.

Conclusion: Anlotinb-related adverse events could be controlled by patient education, prophylactic measures, early and active intervention, and dose modification.

Introduction

Lung cancer is the leading incident cancer and cause of cancer mortality worldwide.[1] Anlotinib is a novel multi-target tyrosine kinase inhibitor (MKI) that inhibits vascular endothelial growth factor receptor (VEGFR) 2/3, fibroblast growth factor receptor (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR) α/β, stem cell factor receptor (c-Kit), and Ret. At the dose of 12 mg once daily at the two-week on/one-week off schedule, anlotinib showed manageable toxicity and antitumor potential.[2] The most common adverse events (AEs) observed in the previous study were hypertension, elevated thyroid-stimulating hormone (TSH), hypertriglyceridemia, and hand-foot syndrome (HFS).[2,3] The toxicity profile of anlotinib was similar to that in other MKIs, such as sorafenib and sunitinib.[4,5]The ALTER-0303 trial (NCT02388919) showed anlotinib significantly improved overall survival and quality of life in advanced non-small cell lung cancer (NSCLC).[6,7]Anlotinib was approved for advanced NSCLC in the third-line or further therapy in China. This study summarizes adverse event management in the ALTER-0303 trial.

Methods

Study design

The full details of the study design have been published.[8] The study was a multicenter, double-blinded, randomized phase III trial comparing anlotinib and placebo in advanced NSCLC patients who had received at least two previous chemotherapy and epidermal growth factor receptor/anaplastic large-cell lymphoma kinase targeted therapy regimens. Pathological stage IIIB/IV advanced NSCLC patients who had failed at least two previous chemotherapy and epidermal growth factor receptor/anaplastic large-cell lymphoma kinase targeted therapy regimens were eligible. Patients were randomized (2:1) to receive anlotinib or placebo once daily (12 mg) from day 1 to 14 of a 21-day cycle until progression or intolerable toxicity. The ethics review board at each site approved the study protocol, and the study was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before undergoing any study procedure. The study was registered at the ClinicalTrials.gov website (ClinicalTrials.gov identifier, NCT 02388919).

The investigator or qualified designee assessed each patient to evaluate for AEs. AEs were graded and recorded throughout the study and during the follow-up period according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. Toxicities were characterized in terms, including seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Patients had follow up every week in the first cycle, and then every two cycles. If clinically indicated, more frequent follow up was conducted.

Dose modification

Dose modification was determined by investigators based on drug-related toxicities graded by National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 and clinical benefit from therapy. The dose could be reduced to 8–10 mg once daily for patients who had grade 3 or 4 treatment-related toxicities, or for patients with intolerable grade 2 toxicity, despite maximum supportive care measures. If dose reduction was necessary, then the dose of anlotinib was reduced to 10 mg once daily. If further dose reduction was necessary, the dosage was reduced to 8 mg once daily. If the dosage of 8 mg once daily was not tolerable, then the patient stopped receiving anlotinib.

Patient education

Before patients received anlotinib/placebo, investigators would assist patients and their families by reviewing potential AEs and effective management strategies according to previous clinical trials, such as hypertension, hand-foot syndrome, and diarrhea. Patients were advised to carefully monitor blood pressure, skin change of hands and feet, and changes in stool quality and quantity. Patients were required to record any symptoms and concomitant medications during treatment. Patients were encouraged to contact investigators to manage toxicities quickly.

Statistical analysis

Proportions were compared using the χ^2-test or Fisher's exact test, as appropriate. Two-sided values of $P < 0.05$ were considered statistically significant. Analyses were calculated by SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Between February 2015 and August 2016, a total of 437 patients were randomized at 31 centers. The baseline characteristics of the anlotinib group ($n = 294$) and the placebo group ($n = 143$) were well balanced in gender, age, histology, stage, gene status, and Eastern Cooperative Oncology Group performance status (Table 1).

The AEs of all grades occurring in at least 10% of patients and with statistical difference between the two groups are shown in Table 2.

Table 1 Patient demographics and baseline disease characteristics

Characteristics	Placebo (*n* = 143)	Anlotinib (*n* = 294)	
Gender, *n* (%)			
Male	97 (67.8)	188 (63.9)	*P* = 0.455
Age (years)			
Mean	56.8	57.9	*P* = 0.207
Range	31.00–74.00	20.00–75.00	
Histology, *n* (%)			*P* = 0.145
Adenocarcinoma	108 (75.5)	228 (77.6)	
Squamous cell	33 (23.1)	53 (18.0)	
Others	2 (1.40)	13 (4.42)	
Stage, *n* (%)			*P* = 1.000
IIIB	7 (4.9)	15 (5.1)	
IV	136 (95.1)	277 (94.2)	
EGFR mutation (%)	45 (31.5)	93 (31.6)	*P* = 1.000
ALK rearrangement (%)	2 (1.4)	5 (1.72)	*P* = 1.000
ECOG PS (%)			*P* = 0.246
0	22 (15.4)	59 (20.1)	
1	120 (83.9)	233 (79.3)	
2	1 (0.7)	2 (0.7)	

ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

Table 2 Adverse events of significant difference between treatment groups (for all graded) in patients with advanced non-small cell lung cancer

	Anlotinib (*n* = 294)		Placebo (*n* = 143)			
Adverse events	All AEs, *n* (%)	Grades ¾, *n* (%)	All AEs, *n* (%)	Grades 3/4, *n* (%)	P1	P2
Hypertension	199 (67.7)	40 (13.6)	24 (16.8)	0 (0.0)	0.00	0.00
Fatigue	153 (52.0)	1 (0.34)	41 (28.7)	0 (0.0)	0.00	1.000
TSH elevation	137 (46.6)	1 (0.3)	12 (8.4)	0.0	0.00	1.000
Anorexia	135 (45.9)	3 (1.0)	46 (32.2)	3 (2.1)	0.0071	0.398
Hypertriglyceridemia	131 (44.6)	9 (3.1)	34 (23.8)	0 (0.0)	0.00	0.034
Hand-foot syndrome	129 (43.9)	11 (3.7)	13 (9.1)	0 (0.0)	0.00	0.019
Hypercholesteremia	123 (41.8)	0 (0.0)	20 (14.0)	0 (0.0)	0.00	NA
Cough	122 (41.5)	3 (1)	41 (28.7)	1 (0.7)	0.0113	1.000
Diarrhea	104 (35.4)	3 (1.0)	21 (14.7)	0 (0.0)	0.00	0.5541
GGT elevation	92 (31.3)	16 (5.4)	28 (19.6)	10 (7.0)	0.0118	0.523
Proteinuria	85 (28.9)	7 (2.4)	19 (13.3)	1 (0.7)	0.0003	0.2827
Pharyngalgia	83 (28.2)	2 (0.7)	10 (7.0)	0 (0.0)	0.00	1.000
Blood bilirubin elevation	77 (26.2)	5 (1.7)	21 (14.7)	2 (1.4)	0.0071	1.000
Hyponatremia	69 (23.5)	24 (8.2)	12 (8.39)	5 (3.5)	0.0001	0.0687
Weight loss	68 (23.1)	0 (0.0)	12 (8.4)	0 (0.0)	0.0001	NA
Mucositis oral	68 (23.1)	3 (1.0)	4 (2.8)	0 (0.0)	0.00	0.5541
Dysphonia	68 (23.1)	3 (1.0)	7 (4.9)	1 (0.7)	0.00	1.000
Low-density lipoprotein elevation	62 (21.1)	2 (0.7)	11 (7.7)	0 (0.0)	0.0003	1.0000
Hemoptysis	60 (20.4)	9 (3.1)	13 (0.1)	2 (1.4)	0.0026	0.5159
Hematuria	44 (15)	0 (0.0)	8 (5.6)	0 (0.0)	0.0043	NA
Upper respiratory infection	37 (12.6)	0 (0.0)	4 (2.8)	0 (0.0)	0.0007	NA
Urinary tract infection	34 (11.6)	0 (0.0)	6 (4.2)	0 (0.0)	0.0127	NA
Headache	33 (11.2)	0 (0.0)	5 (3.5)	0 (0.0)	0.0063	NA
Decreased platelet count	31 (10.5)	3 (1.0)	6 (4.2)	0 (0.0)	0.0275	0.5541

Reported as adverse events of all grades occurring in at least 10% of patients and with statistical difference between the two groups. P1, p value for adverse events of all grades between the two groups; P2, p value for adverse events of grade ≥ 3 between the two groups. AES, adverse events; GGT, gamma-glutamyltransferase; NA, not available; TSH, thyroid-stimulating hormone.

A total of 32 (10.9%) patients with controlled hypertension were enrolled in the anlotinib group. The median onset time of hypertension was five days (range 2–8 days). Hypertension could be managed with antihypertensive medications (Table 3). Antihypertension medications could control 89.3% of grade 2 and 3 hypertension. Of 40 patients

Table 3 Antihypertensive medication for management of hypertension

Antihypertensive medication	No. patients (%)
Dihydropyridine calcium-channel blockers	108 (36.7)
Converting enzyme inhibitors of angiotensin/ angiotensin receptor blockers	79 (26.9)
Diuretics	57 (19.4)
Beta-blockers	35 (11.9)

with grade ≥3 hypertension, 22 patients recovered to grade ≤2, and 17 patients had persistent hypertension.

Fatigue reported by patients in this trial was predominantly grade 1 or 2 (152/153). No pharmacological interventions were given to relieve fatigue.

TSH elevation in this trial was predominantly grade 1 or 2 (136/137). Of 137 patients with TSH elevation, 53 patients received levothyroxine for hypothyroidism. One patient with grade 3 hypothyroidism recovered after receiving levothyroxine.

The median onset time of hypertriglyceridemia in the anlotinib group was 20 days (range 19–38 days). A total of 24 patients received fibrates to reduce the plasma triglyceride level. Of nine patients with grade ≥3 hypertriglyceridemia, seven patients recovered to grade ≤2 hypertriglyceridemia.

Anorexia in this trial was predominantly grade 1 or 2 (132/135). No pharmacological interventions were taken to relieve anorexia.

The median onset time of HFS in the anlotinib group was 30 days (range 24–41 days). A total of 11 patients received cortisone cream for topical therapy. Of 11 patients with grade ≥3 HFS, 10 patients recovered to grade ≤2 HFS.

Of 104 patients with diarrhea, just three patients had grade 3 diarrhea, and 38 patients received anti-diarrheal medication, such as loperamide or smectite. Diarrhea in this trial could be controlled by anti-diarrhea medication in most patients. Just two patients with grade 3 diarrhea required dose reduction.

Seven patients reported grade 3 proteinuria, and four of them resolved.

Dose reductions and drug discontinuations were required in 24 (8.2%) and 31 (10.5%) patients in the anlotinib group, respectively. (Tables 4,5) In 16 patients who were aged >70 years in the anlotinib group, no patient required dose modification and only one patient discontinued anlotinib. In the subgroup that experienced dose modification, the objective response rate, disease control rate, and median progression-free survival were 12.5%, 87.5%, and 8.17 months, respectively. Median overall survival was not reached.

Table 4 Dose reductions of anlotinib due to adverse events in patients with advanced non-small cell lung cancer

Adverse events	No. patients (%)	Dose modification
Hand-foot syndrome	7 (2.3)	12 mg → 10 mg
Hypertension	3 (1.0)	12 mg → 10 mg
Hypertriglyceridemia	2 (<1)	12 mg → 10 mg
Diarrhea	1 (<1)	12 mg → 10 mg
	1 (<1)	12 mg → 10 mg → 8 mg
Liver dysfunction	1 (<1)	12 mg → 10 mg
	1 (<1)	12 mg → 10 mg → 8 mg
Anorexia	2 (<1)	12 mg → 10 mg
Oral mucositis	2 (<1)	12 mg → 10 mg
Arrhythmia	2 (<1)	12 mg → 10 mg
Fatigue	1 (<1)	12 mg → 10 mg
Dyspnea	1 (<1)	12 mg → 10 mg

Discussion

In the present phase I clinical trial, the most common grade 3 AEs during anlotinib treatment were hypertension (10%), triglyceride elevation (10%), hand-foot skin reaction (5%), and lipase elevation (5%).[2] In the phase II clinical trial, the most common treatment-related grade ≥3 AEs in the anlotinib group were hypertension (10.00%), elevated triglyceride (5%), and HFS (3.33%).[3] The safety profiles of anlotinib in these clinical trials were consistent.

Sorafenib is a MKI that targets VEGFR, PDGFR, c-KIT, and Raf. It is approved for unresectable or metastatic hepatocellular carcinoma. The most common grade 3–4 adverse events included HFS (10.7%), diarrhea (6.0%), fatigue (3.4%), and hypertension (2.0%).[9] Sunitinib is a selective inhibitor of VEGFR, PDGFR, and stem-cell factor receptor (Kit). It is approved for metastatic renal cell carcinoma and gastrointestinal stromal tumors. The most common grade 3–4 non-hematological AEs in Asian patients are HFS (13%), fatigue (8%), diarrhea (7%), and asthenia (6%). The most common grade 3–4 hematological AEs in Asian patients are thrombocytopenia (26%), neutropenia (17%), anemia (14%), and leukopenia (3%).[10] It seemed that grade 3–4 HFS, diarrhea, and hematological AEs occurred at lower incidences, but grade 3–4 hypertension occurred at a higher incidence in patients receiving anlotinib than those receiving sunitinib.

Management of AEs during treatment with anlotinib will allow patients to benefit maximally from anlotinib.

Hypertension is a common adverse effect in patients treated with VEGF-targeted agents, such as anlotinib, sunitinib, sorafenib, and bevacizumab.[11] The exact mechanism of anlotinib-associated hypertension is unknown. General hypertension management according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 is recommended. Patients with grade 2 hypertension should begin monotherapy drug treatment. Patients with grade 3 hypertension should be treated with more than one drug or more intensive therapy than previously used, and withhold anlotinib until recovery to grade ≤2, then resume at a reduced dose. Patients with malignant

Table 5 Anlotinib discontinuations due to adverse events among patients with advanced non-small cell lung cancer

Adverse events	No. patients (%)	Adverse events	No. patients (%)
Hemoptysis	7 (2.3)	Gastrointestinal hemorrhage	1 (<1)
Pneumonia	3 (1.0)	Hypophosphatemia	1 (<1)
Venous thromboembolism	3 (1.0)	Oral mucositis	1 (<1)
Interstitial lung disease	2 (<1)	Fatigue	1 (<1)
Pneumothorax	2 (<1)	Hand foot syndrome	1 (<1)
Proteinuria	2 (<1)	Sepsis	1 (<1)
Respiratory failure	2 (<1)	Disturbance of consciousness	1 (<1)
Hypertension	1 (<1)	Appendicitis	1 (<1)
Abdominal pain	1 (<1)		

Number of patients who discontinued anlotinib due to adverse events.

hypertension, transient or permanent neurologic deficit, or hypertensive crisis require urgent intervention and should permanently discontinue anlotinib. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are most commonly used. If hypertension persists, other antihypertensive agents, such as calcium-channel blockers, diuretics, beta-blockers, alpha-blockers, and nitrates, can be added. Anlotinib is metabolized by CYP3A4. The use of verapamil and diltiazem, which are both CYP3A4 inhibitors, should be avoided. Blood pressure may normalize during off-treatment periods, and antihypertensive medication may need to be withheld.

Fatigue frequently occurs in patients with advanced NSCLC, so it was not clear whether the fatigue is drug-related or due to other factors. Patients should be evaluated for other contributing factors, such as emotional distress, pain, anemia, nutritional problems (weight or food intake changes, imbalances in fluids/electrolytes), sleep disturbances, and endocrine disorders (hypothyroidism). Medication is usually not required for patients with fatigue.

A number of proposed molecular mechanisms have been suggested for tyrosine kinase inhibitor-induced hypothyroidism, these included VEGF inhibition, inhibition of radioiodine thyroid uptake, and autoimmune mechanism.[12] Patients with symptoms of hypothyroidism or TSH >10 mU/L are recommended to start levothyroxine at 25 to 50 mcg daily with dose adjustments every six weeks. Hypothyroidism generally does not require dose reduction and discontinuation.

HFS, also known as palmar-plantar erythrodysesthesia, is a painful erythematous condition occurring most commonly on the pressure and flexure points of the hands and feet. The mechanism of MKI-induced hand-foot syndrome is unknown. Inhibition of VEGFR and PDGFR could potentially prevent the vascular repair mechanism in high-pressure areas, which may be repeatedly exposed to subclinical trauma.[13] Before anlotinib treatment, frequent emollients should be used on hands and feet to maintain skin hydration, manicure or pedicure to control calluses, protect pressure points and tender areas of feet with insole cushions, shock-absorbing soles, and comfortable shoes. Throughout anlotinib treatment, patients should avoid hot water, and wear thick cotton gloves and socks. If required, wear cotton gloves or socks should be worn at night after applying emollients. For patients with grade 1 and 2 HFS, topical therapies, such as emollient cream, antibiotics, cortisone cream, and topical analgesic, were enough. For grade 3 HFS, consider withholding anlotinib until recovery to grade ≤1, then resume at a reduced dose; for persistence or recurrence, permanently discontinue anlotinib.

Diarrhea is a frequent side-effect of MKIs. The underlying mechanism has not been elucidated. VEGF inhibitors may cause changes in the bowel mucosa, leading to diarrhea.[14] Patients are advised to avoid caffeine and lactose-containing products during anlotinib treatment.

The mechanism of VEGF inhibitors-induced proteinuria may include inhibition of VEGF on podocytes, glomerular endothelial cell detachment and hypertrophy, and glomerular thrombotic microangiopathy.[14] Patients with proteinuria ≥2.0 g/L should withhold anlotinib until proteinuria <1.0 g/L, then resume at a reduced dose.

In the elderly patients (≥70 years) subgroup of the ALTER0303 trial, hypertension (81.25%), hand-foot syndrome (75%), and TSH elevation (68.75%) were the most common AEs, which were tolerable.[15]

The efficacy in the subgroup that experienced dose modification was not inferior to the efficacy in the whole group, but the sample size was small. As hypertension and HFS were associated with the efficacy of anlotinib treatment,[16] patients who experienced dose modification due to hypertension and HFS might have longer progression-free survival.

Anlotinb-related AEs could be controlled by patient education, prophylactic measures, early and active intervention, and dose modification.

Acknowledgments

We thank all patients and their families in this study. This work was supported by the Chia-tai Tianqing Pharmaceutical Group Co. Ltd.

Disclosure

No authors report any conflict of interest.

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