The Oncologist®

Clinical Trial Results

A Phase I Study of the Safety and Pharmacokinetics of Higher-Dose Icotinib in Patients With Advanced Non-Small Cell Lung Cancer

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Trial Information

- **ClinicalTrials.gov Identifier:** ChiCTR-TNRC-08000194 (Chinese Clinical Trial Registry)
- **Sponsor:** Betta Pharmaceuticals Co., Ltd.
- **Principal Investigator:** Jianzhong Shentu
- **IRB Approved:** Yes

Lessons Learned

- This phase I study evaluated the maximum tolerated dose, dose-limiting toxicities, safety, pharmacokinetics, and efficacy of icotinib with a starting dose of 250 mg in pretreated, advanced non-small cell lung cancer patients. We observed a maximum tolerated dose of 500 mg with a favorable pharmacokinetics profile and antitumor activity.
- These findings provide clinicians with evidence for application of higher-dose icotinib.

Abstract

Background. Icotinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has shown favorable tolerability and antitumor activity at 100–200 mg in previous studies without reaching the maximum tolerated dose (MTD). In July 2011, icotinib was approved by the China Food and Drug Administration at a dose of 125 mg three times daily for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one platinum-based chemotherapy regimen. This study investigated the MTD, tolerability, and pharmacokinetics of higher-dose icotinib in patients with advanced NSCLC.

Methods. Twenty-six patients with advanced NSCLC were treated at doses of 250–625 mg three times daily The *EGFR* mutation test was not mandatory in this study.

Results. Twenty-four (92.3%) of 26 patients experienced at least one adverse event (AE); rash (61.5%), diarrhea (23.1%), and oral ulceration (11.5%) were most frequent AEs. Dose-limiting toxicities were seen in 2 of 6 patients in the 625-mg group, and the MTD was established at 500 mg. Icotinib was rapidly absorbed and eliminated. The amount of time that the drug was present at the maximum concentration in serum (T_{max}) ranged from 1 to 3 hours (1.5–4 hours) after multiple doses. The $t_{1/2}$ was similar after single- and multiple-dose administration (7.11 and 6.39 hours, respectively). A nonlinear relationship was observed between dose and drug exposure. Responses were seen in 6 (23.1%) patients, and 8 (30.8%) patients had stable disease.

Conclusion. This study demonstrated that higher-dose icotinib was well-tolerated, with a MTD of 500 mg. Favorable antitumor activity and pharmacokinetic profile were observed in patients with heavily pretreated, advanced NSCLC. ***The Oncologist*** 2016;21:1294–1295d

Discussion

Icotinib is a selective, oral tyrosine kinase inhibitor (TKI) targeting EGFR [1]. Its clinical investigation began in 2007, which included dose escalation and assessment of different dosing schedules [2–4]. MTD was not reached in these studies, and the recommended dose was established at 125 mg [2–6]. Oral icotinib was rapidly absorbed and eliminated in NSCLC patients, with a T_{max} of 3 hours and a $t_{1/2}$ of 6 hours [4, 7]. Increased drug absorption and exposure were observed when icotinib was administered with high-fat and high-calorie food [4]. Additionally, Ni et al. reported a significant relationship between drug exposure and clinical benefits [7], whereas Zhao et al. found no dose, exposure, safety/efficacy association in another study [3].

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Table 1. Dose escalation and dose-limiting toxicities

Dose level	Dose of drug (mg)	Patients enrolled (*n*)	Patients evaluable for toxicity (*n*)	Patients with a dose-limiting toxicity (*n*)	Dose-limiting toxicity information
1	250	5	5	0	
2	300	3	3	0	
3	350	3	3	0	
4	400	3	3	0	
5	500	6	6	1	Grade 3 rash
6	625	6	6	2	Grade 3 rash/grade 3 hand and foot syndrome

The present study documented a relatively higher incidence of AEs in patients receiving higher-dose (250–625 mg) icotinib, with an MTD of 500 mg three times per day The dose-limiting toxicities (DLTs) included grade 3 rash and grade 3 hand and foot syndrome (Table 1). Three patients had serious AEs (SAEs; 1 in the 500-mg group and 2 in the 625-mg group); all SAEs were ameliorated by discontinuation or dose reduction. Oral icotinib is rapidly absorbed and eliminated, which was consistent with the results obtained from previous studies assessing low-dose icotinib [2, 4, 7]. Dose-dependent increases in icotinib C_{max} and area under the curve (AUC) were observed over the dose ranges of 250–350 mg and 400–625 mg, which may be due to its solubility in water (Fig. 1). This trend was also seen in a population pharmacokinetic study, in which icotinib displayed a saturated absorption rate of 204 (oral icotinib, 350 mg) and 245 (oral icotinib, 600 mg) μg per hour in healthy persons [9]. No dose, exposure, safety/efficacy relationship was found in our study.

Antitumor activity was observed over the entire dose range (250–625 mg). The overall response rate (ORR) and disease control rate (DCR) were 23.1% and 53.9%, respectively. In another phase I study evaluating icotinib, tumor response was shown from 100 to 150 mg with an ORR of 21.9% and DCR of 43.8% [2]. These results suggested that the safe and effective range for icotinib is 100–500 mg.

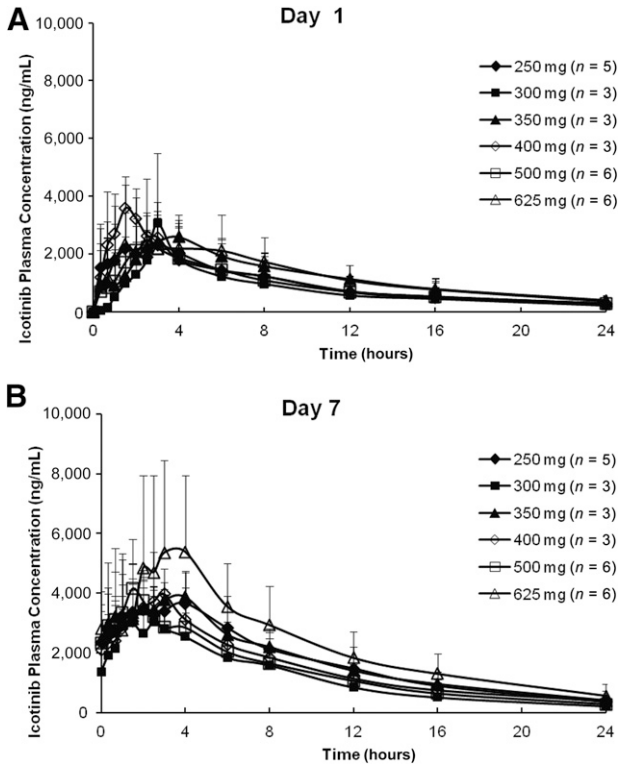

Figure 1. Mean plasma concentration-time profiles of icotinib. **(A)**: On day 1 after single oral doses of 250, 300, 350, 400, 500, and 625 mg. The error bars represent SDs. **(B)**: On day 7 after multiple oral doses of 250, 300, 350, 400, 500, and 625 mg. The error bars represent SDs.

In summary, good tolerability, feasibility of prolonged treatment, antitumor activity, and pharmacological profile of higher-dose icotinib were shown in the present study, which support the application and further investigation of higher-dose icotinib.

Trial Information	
Disease	Lung Cancer: NSCLC
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	1 prior regimen
Type of study - 1	Phase I
Type of study - 2	3+3 design
Primary Endpoint	Toxicity
Primary Endpoint	Tolerability
Secondary Endpoint	Maximum Tolerated Dose
Secondary Endpoint	Pharmacokinetics
Secondary Endpoint	Efficacy
Additional Details of Endpoints or Study Design	This study was conducted between October 9, 2009, and June 15, 2011. Patients were assigned sequentially to escalating dose levels of icotinib following a 3+3 design with a starting dose of 250 mg three times per day. Within a 28-day cycle, a single dose of icotinib was administered orally on day 1 and day 7, followed by 24-hour blood sampling for pharmacokinetics (PK) assessments. For the remaining days, icotinib was administered three

	times daily. After the first cycle, all patients received continuous icotinib until disease progression or unacceptable toxicities. The doses to be investigated were 300 mg, 350 mg, 400 mg, 500 mg and 625 mg; at least 3 patients were treated in each cohort. DLTs were defined as any grade 3 or higher toxicity per Common Terminology Criteria for Adverse Events, version 3.0. The MTD was the lower dose after the one at which 1 of 3 or 2 of 6 patients developed a DLT. The decisions for dose escalation were based on the observed toxicities during the first treatment cycle (28 days). Dose escalation was designed to be stopped when MTD or 625 mg was achieved. In case of DLT, icotinib could be discontinued for no more than 14 days. If DLT was not relieved after discontinuation, icotinib could be reduced no more than twice by one dose level in the same patient. *EGFR* mutation status was not a requirement in this study.
Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working name	Icotinib
Trade name	Conmana
Company name	Betta Pharmaceuticals Co., Ltd.
Drug type	Small molecule
Drug class	EGFR
Dose	mg per flat dose
Route	p.o.
Schedule of Administration	Orally administered three times daily

Patient Characteristics

Number of patients, male	14
Number of patients, female	12
Stage	TNM Staging IIIB: 5 IV: 21
Age	Median (range): 57 (34, 70)
Number of prior systemic therapies	Median (range): 2 (1, 11)
Performance Status: ECOG	0 — 7 1 — 19 2 — 3 — Unknown —
Other	Prior treatment Chemotherapy: 26 No. of previous chemotherapy 1: 22 ≥2: 4 Radiotherapy: 5 Surgery: 5
Cancer types or histologic subtypes	Adenocarcinoma, 22 Squamous cell carcinoma, 1 Not clear, 3

Primary Assessment Method

Control Arm: Total Patient Population	
Number of patients enrolled	26
Number of patients evaluable for toxicity	26
Number of patients evaluated for efficacy	26
Response assessment CR	$n = 0$ (0)
Response assessment PR	$n = 6$ (23.1)

Response assessment SD	$n = 8$ (30.8)
Response assessment PD	$n = 12$ (46.1)
(Median) duration assessments PFS	59 days, confidence interval (CI): 33–227
(Median) duration assessments OS	308 days, CI: 262–516
(Median) duration assessments response duration	227 days

Adverse Events

All Dose Levels, All Cycles

Name	*NC/NA	1	2	3	4	5	All Grades
Rash: acne/acneiform	−1%	59%	24%	18%	0%	0%	101%
Diarrhea	0%	83%	17%	0%	0%	0%	100%
Ulceration	0%	67%	33%	0%	0%	0%	100%
Dry skin	0%	100%	0%	0%	0%	0%	100%
Rash/desquamation	0%	100%	0%	0%	0%	0%	100%

Adverse Events Legend
All patients were evaluable for toxicity. Treatment-related AEs with incidence >5% were listed.
*No Change From Baseline/No Adverse Event

Serious Adverse Events

Name	Grade	Attribution
Rash	3	Probable
Rash	3	Probable
Hand and foot syndrome	3	Probable

Serious Adverse Events Legend
Three patients experienced treatment interruption and dose reduction due to SAEs: One in the 500-mg group for grade 3 rash recovered after a 5-day discontinuation of icotinib and dose reduction to 250 mg; one in the 625-mg group for grade 3 rash relieved after dose reduction to 250 mg; one in the 625-mg group for grade 3 hand and foot syndrome relieved after dose reduction to 250 mg.

Dose level	Dose of drug: icotinib	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
1	250 mg	5	5	0	
2	300 mg	3	3	0	
3	350 mg	3	3	0	
4	400 mg	3	3	0	
5	500 mg	6	6	1	Grade 3 rash
6	625 mg	6	6	2	Grade 3 rash/grade 3 hand and foot syndrome

Pharmacokinetics/Pharmacodynamics

Dose level	Dose of drug: icotinib	Number enrolled	Cmax (μg/L) mean ± SD	T_{max} (h) (min– max)	AUC_{0-12} (h*12 μg/L) mean ± SD	$t_{1/2}$ (h) mean ± SD
1	250 mg	5	3036.5	1.53	23020.61	6.67
2	300 mg	3	3124.15	3.17	18345.84	5.31
3	350 mg	3	3139.78	2.83	28786.93	7.48
4	400 mg	3	4040.79	1.22	24977.51	8.69
5	500 mg	6	2774.39	1.97	21458.89	7.86
6	625 mg	6	3362.82	3.75	29620.49	6.7

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

This phase I study demonstrated that oral icotinib was well tolerated at the dose range of 250–500 mg in pretreated, advanced NSCLC patients. The MTD was established at 500 mg. Incidence of AEs was higher than seen in prior studies evaluating normal dose (125 mg three times daily) without a new safety signal [1, 2]. In addition, favorable antitumor activities and PK profile was also documented.

Phase I studies of icotinib began in 2007 and consisted of dose-escalation and assessment of different dosing schedules in both healthy persons and patients with solid tumors [3–5]. Icotinib was well tolerated in healthy persons with a single dose ranging from 75 to 1,025 mg, even at the highest dose [5]. In NSCLC patients, mild and manageable AEs were seen when icotinib was orally administered at a dose of 75–150 mg three times daily [3]. The most frequently occurring AEs were rash (16 of 36 [44.4%]) and diarrhea (8 of 36 [22.2%]); the only 2 grade 3 AEs (grade 3 hepatic aminotransferase elevation and grade 3 mouth ulceration) were recorded in the 500- and 625-mg group, with no other grade 3 or higher AEs. MTD was not reached, and the recommended dose was established at 125 mg [3]. Another phase I study assessed the safety and activity of icotinib in 40 NSCLC patients with different dosing schedules (150 and 200 mg twice daily and 125 mg three times daily) [4]. The safety profile was similar to that in other studies, with an overall incidence of 65%. However, an interstitial lung disease (ILD) was recorded in the 200-mg twice-daily group [4].

Oral icotinib was rapidly absorbed and eliminated in healthy persons with a T_{max} of 2 hours and a $t_{1/2}$ of 6 hours [5]. Increased drug absorption and exposure of icotinib were observed when the drug was administered with high-fat and high-calorie food [5]. Similar PK patterns of icotinib were documented in cancer patients. A 3-hour T_{max} and a 6-hour $t_{1/2}$ were seen after oral icotinib at 75–150 mg three times daily [3]. Steady state was reached within 15 days. Similar values for T_{max} and $t_{1/2}$ were demonstrated in a study performed in NSCLC patients with icotinib at 150 and 200 mg twice daily [6]. Both studies revealed increased drug exposure with rising dose. Additionally, Ni et al. reported a significant relationship between drug exposure and clinical benefits [7], whereas Zhao et al. found no dose, exposure, safety/efficacy association in another study [3].

The present study documented a relatively higher incidence of AEs in patients receiving higher-dose (250–625 mg) icotinib, with an MTD of 500 mg three times per day. Most toxicities were mild to moderate, and only 2 grade 3 rash and 1 grade 3 hand and foot syndrome were recorded (Table 1). The most frequent AEs were grade 1 and 2 rashes (14 of 26 [53.8%]), diarrhea (6 of 26 [23.1%]), and mouth ulceration (3 of 26 [11.5%]). Three patients had SAEs (1 in the 500-mg group and 2 in the 625-mg group), and all SAEs were relieved after discontinuation or dose reduction. No changes in icotinib safety profile were observed during prolonged administration. PK analysis indicated that single-dose oral icotinib is rapidly absorbed and eliminated, which was consistent with the results obtained from previous studies assessing low-dose icotinib [3, 5, 6]. Dose-dependent increases in icotinib C_{max} and AUC were observed over the dose ranges of 250–350 mg and 400–625 mg, which may be due to the drug's solubility in water (Fig. 1). This trend was also seen in a population PK study, in which icotinib displayed a saturated absorption rate of 204 (icotinib 350 mg), and 245 (icotinib 600 mg) μg per hour in healthy persons [8]. In addition, no dose, exposure, safety/efficacy relationship was found in our study.

ILD is a major safety concern for EGFR TKIs, with an morbidity and mortality of 1.6% and 13.0%, respectively [9]. For icotinib, 1 and 4 drug-induced ILDs were reported in a phase I study ($n = 40$) and a postmarketing phase IV study that included 6,087 patients, respectively [2, 4]; no ILDs were observed in the current study.

Clinical activities of icotinib were revealed in patients with heavily pretreated NSCLC, and evidence of antitumor activity was observed over the entire dose range (250–625 mg). The ORR and DCR were 23.1% and 53.9%, respectively. In another phase I study evaluating icotinib from 75 to 150 mg, tumor responses were observed from 100 to 150 mg with an ORR of 21.9% and DCR of 43.8% [3]. These results suggested that the safe and effective dose range for icotinib is 100–500 mg. Icotinib also provided clinical benefit in terms of progression-free survival (PFS; 59 days) and overall survival (308 days), and PFS for patients with disease control was 227 days.

Information available on the efficacy and safety of higher-dose icotinib has increased with time. Liu et al. reported that patients who progressed with 125-mg icotinib continued to benefit from higher-dose icotinib (250 or 375 mg), with tolerable toxicities [10]. Higher-dose icotinib also had potential activity in treating brain metastasis (BM). A phase I dose-escalation study evaluated the safety of the combination of icotinib and whole-brain radiotherapy from BM in patients with NSCLC bearing *EGFR* mutations [11]. The MTD of icotinib was 500 mg, and icotinib penetration into brain achieved the peak at a dose of 375 mg by cerebrospinal fluid analysis. Tumor response was seen in 12 of 15 patients; the remaining 3 patients achieved stable disease as best response [11]. Higher-dose icotinib was also explored in other solid tumors; Huang et al. found icotinib was effective and well-tolerated in esophageal cancer with an ORR of 16.7%, and a DCR of 48.9% [12]. Currently, icotinib has been approved by the China Food and Drug Administration for the treatment of pretreated, unselected NSCLC (July 2011) and NSCLC positive for *EGFR* mutation (November 2014).

Our study has limitations, especially the lack of biomarker analysis. In addition, *EGFR* mutation testing was not widely recognized for previously treated patients in China during the study design. Furthermore, these results should be considered in the context that this study was a single-arm trial with limited sample size.

In summary, good tolerability, feasibility of prolonged treatment, antitumor activity, and an acceptable pharmacological profile of higher-dose icotinib were shown in the present study. The MTD was established at 500 mg three times daily, and the safe and effective dose ranged from 250 to 500 mg, which supports the application and further investigation of higher-dose icotinib.

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Disclosures

Fenlai Tan: Betta Pharmaceuticals Co., Ltd. (E); **Lieming Ding:** Betta Pharmaceuticals Co., Ltd. (E); **Yinxiang Wang:** Betta Pharmaceuticals Co., Ltd. (E). The other authors indicate no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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