Leukemia Research 61 (2017) 89–95

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

A phase 1 study of the Janus kinase 2 (*JAK2*)^{V617F} inhibitor, gandotinib (LY2784544), in patients with primary myelofibrosis, polycythemia vera, and essential thrombocythemia

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ARTICLE INFO

Keywords:
Myeloproliferative
Neoplasm
JAK-2
Gandotinib
Dosage

ABSTRACT

Mutations in Janus kinase 2 (*JAK2*) are implicated in the pathogenesis of Philadelphia-chromosome negative myeloproliferative neoplasms, including primary myelofibrosis, polycythemia vera, and essential thrombocythemia. Gandotinib (LY2784544), a potent inhibitor of *JAK2* activity, shows increased potency for the *JAK2*^{V617F} mutation. The study had a standard 3 + 3 dose-escalation design to define the maximum-tolerated dose. Primary objectives were to determine safety, tolerability, and recommended oral daily dose of gandotinib for patients with *JAK2*^{V617F}-positive myelofibrosis, essential thrombocythemia, or polycythemia vera. Secondary objectives included estimating pharmacokinetic parameters and documenting evidence of efficacy by measuring clinical improvement. Thirty-eight patients were enrolled and treated (31 myelofibrosis, 6 polycythemia vera, 1 essential thrombocythemia). The maximum-tolerated dose of gandotinib was 120 mg daily, based on dose-limiting toxicities of blood creatinine increase or hyperuricemia at higher doses. Maximum plasma concentration was reached 4 h after single and multiple doses, and mean half-life on day 1 was approximately 6 h. Most common treatment-emergent adverse events were diarrhea (55.3%) and nausea (42.1%), a majority of which were of grade 1 severity. Best response of clinical improvement was achieved by 29% of myelofibrosis patients. A ≥50% palpable spleen length reduction was observed at any time during therapy in 20/32 evaluable patients. Additionally, ≥50% reduction in the Total Symptom Myeloproliferative Neoplasm Symptom Assessment Form Score was seen in 11/21 (52%) and 6/14 patients (43%) receiving ≥120 mg at 12 and 24 weeks respectively. Gandotinib demonstrated an acceptable safety and tolerability profile, and findings at the maximum-tolerated dose of 120 mg supported further clinical testing. Clinicaltrials.gov identifier: NCT01134120.

1. Introduction

The classic chronic myeloproliferative neoplasms (MPNs) are a group of hematologic malignancies characterized by the clonal proliferation of one or more myeloid lineages and include myelofibrosis occurring either *de novo* as primary myelofibrosis (PMF), or as a transformation from other classic MPNs, polycythemia vera (PV) or essential thrombocythemia (ET) [1]. Signs and symptoms of myelofibrosis include anemia, splenomegaly, bone marrow fibrosis, fatigue, weakness, night sweats, and weight loss [2–4], among others.

The mutation in the pseudokinase domain of Janus kinase 2 (*JAK2*); i.e., *JAK2*^{V617F} is present in many patients with PMF, ET, and PV [5–7]

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http://dx.doi.org/10.1016/j.leukres.2017.08.010
Received 26 April 2017; Received in revised form 17 August 2017; Accepted 21 August 2017
Available online 31 August 2017

and results in constitutive activation of *JAK2*. It is found in most patients with PV (> 95%) and in approximately two thirds of patients with ET and PMF [8–11]. Since wild-type *JAK2* plays a central role in multiple stages of hematopoiesis, it would be desirable to treat $JAK2^{V617F}$-positive cases by preferentially inhibiting $JAK2^{V617F}$ while minimizing inhibition of wild-type *JAK2*. Janus kinase *(JAK)* inhibitors can modulate *JAK* signal transducer and activator of transcription (STAT) signaling in MPNs [12,13], and they offer clinical benefits to patients with MPNs [14–18]. In addition to *JAK2* mutations, in view of growing evidence of interaction of inflammatory and coagulation pathways and the purported reduction of inflammatory response by JAK2 inhibitors, we selected, among other markers, the changes of plasma levels of C4B binding protein (C4BP) after gandotinib therapy. C4b protein has a known role in complement activation and also binds protein C [19]. Protein C is the principal negative regulator of coagulation factors Va and VIIIa. C4BP is an important binding partner to vitamin K-dependent protein S in circulation. The high-affinity binding of protein S to C4BP serves the purpose of localizing complement regulatory activity close to the phospholipid membranes [20,21], affecting the regulation of blood coagulation [22]. Therefore, we assessed if C4BP levels correlate with the occurrence of thrombotic events during the study, and performed *ad hoc* analysis to compare C4BP levels with different parameters of clinical response.

Gandotinib (LY2784544) is a potent inhibitor of $JAK2^{V617F}$ [23]. Inhibition of the constitutive activity of the mutant *JAK2* could have a significant impact on the course of disease, disease complication rates, survival, and quality of life for patients with BCR-ABL1-negative classic MPN.

This phase 1 study evaluated the safety, tolerability, and pharmacokinetic parameters of gandotinib, and explored the potential efficacy of this study drug in patients with non-chronic myelogenous leukemia MPN harboring the $JAK2^{V617F}$ mutation.

2. Materials and methods

2.1. Study population

Patients had a diagnosis of PV, ET, or myelofibrosis, as defined by the World Health Organization diagnostic criteria for MPNs [24]; detailed inclusion/exclusion criteria are described in the supplement.

2.2. Study design

This study was performed in accordance with the principles of good clinical practice to ensure compliance with appropriate ethical and quality standards. This was a multicenter, nonrandomized, open-label, phase 1 study of gandotinib that included a dose-escalation part followed by a maximum tolerated dose (MTD) dose-confirmation part (Fig. 1).

A 3 + 3 dose-escalation paradigm was used (further details of the study design are provided in the supplement). To evaluate the safety of a dose level, all subjects in a cohort must have received 1 cycle (28 days) of therapy. Part A1 was used to define the MTD of gandotinib at a fixed daily dose. As the predicted efficacious human exposure target was not reached at 120 mg (Supplementary Table S1 and Supplementary Fig. S1A), the study was amended after identification of dose-limiting toxicity (DLT) chemistry changes suggesting potential tumor lysis and renal function impairment at doses > 120 mg. The amendment used a lead-in period where patients received 120 mg daily for 14–28 days prior to increasing to higher doses in an attempt to avoid the previously observed chemistry changes. In part A1, cycles 1 and beyond consisted of 28 days. In part A2, which tested the lead-in strategy, cycle 1 could be 42–56 days, depending on the length of the lead-in period (i.e., a 14 or 28 day lead in plus 28 day DLT period for the higher dose). Dose escalation was based primarily on safety with attention to signs of toxicity including tumor lysis syndrome [25,26]. If evidence of tumor lysis syndrome was observed, the patient was to be managed and re-evaluated appropriately. To prevent and manage potential tumor lysis syndrome, allopurinol could be administered based on MPN subtype and investigator discretion.

Patient-reported quality-of-life measures were assessed by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) [27] and the European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) [28]. Patient-reported outcomes (PRO) data were collected at baseline, approximately every other cycle for the first year of therapy, quarterly after year 1, and at the post-therapy follow-up visit.

To explore safety and tolerability, the putative recommended phase 2 daily dose was explored during the dose-confirmation portion of the study (part B). Patients in part B were treated at doses no greater than the defined MTD from part A2. Part B was intended to target an enrollment of 10 patients.

2.3. Statistical methods

The analysis for this study was primarily descriptive and details are provided in the supplement. Data analysis was provided by received dose groups and for all study patients combined wherever appropriate. For continuous variables, summary statistics included number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints were summarized using frequency and percentages. Missing data were not imputed.

3. Results

3.1. Patient disposition

Of the 47 patients that entered the study, 38 were enrolled and received at least 1 dose of the study treatment. Of the 38 treated patients, 36 had discontinued treatment and 2 patients remained on treatment at the time of the database lock for this report (Supplementary Fig. S2). Across all cohorts, the most common reasons for discontinuation from study treatment were physician decision (n = 17), adverse events (n = 11), patient decision (n = 4), and progressive disease (n = 3). The most frequent adverse event that resulted in treatment discontinuation was renal failure (n = 4).

3.2. Patient demographics and baseline characteristics

The majority of patients were Caucasian (97.4%) and non-Hispanic (89.5%). Of 38 patients, 21 (55.3%) were male. The median body mass index (BMI) was 26 kg/m^2 (range: 18–41), and the mean and standard deviation of the baseline characteristic was 26.6 ± 5.24 kg/m^2 which makes the overall population BMI relatively consistent. The majority of patients had myelofibrosis followed by PV and ET (Table 1). The clinicpathologic diagnosis in all patients was confirmed according to 2008 World Health Organization criteria [24]. Thirty-three patients (86.8%) reported receiving prior systemic therapies before enrollment into the study. The most commonly received prior therapy was hydroxyurea. On study, the most frequently used concomitant drugs were allopurinol (27 patients [71.1%]) and aspirin (18 patients [47.4%]). Median time from diagnosis to study therapy was 438.5 days (range: 21–5498); the median regimen number of prior systematic treatments was 2 (range: 1–8).

3.3. Dose-limiting toxicity and maximum tolerated dose

This study sequentially tested daily oral administration of gandotinib at 30, 60, 120, 240, and then an intermediate dose of 200 mg. Table 2 summarizes the observed DLTs by received dose during cycle 1. No DLTs were seen at the first 3 tested doses. At 240 mg, one DLT was observed, and subsequently at 200 mg, 3 DLTs were observed. The