Phase I Study of a Novel Oral Janus Kinase 2 Inhibitor, SB1518, in Patients With Relapsed Lymphoma: Evidence of Clinical and Biologic Activity in Multiple Lymphoma Subtypes

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ABSTRACT

Purpose

The Janus kinase 2/signal transducers and activators of transcription (JAK2/STAT) pathway plays an important role in the pathogenesis of hematologic malignancies. We conducted a phase I dose-finding and pharmacokinetic/pharmacodynamic study of SB1518, a potent JAK2 inhibitor, in patients with relapsed lymphoma.

Patients and Methods

Patients with relapsed or refractory Hodgkin or non-Hodgkin lymphoma of any type except Burkitt's or CNS lymphoma were enrolled. Patient cohorts received escalating doses of SB1518 orally once daily for 28-day cycles. Response was evaluated after 8 weeks.

Results

Thirty-four patients received doses of 100 to 600 mg/d. The maximum tolerated dose was not reached. Treatment was well tolerated, with mostly grade 1 and 2 toxicities. Gastrointestinal toxicities were the most common treatment-related events. Cytopenias were infrequent and modest. Pharmacologically active concentrations were achieved at all doses. Dose-related linear increases in area under the concentration-time curve were seen on day 1, with no significant accumulation on day 15. Mean terminal half-life was 1 to 4 days, and mean time to peak concentration ranged from 5 to 9 hours. SB1518 inhibited JAK2 signaling at 4 hours postdose at all levels. Increases in fms-like tyrosine kinase-3 (FLT-3) ligand, reflecting FLT-3 inhibition, were seen in most patients. There were three partial responses (≥ 300 mg/d) and 15 patients with stable disease (SD), with most responses lasting longer than 2 months. Seven of 13 SDs had tumor reductions of 4% to 46%.

Conclusion

SB1518 has encouraging activity in relapsed lymphoma, providing the first proof-of-principle of the potential therapeutic value of targeting the JAK/STAT pathway in lymphoma in the clinical setting.

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INTRODUCTION

The Janus kinases (JAKs) are a family of four intracellular nonreceptor tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that primarily transduce signals from cell-surface receptors activated by cytokines and growth factors.¹ In humans, JAK3 expression is restricted to hematopoietic cells, whereas the remaining three JAK family members are ubiquitously expressed. After a cytokine is engaged with its receptor, members of the JAK family are phosphorylated, leading to the recruitment and phosphorylation of signal transducers and activators of transcription (STAT) proteins on tyrosine residues. Phosphory-

lated STAT proteins then dimerize, translocate to the nucleus, and trigger the transcription of target genes involved in cell proliferation, survival, angiogenesis, and immunity.² In humans, the STAT family of transcription factors consists of seven members; STAT2, STAT4, and STAT6 are activated specifically by a small subset of cytokines (interferon α , interleukin [IL] -6, IL-12, and IL-13, respectively).³ In contrast, STAT1, STAT3, STAT5a, and STAT5b can be activated not only by a large array of cytokines, but also by growth factors and some G-protein coupled receptor agonists.⁴

Aberrant activation of the JAK/STAT pathway has been linked to the oncogenic process in a variety

of cancers, including Hodgkin lymphoma and non-Hodgkin lymphoma, making it an appealing target for pathway-directed therapy.⁵⁻⁸ In rare cases, aberrant activation of the JAK/STAT pathway in a variety of lymphomas has been linked to genomic gains of JAK2, inactivating mutations of suppressors of cytokine signaling (SOCS) proteins, or epigenetic silencing of SOCS1 and Src homology region 2 domain-containing phosphatase-1 proteins.⁹⁻¹⁶ However, in most cases, no genetic abnormalities can be detected, suggesting that JAK/STAT activation is driven by an aberrant deregulation of a network of cytokines and chemokines in the lymphoma microenvironment.^{17,18}

SB1518 is a pyrimidine-based macrocycle small-molecule ATP-competitive inhibitor of JAK2 kinase that potently inhibits wild-type JAK2 (inhibitory concentration₅₀ [IC₅₀] = 23 nmol/L) as well as the JAK2^{V617F} mutant (IC₅₀ = 19 nmol/L).¹⁹ In addition to its JAK2 activity, SB1518 blocks fms-like tyrosine kinase-3 (FLT-3), with an IC₅₀ of 22 nmol/L, and its FLT-3-D835Y mutant (IC₅₀ = 6 nmol/L).^{19,20} SB1518 has also been shown to inhibit the JAK/STAT signaling pathway in a broad spectrum of cancer cell lines, leading to inhibition of cell proliferation and induction of apoptosis.^{19,20} SB1518 has antiproliferative activity against Karpas 1106P, a lymphoma cell line reported to harbor a homozygous deletion in the JAK2 negative regulator, SOCS1. In addition to these features, SB1518 is orally active, efficacious, and well-tolerated in models of JAK2-driven disease. Based on these favorable pharmaceutical and pharmacologic properties, we conducted a phase I clinical trial of SB1518 in patients with relapsed lymphoma.

PATIENTS AND METHODS

Study Population

Patients with refractory or relapsed lymphoma of any histology except Burkitt's or CNS lymphoma were candidates for this study. Other eligibility criteria included age $\geq$ 18 years; ECOG performance score $\leq$ 2; adequate bone marrow, renal, and hepatic function (absolute neutrophil count $\geq$ 1,500/ μ L, platelet count $\geq$ 100,000/ μ L, hemoglobin $\geq$ 9.0 g/dL, serum creatinine $\leq$ 1.5 g/dL, or a calculated creatinine clearance $\geq$ 50, and transaminases $\leq$ 1.5 times the upper limit of normal or $\leq$ 2.5 times the upper limit of normal in cases of liver involvement); at least one bidimensionally measurable disease site (at least one target lesion measuring 2 cm in diameter); a Bazett-corrected Q-T interval $\leq$ 0.45 seconds; discontinuation of any chemotherapy or radiotherapy at least 4 weeks before study entry; and discontinuation of any radioimmunotherapy at least 12 weeks before study entry. Patients were required to have undergone at least two prior treatment regimens, one of which must have been an anthracycline-containing combination regimen. Prior stem-cell transplantation was permitted. Patients with known HIV infection were excluded. The study was approved by the MD Anderson Cancer Center institutional review board. Each participant provided informed consent before initiating study procedures.

Study Design

This trial was an open-label dose-escalation study of SB1518 as a single agent administered orally once a day. Patients were treated at escalating dose levels using a standard 3 + 3 design. One cycle was defined as 4 weeks of therapy without interruption. Patients were allowed to continue therapy until disease progression or prohibitive toxicity. The starting dose was 100 mg. Dose escalation was guided by the safety evaluation during the first cycle of treatment.

Pretreatment, Safety, and Efficacy Evaluations

Pretreatment evaluations consisted of a physical examination, an assessment of Eastern Cooperative Oncology Group (ECOG) performance status and vital signs, 12-lead ECG, CBC, and blood chemistry tests. A bone marrow

biopsy and/or aspirate and a computed tomography (CT) scan and/or positron emission tomography scan were performed to evaluate baseline disease status.

Follow-up safety evaluations were performed at the beginning of each treatment cycle, additionally as needed, and at study termination and consisted of a physical examination, an assessment of vital signs and ECOG performance status, CBC, and blood chemistry tests. Adverse events and toxicity were evaluated according to National Cancer Institute Common Criteria for Adverse Events version 3.0 and were monitored continuously. A dose-limiting toxicity was defined as any treatment-related grade 3 or 4 non-hematologic toxicity (except nausea/vomiting responsive to antiemetic therapy), grade 4 neutropenia lasting $\geq$ 7 days, grade 3 or 4 neutropenic fever with or without infection, grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding.

Tumors were assessed by CT and/or positron emission tomography scan after every two cycles. Bone marrow biopsy was required to confirm complete remissions. Treatment response was evaluated using International Working Group criteria.²¹

Pharmacokinetic Evaluation

Sample collection. Blood samples for pharmacokinetic (PK) analysis were collected in K₂EDTA tubes just before dosing and at postdose hours 0.5, 1, 2, 3, 4, 5, 6, 8, and 24 $\pm$ 2 on days 1 and 15 $\pm$ 3 of cycle 1. The samples were centrifuged at 1,000 g for 10 minutes at 4°C and the plasma was transferred to labeled cryovials and stored at -70°C until analysis.

Bioanalytical method. A validated bioanalytical method was used to measure SB1518 concentration in plasma and was performed at Quintana Analytica S.R.O. (Prague, Czech Republic). The method employed a liquid chromatography tandem mass spectrometry procedure, with EX-72, a chemical analog of SB1518, as the internal standard. The method was validated through the quantitation range of 20 to 20,000 ng of SB1518/mL of plasma. The lower limit of quantitation was 20 ng/mL.

Calculation of pharmacokinetic parameters. PK parameters were calculated by a noncompartmental method using WinNonlin (Scientific Consultant, Apex, NC) version 5.2.1 (Pharsight Corporation, Mountain View, CA). Peak plasma concentration (C_{max}) and time to peak concentration were estimated from the plasma drug concentration-time curve. The area under the concentration-time curve from 0 to 24 hours (AUC₀₋₂₄) was calculated by the linear up-log down trapezoidal method for the observed values. The terminal half-life was estimated from the linear portion of the log-linear curve of the terminal phase, using at least three time points. Dose linearity on day 1 was assessed by plotting the log AUC₀₋₂₄ versus the log dose using GraphPad Prism, version 5 (GraphPad Software, La Jolla, CA). The linearity and slope were assessed at the 95% confidence level.

Pharmacodynamic Analysis

The effect of SB1518 treatment on the JAK2/STAT signaling pathway was assessed on day 1 of cycle 1 using flow cytometry and Western blot analysis. In addition, plasma levels of the cytokine FLT-3-ligand (FLT-3L), which reflects FLT-3 inhibition, was evaluated on days 1 and 29. Detailed methods of sample collection, flow cytometry, Western blot, and cytokine analysis are provided in the Appendix (online-only).

RESULTS

Patient Disposition

Thirty-four patients received at least one dose of study drug at one of five dose levels: 100 mg/d (n = 3), 200 mg/d (n = 6), 300 mg/d (n = 6), 400 mg/d (n = 7), and 600 mg/d (n = 12). Patient characteristics are listed in Table 1. Seventeen patients were treated for more than 3 months, and six were treated for more than 6 months. Median time on study drug was 88 days (range, 1 to 574 days). Thus far, 31 patients have discontinued therapy for disease progression or lack of response (n = 21), investigator or patient preference (n = 5),

Table 1. Demographic and Baseline Characteristics (N = 34)

Characteristic	No. of Patients	%
Age, years*		
Median	49	
Range	22-80	
Sex		
Male	24	
Female	10	
Lymphoma type		
Classic Hodgkin	14	
Non-Hodgkin	20	
Follicular	10	
Mantle cell	5	
Diffuse large B cell, undetermined B cell	4	
Small lymphocytic	1	
ECOG performance status		
0	24	71
1	8	24
2	2	6
No. of prior systemic treatment regimens*		
Median	5	
Range	2-15	
Transplantation recipients		44
Autologous		41
Allogeneic		15
Prior rituximab therapy		68
Rituximab refractory		52

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
 *Includes data for an enrolled patient who withdrew from the study before receiving treatment.

treatment-related adverse events (n = 2), dosing noncompliance (n = 1), interruption of dosing during a prolonged hospitalization for treatment-unrelated adverse events (n = 1), or death (n = 1).

Safety and Tolerability

Thirty-one patients (91%) experienced at least one adverse event. The most frequent events (> 10% of patients) were GI toxicities: diarrhea (32%), nausea/vomiting (29%), constipation (26%), and decreased appetite (12%) (Table 2). GI toxicities were also the most common treatment-related events. Grade 3/4 nonhematologic toxicities were infrequent. One dose-limiting toxicity each was experienced

Table 2. Treatment-Related Adverse Events With a Total Incidence of More Than 10%

Adverse Event	Grade 1 or 2		Grade 3 or 4		All Grades	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Diarrhea	11	32	—	—	11	32
Nausea	10	29	—	—	10	29
Constipation	9	26	—	—	9	26
Fatigue	5	15	1	3	6	18
Pyrexia	6	18	—	—	6	18
Decreased appetite	4	12	—	—	4	12
Neutropenia	2	6	2	6	4	12
Anemia	3	9	1	3	4	12
Thrombocytopenia	3	9	1	3	4	12

at the 300 mg/d (grade 4 neutropenia), 400 mg/d (grade 4 thrombocytopenia), and 600 mg/d level (grade 4 sepsis). Dose escalation was stopped at the 600 mg/d level based on oral exposure levels yielding significant progressive disease activity. Dose was not further escalated to achieve the maximum tolerated dose (MTD) in the interest of patients' long-term tolerability of chronic grade 2 toxicity. Furthermore, the recommended dose level of 400 mg/d for a phase II trial is to allow combining with chemotherapy. Most of the serious adverse events were unrelated to the study drug. One patient (dose level, 200 mg/d) experienced an episode of cerebrovascular ischemia, one patient (dose level, 600 mg/d) developed a pulmonary embolism, and another patient (dose level, 600 mg/d) developed non-neutropenic sepsis. These three events were possibly treatment related.

Pharmacokinetics

Thirty-two patients were assessed for day 1 and day 15 PK: 100 mg/d, n = 3; 200 mg/d, n = 6; 300 mg/d, n = 6; 400 mg/d, n = 7; and 600 mg/d, n = 10. The PK profile of SB1518 is shown by dose level in Figure 1, and the PK parameters are summarized in Appendix Table A1. The plasma PK of SB1518 was characterized by moderately fast absorption followed by a long terminal phase (Fig 1A). Mean time to peak concentration ranged between 5 and 9 hours on day 1, and the mean terminal half-life was 1 to 4 days. The PK of SB1518 on day 1 and day 15 was similar, and there was no significant accumulation on day 15 (Appendix Table A1), with mean AUC and C_{max} on day 15 being less than twice that on day 1. At all doses studied, the peak plasma concentration of SB1518 was 5 µg/mL or above, well exceeding the IC₅₀ for JAK2/FLT-3 inhibition (11 ng/mL) and the IC₅₀ for cell proliferation activity in the Karpas1160 cell line (110 ng/mL; Fig 1A). A significant dose-related linear increase in AUC₀₋₂₄ was observed (Fig 1B).

Pharmacodynamics

Inhibition of phosphorylated STAT3 (pSTAT3) and STAT5 was observed at all dose levels with no apparent dose dependency. All 16 samples evaluated by flow cytometry showed inhibition of pSTAT3 and pSTAT5, and 28 of 29 samples evaluated by Western blot analysis showed inhibition of pSTAT5. Mean percent maximum inhibition relative to pretreatment in patients ranged from 37% to 53% with 51% at the highest dose level (600 mg/d; Table 3). The level of STAT inhibition using flow cytometry is more variable compared with the Western blot analysis, which is due to the low numbers of analyzable samples. Samples from the same patient showed similar pSTAT5 inhibition rates when analyzed by Western blot and flow cytometry. Plasma levels of FLT-3L increased dramatically in 21 of 22 patients by day 29 (Appendix Table A2). No correlation with response or time to survival was apparent. The increase in plasma FLT-3L on day 29 compared with day 1 was significant ($P < .001$; Fig 2).

Efficacy

Thirty-one patients had pre- and postbaseline CT assessments. Seventeen patients (55%) showed a reduction in target tumor measurements ranging from 4% to 70% (Fig 3). Objective responses were seen in three patients treated at the 300 mg/d, 400 mg/d, and 600 mg/d dose levels, respectively; two of these patients had mantle-cell lymphoma, and one had follicular lymphoma. The response rate among the 22 evaluable patients treated at the highest dose levels (300 to 600 mg/d) was 14%. Among the three patients who achieved a PR, time to best response ranged from 50 to 60 days, and progression-free survival

Fig 1. (A) Mean plasma concentration-time profiles of SB1518 on day 1 following single oral doses of 100, 200, 300, 400, and 600 mg. The error bars represent the SEM. The potencies of SB1518 on the target enzymes and cell line are indicated with horizontal dashed lines. (B) Relationship between log mean area under the concentration-time curve (AUC_{0-24} ; day 1) and log dose. The linearity was assessed at the 95% confidence level. The error bars represent the SEM. The estimated values of the slope and the regression coefficient are also shown in the inset along with the P values. FLT-3L, fms-like tyrosine kinase-3 ligand; JAK2, Janus kinase 2.

ranged from 120 to 249 days. Among all evaluable patients, median progression-free survival was 120 days, and the median survival was 130 days.

DISCUSSION

Although a variety of JAK2 inhibitors have entered clinical testing for myelofibrosis and autoimmune disorders,²²⁻²⁵ our study is the first

Table 3. Inhibition of pSTAT5 in PBMCs (Western Blot) and pSTAT3/5 in Whole Blood (flow cytometry) on Day 1, Cycle 1

Dose (mg/d)	Mean Percent Maximum Inhibition Relative to Pretreatment					
	pSTAT3 by Flow Cytometry		pSTAT5 by Flow Cytometry		pSTAT5 by Western Blot	
	No. of Patients	%	No.	%	No.	%
100	2	32	2	21	2	37
200	5	38	5	39	6	51
300	4	53	4	66	6	40
400	2	22	2	19	6	53
600	4	50	4	51	9	52

NOTE. Percent of inhibition of pSTAT3/5 on Day 1 after SB1518 treatment was determined on analyzable samples. Mean percent of maximum inhibition relative to pretreatment is shown per cohort.

Abbreviations: PBMC, peripheral-blood mononuclear cell; pSTAT, phosphorylation of signal transducers and activators of transcription.

clinical trial that investigated the safety and efficacy of a JAK2 inhibitor in lymphoma. In our study, we did not identify the MTD within the applied dose-escalation schedule, although we observed sporadic dose-limiting toxicities. Most of the adverse events were gastrointestinal in nature and of grade 1 or 2 severity. Importantly, hematologic toxicities were observed infrequently, suggesting that SB1518 can be combined with conventional chemotherapy agents. Though the MTD was not reached, the pharmacokinetic and pharmacodynamic data provided ample basis to recommend 400 mg/d as the dosage for phase II study. First, there were no major differences between 400 mg/d and 600 mg/d with respect to C_{max} or AUC_{0-24} . Second, STAT3 and STAT5 phosphorylation was inhibited at all dose levels, with no evidence of a dose-response effect. Third, serial cytokine measurements showed an increase in plasma FLT-3L in 21 of 22 patients who spanned the range of dose levels indicative of biologic activity. Finally, even at the lowest dose level of 100 mg/d, the achieved mean C_{max} was well above the

Fig 2. Plasma levels of fms-like tyrosine kinase-3 ligand (FLT-3L) after 29 days of SB1518 treatment were significantly higher compared with those on day 1 ($P < .001$; paired t test; $n = 22$).

Fig 3. Waterfall plot demonstrating percent change from baseline in target tumor dimensions (best response) among evaluable patients ($n = 31$). (A) Best responses by dose level. (B) Best responses by prior rituximab exposure. Labels in the x axis identify the histologic subtypes. BC, unclassified B-cell lymphoma; FL, follicular lymphoma; DLBC, diffuse large B-cell lymphoma; MCL, mantle-cell lymphoma; CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; HL, Hodgkin lymphoma.

IC_{50} concentrations that were required for inhibition of lymphoma cell lines proliferation in vitro (Fig 1).

Dysregulated pretreatment levels of cytokines and chemokines have been associated with a poor prognosis in a variety of malignancies, including lymphoma.²⁶⁻³⁰ In this phase I trial, which included patients with a variety of histologies treated at different dose levels, we observed no association between baseline cytokine/chemokine levels and response or resistance to SB1518. Similarly, there was no pattern of treatment-induced cytokine/chemokine changes that could predict treatment outcome. However, we did observe an almost uniform increase in plasma FLT-3L in 95% of the patients, regardless of treatment outcome. FLT-3L plays a role in physiologic hematopoiesis, and aberrant expression and activa-

tion of FLT-3 has been associated with a variety of leukemia.³¹ Furthermore, elevated circulating serum FLT-3L has been observed in patients receiving chemotherapy and was reported to predict chemotherapy-induced myelosuppression.³² In our study, the increase in plasma FLT-3L is likely related to a negative feedback loop as a result of FLT-3 inhibition by SB1518. The effects of SB1518 on plasma cytokine/chemokine levels should be studied in more homogeneous patient populations in phase II trials to clarify their clinical significance, especially as a predictive biomarker for tumor response and/or myelosuppression.

SB1518 shows effective inhibition of STAT signaling already at the lowest dose level without apparent dose-dependency. In contrast, preclinical experiments with similar exposure to SB1518 ($\mu\text{g/mL}$)

have shown a dose-dependent inhibition of STAT5 signaling in an acute myelocytic leukemia xenograft model.²⁰

Our study provides the first proof-of-principle of the potential therapeutic value of targeting JAK2 in patients with lymphoma. SB1518 induced partial remissions in two patients with mantle-cell lymphoma and in one patient with follicular lymphoma. These responses were achieved at doses of 300 mg/d or higher. Importantly, SB1518 also decreased tumor measurements in 17 (55%) of 31 evaluable patients; 13 of these 17 patients were treated at or above 300 mg/d. All responses were observed in patients with mantle-cell lymphoma, indolent lymphoma, or Hodgkin lymphoma. Interestingly, no responses were observed in the five patients with relapsed diffuse large B-cell lymphoma, but this finding may be related to the small sample size.

Collectively, our data demonstrate that SB1518 is well tolerated in patients with relapsed lymphoma and has promising activity. The data warrant further efficacy studies of JAK/STAT pathway inhibitors, either alone or in combination regimens. Future studies should incorporate biomarker analysis that may predict response to JAK/STAT targeted therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are

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