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Prolonged Subcutaneous Administration of 852A, a Novel Systemic Toll-like Receptor 7 Agonist, to Activate Innate Immune Responses in Patients with Advanced Hematologic Malignancies

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Abstract

The toll-like receptor (TLR) 7 agonist 852A, a small-molecule imidazoquinoline, stimulates plasmacytoid dendritic cells to produce multiple cytokines. We conducted a Phase II study of 852A in patients with recurrent hematologic malignancies. The primary objective was assessing the activity of 852A administered subcutaneously twice weekly for 12 weeks. Secondary objectives were assessing the safety of 852A and its ability to activate the immune system with prolonged dosing.

Methods—Patients with relapsed hematologic malignancies of any age with adequate organ function were eligible. Patients initiated dosing at 0.6 mg/m^2 twice weekly and escalated by 0.2 mg/m^2 after every 2 doses as tolerated to a target dose of 1.2 mg/m^2. Patients with responses or stable disease were eligible for additional cycles.

Results—Seventeen patients (15 males) entered the study: 6 with AML, 5 ALL, 4 NHL, 1 Hodgkin's lymphoma, and 1 multiple myeloma. The mean age was 41 years (12–71 years). The median number of prior chemotherapy regimens was 5 (range=1–14). Thirteen patients completed all 24 injections. Grade 3–4 toxicities included nausea, dyspnea, fever, myalgia, malaise, and cough. Responses included 1 complete response (ALL), 1 partial response (AML), 2 stable disease (AML and NHL), and 9 progressive disease.

Conclusions—This is the first in-human hematologic malignancy trial of a subcutaneously (SC) delivered TLR7 agonist using a prolonged dosing schedule. 852A was safely administered up to 1.2 mg/m^2 twice weekly with evidence of sustained tolerability and clinical activity in hematologic malignancies. Systemic TLR agonists for the treatment of hematologic malignancies warrant further study.

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Keywords

acute leukemia; immunotherapy; 852A; phase 2

Introduction

Activation of the immune system is an attractive approach to improving cancer therapy. The innate immune system recognizes tumor cells and pathogens through pathogen-associated molecular patterns (PAMPS) that activate the innate immune system through toll-like receptors (TLRs). TLRs are a group of transmembrane pattern recognition receptors that exist in homo or heterodimers and have cytoplasmic domains homologous to the interleukin-1 receptor[1]. There are 10 known TLRs in humans that sense a broad spectrum of pathogens, including fungi, bacteria, viruses, and protozoa[2]. TLRs are preferentially expressed on cells of the innate immune system, including monocytes, macrophages, and dendritic cells[3]. Activation of some TLRs using bacterial components (BCG, CpG DNA) and viral components (RNA) has shown anti-tumor effects in preclinical murine models[4]. Previous work from our laboratory in murine models of acute myelogenous leukemia (AML) and rhabomyosarcoma have shown anti-tumor responses to CpG DNA therapy[5, 6]. Although the mechanism of action these TLR agonists use to mediate their anti-tumor effects is unknown, it appears that direct activation of the innate immune system is a prerequisite to tumor eradication.

Molecule 852A (also known as S-32865, is N-[4-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide) is a novel immune response modifier related to the imidazoquinoline molecule imiquimod, which acts as a TLR7 agonist. It is hypothesized that 852A may be effective in treating cancer, as *in vitro* studies have shown that 852A directly activates antigen-presenting cells such as dendritic cells, resulting in (1) the production of various cytokines, including IFN-α and TNF-α, both of which may inhibit tumor growth or viability; (2) the expression of the chemokine receptor CCR7 required for dendritic cell migration to lymphoid tissue; and (3) the expression on antigen-presenting cells of co-stimulatory molecules required for T-cell activation[7, 8]. There is some suggestion that activation of TLRs may induce direct apoptosis of tumors[9, 10], providing a second potential mechanism of action for this agent. Because work in cell lines and primary leukemia cells shows that some hematologic malignancies [including acute lymphoblastic leukemia (ALL), AML, and chronic lymphocytic leukemia (CLL)] express TLR7[11], we have a Phase II study to evaluate the efficacy of 852A in treating refractory hematologic malignancies.

852A has been tested in a Phase I study (1493-852A)[12], where it was administered intravenously (IV) to 25 patients with refractory solid organ tumors three times a week for two weeks at doses ranging from 0.15 to 2.0 mg/m^2. The maximum tolerated dose was determined to be 1.2 mg/m^2 and the most frequently observed dose-limiting toxicity was transient fatigue at doses of 1.2 mg/m^2 or higher. A second phase I/II study in patients with CLL investigated 852A given intravenously weekly as a “pre-treatment” prior to other systemic chemotherapy. There was minimal toxicity of the 852A, but limited observed efficacy to clear circulating CLL cells[13]. A proposed reason for the lack of response was the IV route of administration.

More recently 852A’s bioavailability, dose proportionality, and tolerability were evaluated in a Phase I study (1525-852A) that enrolled healthy volunteers. Subjects received 2 mg of 852A by IV, SC, and oral routes. A second cohort received escalating doses (0.5, 1.0, and 2.0 mg) by SC injection. Absolute bioavailability for SC delivery determined over a 24-hour

period was approximately 80%. Pharmacokinetic data for C_{max} and $AUC_{(0-t)}$ showed dose proportionality for SC delivery. No local injection-site adverse reactions were noted. Clinical signs and symptoms consistent with cytokine induction were observed at higher doses, but did not reach clinical significance.

Preclinical data and observations from study 1493-852A suggest that lower frequency of dosing has the potential to be better tolerated and is less burdensome to trial participants. We therefore conducted the current Phase II study of 852A given SC to minimize patient inconvenience and to allow for self-administration in patients who have hematologic malignancies that respond and who are able to tolerate the drug for an extended period of time. As individual patient response in previous studies varied for both adverse events and cytokine production, dose adjustments based on individual tolerability were allowed in this trial.

Materials and Methods

We conducted a Phase II assessment of 852A. Male or female patients of any age with relapsed or refractory hematological malignancy, with a Karnofsky Performance status >50% for patients >10 years of age or a Lansky Performance status >50% for patients <10 year of age, and adequate organ function (total bilirubin ≤2.5 times upper limits of normal, AST(SGOT)/ALT(SGPT) ≤5 times upper limits of normal, and creatinine <2.0 mg/dL OR calculated creatinine clearance ≥50 mL/min for subjects with creatinine levels above normal) were eligible to participate. All patients had recovered from the toxic side-effects of prior therapies, and did not have prolonged QTc (>450 msec in males and >470 msec in females) on screening EKG. Drugs known to cause prolonged QTc were not allowed for patients on the trial. All patients consented to participate in the study, which was reviewed and approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota according to the Declaration of Helsinki.

The patients assessed were enrolled in one of two clinical trial cohorts, MT2005-20 or the identical trial used for compassionate reasons prior to the study being formalized. A previous Phase I study conducted at the University of Minnesota (Study 1493) defined the recommended intravenous Phase II dose as 1.2 mg/m^2 administered twice weekly[12]. In the current study, patients initiated dosing at 0.6 mg/m^2 twice weekly and escalated by 0.2 mg/m^2 after every two doses as tolerated to the targeted dose of 1.2 mg/m^2. All doses were administered SC. Patients were monitored for toxicity and evaluated using CTCAE (v.3). If intolerable side effects were experienced, the patient's treatment was discontinued for at least one week and steroids (oral prednisone therapy) were initiated. If symptoms resolved or reverted to ≤ Grade 2, dosing of 852A was resumed at 0.6 mg/m^2 or decreased by 0.2 mg/m^2 from the last administered dose. A total course of 24 doses or 12 weeks of therapy was planned, with patients eligible to continue treatment if there was no progression of disease or unacceptable toxicity.

Additional supportive care was provided with scheduled ibuprofen or acetaminophen 30 minutes prior to 852A administration and then given as required thereafter. Allopurinol was given to all patients for at least two weeks at the initiation of therapy. Patients with acute leukemia received hydroxyurea and/or oral etoposide to maintain the peripheral blast count ≤ 10,000. Patients were monitored twice weekly for hematological and non-hematological toxicity.

Patient disease response was assessed after every 8 doses (acute leukemia) or every 12 doses (multiple myeloma or lymphomas). Patients continued on therapy as long as there was no evidence of disease progression or intolerable toxicity. Patients also had a complete

assessment 30 days after completing therapy. Responses were evaluated as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) based on disease-specific WHO response criteria[14]. Briefly, for acute leukemia CR is defined as absence of circulating blasts and ≤ 5% blasts in bone marrow with recovered blood counts (ANC ≥ 1000 and PLT ≥ 100, 000) and no other evidence of disease; PR as > 5 and < 25% blasts in the bone marrow; SD as persistence of marrow blasts not meeting PR or CR criteria without evidence of worsening and PD as increasing peripheral or bone marrow blasts or other sites of extramedullary disease. For multiple myeloma CR is defined as absence of myeloma protein in the serum and urine with < 3% plasma cells in the bone marrow; PR as not meeting the criteria for CR or SD, SD as < 20% variance in myeloma protein over a 4 week period and PD as an increase of > 50% in serum or urine myeloma protein or >50% increase in myelomas. Finally for lymphoma CR is defined as lymph nodes returning to normal size, resolution of hepatosplenomegally and absence of bone marrow involvement; a PR as a ≥ 50% reduction in disease burden; SD as not meeting the criteria for CR, PR or PD; and PD as a 25% increase in disease burden.

Additional *in vitro* assays were performed to assess the effect that 852A had on initiating an immune response. These assays included cytokine analysis, and immunophenotyping by flow cytometry for NK and T-cell activation as indicated by CD69 expression. Blood samples were drawn and serum separated from cells at baseline prior to the first dose, two hours post first dose, prior to and two hours post second dose, at mid-therapy (pre and post dose 10–14) and at the end of therapy (dose 24). Serum cytokine levels were determined by multiplex analysis on the Luminex platform (Luminex Corp, Austin, TX) using a 22-plex (Human cytokine panel A) from R&D Systems (Minneapolis, MN) and a 7-plex panel (for CD40L, IL-12p70, IL-7, IL12p40, IL-13, IL-15, and IP-10/CXCL10) from Millipore-Linco (Billerica, MA). Frequency and phenotype of lymphocyte populations were determined by flow cytometry analysis using methods previously described[12].

Statistical analyses are descriptive in nature due to the limited number of patients included in the study.

Results

A total of 17 patients were enrolled on this trial (Table I). The majority of the patients were male Caucasians (82%). The median age was 41 yrs (range 12–72 yrs). The diagnoses were divided between ALL (5 pts), AML (6 pts), non-Hodgkin's lymphoma (NHL, 4 pts); Hodgkin's lymphoma (1 pt), and multiple myeloma (1 pt). The majority of patients (65%) were treated on the compassionate use cohort and most (76%) had relapsed disease. Patients had generally received more than two prior chemotherapy regimens for their diagnosis with the median number of regimens received being five. A total course of therapy was targeted at 24 doses with 6 of these doses being dose escalation. All patients (17) received the starting dose of 0.6 mg/kg; 16 (94%) escalated to 0.8 mg/kg, 14 (82%) escalated to 1.0 mg/kg, and 11 (65%) were able to achieve the target dose of 1.2 mg/kg. Approximately one-third of patients were not able to achieve full dose due to either progressive disease or toxicity. The median number of doses received was 16 (range 3–31), with most patients receiving only 2 doses each of the escalation schedule.

Toxicity assessment for patients indicated that the drug was well tolerated, with the majority of the toxicities being CTCAE (v.3) grade 2 or less (Table II). Only three patients reported grade 4 toxicities of malaise (2 pts) and of myalgia (1 pt). Grade 3 toxicities included nausea (2 pt), dyspnea (4 pts), fever (2 pts), myalgia (6 pts), sweats (1 pt), malaise (7 pts), and cough (1 pt).

Correlative biology studies were performed for the six patients on the therapeutic clinical trial. Four patients had complete or almost complete sample collection (missed 2 or fewer time points), allowing for analysis of peripheral blood immunophenotyping and cytokine responses after several doses of drug. Flow cytometric analysis of NK ($CD45^+/CD3^-/CD56^+/CD69^+$) cells and T ($CD45^+/CD3^+$) cells showed that there was a variable increase in cell number following a dose of drug but this returned to baseline levels prior to the next dose (data not shown). Analysis of serum cytokine levels prior to and after doses did not show any significant differences; however, levels of IP-10, IL1-RA, and IFN-γ were variably increased as previously observed in the Phase I study[12]. In Table III we compare pre-therapy IP-10 and IFN-γ to the maximum value of each of these cytokines at any point during therapy. Although there was considerable variability among the four patients studied, each showed an increase in these inflammatory cytokines in at least one time point.

Interestingly, a patient with NHL, who had the highest increase in T-cell response over time (baseline to after final dose; 3.5×10^9 cells/L to 4.55×10^9 cells/L: 30% increase) and the highest peaks in NK cell response (0.88×10^9 cells/L to 3.18×10^9 cells/L: 360% increase), achieved SD and went on to allogeneic transplant. One patient with ALL achieved a CR with receiving single 852A as therapy for relapsed disease after allogeneic bone marrow transplantation. The overall response rate for the combined patient group (clinical trial and compassionate use) was 18% at 1 yr [1 CR (ALL), 1 PR (AML), 2 SD (AML, NHL) (Table IV)]. The median survival was 3.5 months (7 days – 23 months).

Discussion

The TLR agonists have been used as immune adjuvants in clinical trials for B-cell malignancies and in combination with chemotherapy for lung carcinoma[15]. We performed the first Phase II clinical trial of an imidiquinolone, 852A, administered as a single agent with prolonged dosing in patients with relapsed/refractory hematologic malignancies. We have shown that the drug is well tolerated, has some evidence of activity in a variety of hematologic malignancies, and is associated with measurable immune activation.

Several Phase I studies have investigated the tolerability of a variety of TLR agonists[16–19]. The imidiquinolones activate the innate immune system and are associated in humans with increases in NK and T-cell activation[20]. Consistent with our Phase I study of 852A, we detected transient increases in NK cell activation and a more sustained response in the T-cell population in the patient with NHL who achieved SD. Variable responses were seen in the cytokines IP-10 and IL1-RA (data not shown). Although the study was limited in patient numbers, it does appear that there may be an association between immune activation and response to 852A.

The toxicities of 852A were expected and generally tolerable with only three reported grade 4 toxicities. The grade 3 myalgia was manageable with prednisone and allowed dose escalation in patients to occur. No patients were hospitalized due to toxicity.

Studies evaluating TLR agonists in hematologic malignancies have mainly focused on CLL, where the course is more indulant. Several reports have suggested responses in patients with refractory/relapsed CLL when the TLR agonist has been used as a single agent[21]. Spaner et al[13]failed to demonstrate a clinical or immunological response to 852A when administered weekly by IV. This is in contrast to our data that suggest the subcutaneous route given twice weekly may be more effective in generating an anti-leukemia response. A study evaluating the TLR9 agonist CpG 7909 in CLL demonstrated immune activation and prolonged stable disease[22]. TLR9 may be responsible for more of an antigen-presenting cell activation than a direct NK or T-cell activation as occurs with the TLR7/8 agonists.

There may also be direct effects of either of the TLR agonists on the cancer cells. It has been shown that leukemias, AML and CLL specifically, have receptors for TLR7/8 or 9[23]. The engagement of TLR7 has been shown to activate apoptosis and differentiation in AML blasts, suggesting that agents like 852A might be specifically able to sustain longer responses in AML[24]. Of the patients on our study with AML, one had prolonged SD and one achieved PR. The patient with the PR received an allogeneic cord blood transplant and died of transplant-related complications, but was in remission at the time of death.

Many studies suggest that immune-based therapies have the greatest chance of response and potential for clinical benefit in the setting of minimal residual disease. As such, a study conducted in relapsed/refractory patients with hematological malignancies that rapidly progress is not the best test of an agent's potential activity or clinical utility. All 17 patients entered on this study had actively progressive disease that limited the extent to which therapy could be escalated and true activity assessed. The ideal study would be to assess toxicity and efficacy in patients receiving chemotherapy to determine if relapse of disease could be prevented through activation of the immune system. Based on the responses seen in this limited study, patients with hematological malignancies may benefit from such an approach.

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Table I

Study Characteristics

Study Characteristics	N (%)
Total N	17
Sex/Race	
Male Caucasian	14 (82%)
Female Caucasian	1 (6%)
Male African American	1 (6%)
Female Asian	1 (6%)
Diagnosis	
ALL	5 (29%)
AML	6 (35%)
NHL	4 (24%)
Hodgkin's lymphoma	1 (6%)
Multiple Myeloma	1 (6%)
Compassionate Use	
No	6 (35%)
Yes	11 (65%)
Disease status at Tx	
Relapse	13 (76%)
Primary Induction Failure	2 (12%)
Refractory	1 (6%)
Unknown	1 (6%)
Number of pre-study RXs	
1	1 (6%)
2	2 (12%)
3	3 (18%)
4	2 (12%)
5	4 (24%)
6	1 (6%)
7	2 (12%)
11	1 (6%)
14	1 (6%)
Age at Enrollment	
Median (range)	41 (12–71 yrs)

Table II

Toxicity - Evaluable Patients Only (N=17)

Maximum grade	N (%)
Nausea	
0 (none)	2 (12%)
1	11 (65%)
2	2 (12%)
3	2 (12%)
Vomiting	
0 (none)	14 (82%)
1	1 (6%)
2	2 (12%)
Dyspnea	
0 (none)	3 (18%)
1	9 (53%)
2	1 (6%)
3	4 (24%)
Fever w/o infection	
0 (none)	5 (29%)
1	5 (29%)
2	5 (29%)
3	2 (12%)
Chills	
0 (none)	3 (18%)
1	10 (59%)
2	4 (24%)
Myalgia	
0 (none)	4 (24%)
1	1 (6%)
2	6 (35%)
3	5 (29%)
4	1 (6%)
Sweats	
0 (none)	1 (6%)
1	9 (53%)
2	6 (35%)
3	1 (6%)
Malaise	
0 (none)	0
1	1 (6%)
2	7 (41%)
3	7 (41%)

Maximum grade	N (%)
4	2 (12%)
Edema	
0 (none)	7 (41%)
1	7 41%)
2	3 (18%)
Cough	
0 (none)	9 (53%)
1	5 (29%)
2	2 (12%)
3	1 (6%)
Pain	
0 (none)	15 (88%)
1	1 (6%)

Table III

Cytokine Response to 852A

Patient	IP-10 (sensitivity 10pg/ml) (mean ±SD)			IFN-γ (sensitivity 10pg/ml) (mean ±SD)		
	Pre-therapy	Peak	Time to Peak (days)	Pre-therapy	Peak	Time to Peak (days)
A	587.7 ±10.9	2398.9 ±155.9	4	1.3 ±0.6	2.5 ±1.7	4
B	1011.5 ±8.9	1618.4 ±34.0	4	4.4 ±0.3	10.3 ±2.6	4
C	1517.7 ±13.8	1517.7 ±13.8	0	1.6 ±0.8	4.2 ±2.3	83
D	3054.1 ±84.1	23,002.8 ±2445.1	3	7.0 ±0.6	72.7 ±1.2	3

Table IV

Response and Duration

	N (%)	Time to Response Median (range)
Complete Response (ALL)	1 (6%)	53 days
Partial Response (AML)	1 (6%)	77 days
Stable Disease (NHL, AML)	2 (12%)	68.5 days (52–85 days)
Disease Progression		
No response	7 (41%)	
Unevaluable *	2 (12%)	
	4 (24%)	

* Defined as not receiving all 12 doses of drug