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Phase I Study of S-trans, Trans-farnesylthiosalicylic Acid (Salirasib), a Novel Oral RAS Inhibitor in Patients with Refractory Hematologic Malignancies

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Abstract

Background—RAS/RAF/MAPK activation (mutational or non-mutational) is a key pathway for survival and proliferative advantage of leukemic cells. Salirasib is an oral RAS inhibitor that causes dislocation of RAS by competing directly with farnesylated RAS in binding to its putative membrane binding proteins. Salirasib does not inhibit farnesyl transferase enzyme.

Methods—We report a phase I study of Salirasib in patients with relapsed/refractory hematologic malignancies. Salirasib was administered orally twice daily on days 1–21 of a 28 day cycle in a "3+3" dose escalation design.

Results—Seventeen patients with relapsed/refractory leukemia were treated for a median of 4 cycles (range, 1–29). Three patients each were enrolled at dose level of 100, 200, 400, 600 and 800 mg twice daily and 2 pts at dose level of 900 mg twice daily. No dose limiting toxicities were encountered. Grade 1–2 diarrhea has been the only frequent non-hematologic toxicity observed in 14 of 17 (82%) patients and was resolved with oral anti-diarrheal. Eight (47%) pts (4 MDS, 2 AML, 1 CMML, and 1 CML) had hematological improvement; 1 in three lineages, 1 in two lineages, and 6 in one lineage. None of the patient achieved complete remission. The responses lasted for a median of 10 weeks (range, 5–115). Study was discontinued for financial constraints.

Conclusion—Salirasib was well tolerated and showed modest activity in relapsed/refractory hematological malignancies. The safety profile of Salirasib and its hematological malignancy relevant target makes it a potential drug to be utilized in combination therapy.

Keywords

RAS/RAF/MAPK activation; *RAS* mutation; *RAS* inhibitor; farnesylation; Leukemia

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Introduction

Human cancers frequently express activating mutations in the oncogenic *RAS*. The frequency of mutated *RAS* genes and the type of mutated *RAS* gene (*H-RAS*, K-RAS, or *N-RAS*) varies widely depending on the tumor type. Mutated *K-RAS*, the most frequently mutated gene in cancer; is detected in high frequencies in pancreatic (90%) and colorectal carcinomas (50%), and is less frequent in hematological malignancies, where *N-RAS* mutations are relatively more frequent.[1–3] *RAS* proteins transduce growth and differentiation signals from receptor tyrosine kinases to the cell nucleus, thereby initiating gene transcription.[4] Mutated *RAS* remains in its active state longer than wild type *RAS*. Consequently the *RAS* signaling is continuously over activated, resulting increase in tumor growth.[5] Activation of RAS pathway can also be mediated alternatively by constitutive activation of tyrosine kinase like FMS like tyrosine kinase 3 (*FLT3*) internal tandem duplication (*ITD*) or mutations in *RAS*-regulating genes mutations.[6–9] By blocking the mutated *RAS* gene product, such malignant transformation can be reversed.[10]

Several studies have reported the incidence and prognostic impact of *RAS* mutation in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) patients. The acquisition of *RAS* mutation in MDS have shown to be associated with increased frequency of transformation to AML and shortened survival.[11,12] Takahashi et al in a retrospective review reported that subset of patients with low/intermediate risk MDS who acquire *RAS* mutation in disease course had shorter transformation free survival to AML and overall survival in contrast to wild type patients.[13]

In view of the importance of oncogenic *RAS* in human cancer, and evidence of oncogenic *RAS* playing a major role in tumor proliferation and maintenance, targeting *RAS* proteins have become one of the novel therapeutic approaches.[14] Direct targeting of *RAS* has been difficult but *RAS* transforming activity can potentially be inhibited using different approaches. One is the inhibition of farnesylation of RAS, as exemplified by the farnesyl transferase inhibitors (FTIs).[15] Several FTIs have reached the clinic, including tipifarnib, lonafarnib, and BMS-214662.[16–19] However, farnesyl transferase inhibitors are not effective *RAS* inhibitors; they do not block the oncogenic activity of the two most frequently occurring oncoproteins *K-RAS* and *N-RAS*, because these two isoforms undergo alternative lipid modification by prenylation.[20,21] Thus, the potential effectiveness of FTIs is limited by the existence of an alternative escape pathway permitting prenylation when RAS farnesylation is blocked by FTIs.[22,23]

Marom et al [24] at Tel Aviv University applied rational drug design to target *RAS* by competitively inhibiting the enzyme prenylated protein methyltransferase (PPMTase), which methylates the carboxyl-terminal S-prenylcysteine in a large number of prenylated proteins including *RAS*. Salirasib (trans-farnesylthiosalicylic acid) (Concordia Pharmaceuticals) is a synthetic S-prenyl derivative of thiosalicylic acid, resembling the carboxyl-terminal farnesylcysteine common to all *RAS* proteins. In cell free system, FTS inhibits *RAS* methylation, but not farnesylation. In intact cells PPMTase inhibition is unlikely to be the mechanism of inhibition for *RAS* mediated growth by FTS, as significantly high concentrations are needed in intact cells to inhibit methylation. In cellular systems, Salirasib

reduces *RAS* in cell membranes by dislodging *RAS* from membrane anchoring sites, and inhibits the growth of all types of *RAS*-driven cancer.[25,26]

Preclinical data showed that exposure to, Salirasib by oral gavage, results in tumor growth inhibition and prolonged survival in xenotranplants of a variety of human tumors in mice. *In vitro* and *ex vivo* studies have shown that Salirasib dislodges the active RAS protein from the cell membrane, thereby blocking the initiation of downstream signaling event, inhibiting tumor cell proliferation and promoting cancer cell apoptosis.[24,27–29] This work has been translated in few clinical trials for patients with solid tumors.[30,31]

Here, we present our result from a phase I trial, exploring role of oral Salirasib in patients with advanced hematological malignancies. The primary objective of this study was to determine the maximum tolerated dose (MTD), pharmacokinetics (PK), and dose limiting toxicities (DLT). Secondary objectives were to evaluate response in patients with advanced hematological malignancies.

Patients and Methods

Patient Population

Patients were eligible if they had relapsed/refractory hematologic malignancies for which no standard therapies were anticipated to result in a durable response or who refused or were considered unsuitable for standard therapy. Other eligibility criteria included age 18 years, Eastern Co-operative Oncology Group (ECOG) performance status of 0–2. In the absence of rapidly progressing disease, the washout from prior treatment to time of study drug administration had to be at least 2 weeks for cytotoxic agents or at least 5 half-lives for non-cytotoxic agents. Patient needed to have adequate organ function as indicated by serum creatinine less than or equal to 2.0 mg/dl; total bilirubin less than or equal to 2.0 mg/dl; ALT and/or AST no more than 3x the upper limit of normal range unless abnormal parameter level was considered related to leukemia. The study protocol was approved by the Institutional Review Board and all patients had to give written informed consent. The trial was registered with www.clinicaltrials.gov NCT00867230.

Study Design

The study design was a 3+3 design with six planned dose levels and accelerated dose escalation. First 2 escalations were at 100%, next 3 were at 50%, 33% and 12% respectively. Escalation to the next dose level was done only after the third patient on the previous dose level was been observed for 4 weeks and no DLT was observed.

The National Cancer Institute Common Toxicity Criteria version 3.0 was used to grade toxicity. DLT was defined as a clinically significant toxicity or abnormal laboratory value assessed as unrelated to disease progression, co-existing illness, or concomitant medications and occurring during the first cycle. This included grade 3 AST/ALT elevations for 7 days, any grade 4 AST/ALT elevation and other clinically significant non-hematological adverse events grade 3. Clinically not significant events like nausea and vomiting grade 3, alopecia, study drug-related fever, electrolyte abnormalities (including K, Na, CL, HCO3, Mg, Ca, and Bilirubin) grade 3 were excluded from defining the DLT.

Response criteria

A complete remission (CR) was defined as disappearance of all clinical evidence of disease with <5% bone marrow blasts, neutrophil count $\geq 1.0 \times 10^9$/L, and platelet count $\geq 100 \times 10^9$/L. Partial response (PR) required all of the hematologic values for a CR but with a decrease of ≥ 50% in the percentage of blasts to 5% to 25% in the BM aspirate. Hematologic Improvement (HI) was defined as reported by Cheson et al.[32] Briefly, in patients with pre-treatment hemoglobin (Hb) levels lower than 11 g/dl, erythroid responses required an increase of at least 1.5 g/dl. Platelet responses were evaluated in patients with pre-treatment platelets lower than 100×10^9/L, requiring an increase of at least 30×10^9/L. Neutrophil response was evaluated in patients with pre-treatment counts lower than 1.0×10^9/L, requiring an increase of at least 0.5×10^9/L.

Statistical Methods

The primary outcome measure in the study was the safety of escalating doses of FTS. The sample size was not determined by statistical power consideration. Descriptive statistics on patient characteristics, analysis of toxicities, and outcome were performed on all patients.

Pharmacokinetic Assessments

Plasma levels of FTS were determined at specified time points by using a high performance liquid chromatography (HPLC) method, with a limit of quantitation at 1 ng/ml. Blood samples for PK analysis was collected during cycle 1 on treatment days 1, 8 and 15 at multiple time points. The following pharmacokinetic parameters were calculated; maximum plasma concentration (C_{max}), the time to C_{max} (T_{max}), terminal half-life ($T_{1/2}$), area under the concentration time curve (AUC), to infinity (AUC_{inf}) and systemic clearance (Cl/F).

Results

Patient characteristics

Seventeen patients were enrolled in the study and all of them were evaluable for response and toxicity. Patient demographics and disease characteristics are listed in Table 1. Eleven (65%) were male. The median age was 72 years (range, 35–85). Eight (50%) patients had AML, 5 (28%) had MDS, 2 (12%) had chronic myelomonocytic leukemia (CMML) and one patient each with myelofibrosis (MF) and chronic myeloid leukemia (CML). Seven patients (41%) had diploid cytogenetics (CG), 5 had (29%) -5/-7, and 2 had (12%) complex (CG). The median number of prior therapies was 2 (range, 0–7). One patient received Salirasib as first line therapy as treating physician felt that the patients is not a candidate of intensive anthracycline or cytarabine based therapy due to advance age, comorbidities and poor performance status. Three (18%) patients received Salirasib as a 1st line therapy. Thirteen patients were evaluated for RAS mutations and only 1 patient had *RAS* mutation (*N-RAS*). Among the other mutation tested is *FLT3 ITD* in 14 (82%) patients and all were wild type.

Dose levels and toxicity

Salirasib was administered orally twice daily on day 1–21 in a 28 day cycle. The starting dose level was 100 mg. Three patients were treated at each dose level from 1 to 5 (100, 200,

400, 600, 800 mg) and 2 patients at 6th dose level (900 mg) (Table 2). Cycle 1 was the DLT defining period. All seventeen patients were evaluable for toxicity. No dose limiting toxicity was observed. Non hematological toxicities are shown in Table 3. The most common toxicity was diarrhea (grade 1 and 2), experienced by 65% of patients. None of the patients with diarrhea required dose interruptions. Other non-hematological toxicities (all grades) included increase in transaminases (47%), hyperbilirubinemia (12%) and increase in creatinine (12%). Only one patient had grade 4 hyperbilirubinemia who had pre-existing grade 3 hyperbilirubinemia secondary to leukemia (Table 3). No DLT defining toxicities were encountered in patients who continued on therapy beyond cycle 1. Further dose escalations were stopped due to logistical reasons, primarily involving a financial decision made by sponsor.

Efficacy

Eight of 17 (47%) patients achieved responses. None of the patient achieved CR, complete remission with incomplete platelet recovery (CRp) or PR. All responders had hematological improvements: 1 with trilineage response, 1 with bilineage and 6 (23.5%) with one lineage responses. Among patients with one lineage response; 3 had improvement in platelet count, 2 had improvement in absolute neutrophil count (ANC), and 1 had improvement in hemoglobin. The patient with trilineage hematopoietic response had MDS with complex CG (including monosomy 7) and received Salirasib as second line therapy. Patient with bilineage response had MDS with marrow fibrosis, achieved improvement in hemoglobin and platelet count. Three patients with improvement in platelet alone had relapsed refractory AML (1), CMML (1), and high risk MDS (1). Two patients with improvement in ANC had multiply relapsed refractory AML and one of them had complex cytogenetics. Another patient with improvement in hemoglobin had CML with refractory disease and failed 6 lines of therapy. Only one patient in the study had RAS mutation; however he was not among responders. Responses were observed at more than one dose level. Two (12%) patients had response at 200mg twice daily dose, 2 (12%) at 400mg, 2 (12%) at 600mg and one patient each had response at 800mg and 900mg twice daily dose level. The median time to response was 30 days (range 9–116 days). The median response duration was 10 weeks (range, 5–115 weeks) and median number of cycles patients received was 4 (range, 1–29). Reponses are summarized in Table 4.

Pharmacokinetics

AUC values showed dose dependence and broadly consistent with linear pharmacokinetics for each analyte. The mean Salirasib metabolite CCA-FTS-103 (mean ± SD) clearance was 103 ± SD 112.5 (L/hr) on day 1 and 81.5 ± 34.9 (L/hr) on day 15. The mean clearance of CCA-FTS-105 (mean ± SD) analyte was 50.3 ± 30.7 (L/hr) on day 1 and not calculated on day 15. The $t_{1/2}$ for CCA-FTS-103 (mean ± SD) was 3.56± 2.19 and 2.09±0.92 on day1 and day 15 respectively. The $t_{1/2}$ for CCA-FTS-105 (mean ± SD) was 4.29±1.87 on day1, not calculated on day 15 (supplemental table 1). Further analytical data regarding average plasma concentration with time, Cmax, and AUC0–8hrs is presented in graphical manner in Supplementary Data (supplemental figure 1A and 1B).

Discussion

This is the first report of prospective clinical trial of Salirasib in patients with hematological malignancies. Our study showed that oral Salirasib is well tolerated at all tested dose levels and DLT's were not observed. The only significant toxicity was diarrhea (grade I-II). None of the patients had grade III-IV toxicity apart from one patient with grade IV hyperbilirubinemia, who had baseline grade III hyperbilirubinemia due to advanced leukemia. In this study 8 of 17 (47%) of patients achieved protocol defined responses. Though all responses were in improvement in cytopenias only, no dose response relationship was seen. In fact 4 (57%) responders received low dose levels of 200mg and 400mg twice daily. The study did not formally determine a MTD, further dose escalations were stopped because of logistical reasons. Correlative studies of target inhibition were unfortunately not included in this trial to answer response relationship with target modulation.

Only one patient enrolled in our study was found to have *RAS* mutation *(N-RAS)*, however was not among the responders. In this study all the responders had unmutated RAS, an observation consistent with several previously published results demonstrating lack of correlation between *RAS* mutational status and response to RAS targeting therapy.[33,34] On the other hand in a more recent trial of trametinib, targeting MAPK kinase (MEK1 and 2) downstream of RAS in myeloid malignancies, most responses including complete remissions were seen in patients with mutations in *RAS* gene.[35] Among the 87 patients enrolled in the clinical trial, 57 (65%) of patients has *NRAS/KRAS* mutation. Among the patients with mutated *NRAS/KRAS* the CR/CRp/marrow CR rate was 21% compare to 3% in patients with wild type *NRAS/KRAS*. Trametinib is active in sequential or combination therapy with BRAF inhibitors in patients with *BRAF* mutant melanoma confirming oncogenic pathway dependent role.[36,37]

In conclusion, oral Salirasib was well tolerated with modest activity in relapsed and refractory hematological malignancies. Because of its very limited toxicity profile with oral dosing and relevance of its target in hematological malignancies, Salirasib can potentially be utilized in combination strategies including that with hypomethylating agents or kinase (FLT3, KIT, MEK) inhibitor targeted therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Practice Points

- Mutated *RAS* (*K-RAS, N-RAS or H-RAS*), is the most frequently mutated gene in human cancer.

- *RAS* proteins transduce growth and differentiation signals from receptor tyrosine kinases to the cell nucleus, thereby initiating gene transcription and leading to tumor growth. By blocking the mutated RAS gene product, such malignant transformation can be reversed.

- The dynamic acquisition of *RAS* mutation in MDS have shown to be associated with increased frequency of transformation to AML and shortened survival.

- In view of the importance of oncogenic *RAS* and evidence of it playing a major role in tumor proliferation and maintenance, targeting *RAS* proteins have become one of the novel therapeutic approaches.

- Salirasib is an oral *RAS* inhibitor; it reduces *RAS* in cell membranes by dislodging from its membrane binding sites, and inhibits the growth of all types of *RAS*-driven cancer. Salirasib is not a farnesyl transferase inhibitor.

- In our phase I study, Salirasib was well tolerated in relapsed/refractory leukemia population. No DLT was observed, and grade 1–2 diarrhea was the only most frequent non- hematological toxicity observed.

- Although modest, Salirasib has shown efficacy in heavily treated, advance leukemia patients. Eight (47%) of patients achieved hematological improvement with durable responses, lasting for a median of 10 (range, 5–115) weeks.

- Salirasib demonstrating good safety profile and relevance of its target in hematological malignancies warrants future combination studies with chemotherapy or targeted agents.

Table 1

Baseline patient characteristics (N=17)

Characteristics	No. (%)
Median age, yrs (range)	72(35–85)
Gender	
Female	6 (39)
Male	11 (61)
Diagnosis	
AML	8 (50)
MDS	5 (28)
CMML/MF	3 (17)
CML	1 (5)
PS median (range)	1 (0–2)
0	5 (28)
1	8 (44)
2	5 (28)
Cytogenetics	
Diploid	7 (41)
Complex	2 (12)
-5/-7	5 (29)
Ph+/Misc	3 (18)
Prior therapy, median (range)	2 (0–7)
RAS mutation (patients evaluable n=14)	1 (7)

AML; acute myeloid leukemia, MDS; myelodysplastic syndrome, CMML/MF; chronic myelomonocytic leukemia/myelofibrosis, CML; chronic myeloid leukemia, PS; performance status.

Table 2

Phase I dosing

Cohort	Days 1 to 21 (mg/BID)	Total dose (mg/cycle)	% increase in dose	No. of patients evaluable for DLT
1	100	4200	-	3/3
2	200	8400	100	3/3
3	400	16800	100	3/3
4	600	25200	50	3/3
5	800	33600	33	3/3
6	900	37800	12	2/2

DLT; dose limiting toxicity

Table 3

Salirasib cycle 1 toxicities (n= 17)

Adverse events	Cohort 1 100mg bid	Cohort 2 200mg bid	Cohort 3 400mg bid	Cohort 4 600mg bid	Cohort 5 800mg bid	Cohort 6 900mg bid	All grade
	n=3 n (%)	n=3 n (%)	n=3 n (%)	n=3 n (%)	n=3 n (%)	n=2 n (%)	n (%)
Diarrhea							
All grade	1 (33)	2 (67)	3 (100)	3 (100)	1 (33)	1 (50)	11 (65)
Grade 1–2	1 (33)	2 (67)	3 (100)	3 (100)	1 (33)	1 (50)	11 (65)
Grade 3–4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALT/AST inc.							
All grade	3 (100)	1 (33)	2 (67)	0 (0)	0 (0)	0 (0)	6 (35)
Grade 1–2	3 (100)	1 (33)	2 (67)	0 (0)	0 (0)	0 (0)	6 (35)
Grade 3–4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bilirubin inc.							
All grade	1 (33)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	2 (12)
Grade 1–2	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)
Grade 3–4	0 (0)	0 (0)	0 (0)	1 (33)*	0 (0)	0 (0)	1 (6)
S. Cr inc.							
All grade	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	2 (12)
Grade 1–2	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	2 (12)
Grade 3–4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ALT; alanine aminotransferase, AST; aspartate aminotransferase, S.Cr; serum creatinine, inc.; increase

*
Baseline grade 3 hyperbilirubinemia secondary to leukemia

Table 4

Patient with hematological response (n=8)

Hematological improvement- Erythroid						
Diagnosis	Dose level mg/BID	Starting Hb g/dl	Best Hb g/dl	Weeks on study	Duration of HI-E (weeks)	
MDS	200	10.4	12.8	7	10	
CML	600	9.3	11.4	30	35	
MDS	600	9.5	12.2	119	63	

Hematological improvement – Neutrophil					
Diagnosis	Dose Level mg/BID	Starting ANC	Best ANC	Weeks on study	Duration of HI-N (weeks)
MDS	200	0.40	1.05	7	6
AML	400	0.285	1.52	8	9
AML	400	0.144	1.4	16	6

Hematological improvement- Platelet					
Diagnosis	Dose Level mg/BID	Starting PLT x 10⁹/L	Best PLT x 10⁹/L	Weeks on study	Duration of HI-PLT (weeks)
MDS	200	53	105	7	5
MDS	200	21	54*	7	6
AML	600	83	221	119	115
MDS	800	17	60*	16	14
CMML	900	12	110	23	22

HI-E: Hematological improvement- erythroid, HI-N: hematological improvement- neutrophil, HI-PLT: hematological improvement-platelet, ANC: absolute neutrophil count, PLT: platelet, Hb: hemoglobin

*Transfusion of platelets required once only during study duration.