ORAL RIGOSERTIB COMBINED WITH AZACITIDINE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) AND MYELODYSPLASTIC SYNDROMES (MDS): EFFECTS IN TREATMENT NAÏVE AND RELAPSED/REFRACTORY PATIENTS

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Background

Azacitidine (AZA) is first line therapy for patients (pts) with higher risk MDS and demonstrated efficacy in older pts with AML (Dombret et al, Blood 2015; Fenaux et al, J Clin Oncol 2010). Rigosertib (RIG) interferes with the RAS-binding domains of RAF kinases and inhibits the RAS-RAF-MEK and the PI3Ks pathways. In vitro, the combination of RIG with AZA synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence-dependent manner (Skidan et al, AACR 2006). RIG's effective inhibition of human hematopoietic tumor cell lines in vitro, favorable clinical adverse event (AE) profile, and its synergy with AZA suggests the potential value of combination treatment.

Aims

Phase I/II results are presented for pts with MDS, either hypomethylating (HMA) treatment naïve or progressing on or failing to respond to prior HMA, and those with AML (per WHO 2002 criteria) with relapsed or refractory disease

Methods

Oral RIG was administered twice daily on Day 1-21 of a 28-day cycle in escalating cohorts and then at the recommended Phase II dose (560 mg qAM and 280 mg qPM). AZA 75 mg/m^2/d SC or IV was administered for 7 days starting on Day 8. A CBC was performed weekly, and a bone marrow aspirate/biopsy were performed at baseline, D29, and then every 8 weeks thereafter. Response was determined by IWG criteria for MDS (2006) and AML (2003). Stable disease in AML was defined as not meeting criteria for any other treatment response (CR, CRi, PR, disease progression, or treatment failure).

Results

The combination of oral RIG and AZA was administered to 54 pts, of whom 40 had MDS; HMA-treatment-naïve (N=23) and previously HMA-failed pts (N=17). 17 MDS pts received prior HMA therapy: 12 AZA, 4 decitabine, and 1 both. Ten pts had AML, and 6 had CMML. 2 MDS patients with 20-<30% marrow blasts were also included in the AML analysis. Median age was 68 years; 67% of pts were male; and ECOG performance status was 0-1 in 95% of pts. Pts have received 1-37+ cycles of treatment (median, 3.5 cycles), with a median duration of treatment of 17 weeks (range 4 to 158+ weeks).

Of the 10 pts with AML, 6 had relapsed AML, 2 secondary AML and 2 with AML transformed from MDS. Eight pts were evaluable for response. There were 3 responses seen, for an ORR of 37.5%, with responses in both secondary and refractory AML. Two additional pts had stable

disease (25%). Responses were durable, with the longest response approaching one year (Table 1).

Among 33 evaluable MDS pts, overall response by IWG criteria was 76%: complete remission (CR) in 8 (24%), concurrent marrow CR (mCR) and hematologic improvement (HI) in 10 (30%), mCR alone in 6 (18%), and HI alone in 1 (3%). Overall response was 85% in HMA naïve pts and 62% in HMA resistant pts. Correlative studies suggest that RIG has chromatin modifying effects in combination with AZA which may overcome clinical AZA resistance (Chaurasia EHA 2017). Median duration of CR was 8 months for the combination. Median time to initial response was 2 cycles, and median time to best response was 3 cycles.

The most frequently reported AEs were diarrhea (70%), nausea (50%), back pain (40%), constipation (40%), fatigue (40%), and peripheral edema (40%).

Table 1.

UPN	Age (years)	Cohort*	DoT (weeks)	Previous Therapy	Status at Study Entry	IWG Response (DoR - weeks)	Reason for Discontinuation
101-003	61	140 bid	4.0	1. Induction 2. Investigational	AML - Refractory	NE	Patient request
101-002	70	140 bid	29.6	Growth Factors	AML - Secondary	MoCR (25.3)	Progressive Disease
102-001	76	140 bid	4.0	Growth Factors	MDS/AML	NE	Toxicity/AE
102-003	78	140 bid	55.1	Growth Factors	MDS/AML	MoCR (43)	Progressive Disease
101-005	73	280 bid	4.0	1. Induction 2. DEC x5	AML – 1st Relapse	TF/I	Death
102-009	71	560/280	12.9	1. Induction x2 2. AZA x25	AML - Relapsed	TF/R	Death
102-007	80	560/280	32.0	AZA x5	AML - Secondary	TF/R	No Hem Response
101-008	57	560/280	8.1	Induction	AML - Refractory	MLFS (4.1)	Inv. Decision
101-009	60	560/280	24.4	Induction	AML - Relapsed	SD	Death
101-007	77	560/280	16.0	1. Induction 2. DEC x12	AML - Relapsed	SD	Progressive Disease

MDS/AML – 20 to <30% blasts

NE – patients off study prior to 12 weeks of combination

MoCR – morphologic complete remission

TF/I – treatment failure/indeterminate

TF/R – treatment failure/resistant

MLFS – morphologic leukemia-free state

SD – stable disease

* Oral rigosertib dose

Conclusion

The combination of oral RIG and standard-dose AZA was well tolerated in repetitive cycles in pts with AML and MDS. Response was observed both in HMA-treatment-naïve pts (85%) and in pts failing HMA therapy (62%), suggesting the addition of RIG can overcome HMA clinical resistance by acting as a chromatin modifying agent. In AML, responses were seen in 37.5% of evaluable pts. Based on these results, continued study in AML is warranted. A Phase III study of the combination of oral RIG and AZA in pts with treatment naïve MDS is planned.

Session topic: 10. Myelodysplastic syndromes - Clinical

Keyword(s): Ras, MDS, Clinical Trial, AML

RIGOSERTIB COMBINED WITH AZACITIDINE EPIGENETICALLY MODULATES CHROMATIN AND HEMATOPOIETIC STEM CELL POPULATIONS IN THE MYELODYSPLASTIC SYNDROME (MDS)

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Background

Azacitidine (AZA) is the standard of care for patients (pts) with higher-risk MDS, however, only 50% of pts respond and the majority will relapse within 2 years. All pts ultimately fail treatment due to primary or secondary resistance. RIGosertib (RIG) is a “ras mimetic” agent that binds to the Ras Binding Domain of RAF kinases and inhibits the RAS-RAF-MEK and the PI3K pathways. Initial results of an ongoing Phase I/II study with RIG combined with AZA, in pts with MDS demonstrated a response rate of: 76% overall; 62% in pts following hypomethylating agent (HMA) failure and 85% in HMA naïve pts (Navada et al ASH 2016).

Aims

To Investigate the in vitro effects of RIG combined with AZA or vorinostat (VOR) on epigenetic and stem cell pathways on two cell lines: AML (BW90), MDS (MDS-L) and on pt bone marrow samples

Methods

We investigated the in vitro effects of RIG combined with AZA or vorinostat (VOR) on two cell lines: AML (BW90), MDS (MDS-L) and on pt bone marrow samples treated on the phase I/II study, obtained prior to and after one cycle of AZA and RIG.

Results

Treatment with RIG alone altered global histone post-translational modifications (PTMs) including methylation (H3K4me3, H3K4me2, H3K27me3, and H3K27me2) and acetylation (H3K9ac, & H3K18ac) levels associated with transcriptional activation or repression in both the cell lines and pt samples.

Q-PCR studies demonstrated that individual treatment of BW90 and MDS-L with RIG or combined with AZA or VOR in sequential treatment (AZA/RIG, RIG/AZA, VOR/RIG or RIG/VOR) altered DNA methyl transferases (DNMT1, 3a and 3b), the class I, II and IV histone deacetylases (HDACs), and chromatin remodeler (KDM2a, SET1, JMJD3 and LRWD1) transcript levels in a cell line specific context.

Sequential treatment of RIG with AZA or VOR demonstrated differential effects on the association of RNA polymerase II (Pol II) with active histone marks (H3K4me3 and H3K4me2) in both cell lines. An overall decrease in association of Pol II/H3K4me2 was observed with the combinations (AZA/RIG, VOR/RIG or vice versa) in MDS-L and BW-90, 10-33% (ANOVA, $p=0.0006$), 9-20% (ANOVA, $p=0.0004$), respectively. Significant differences were observed in association of H3K4me3/Pol II in BW-90 cells (7-30%; ANOVA, $p<0.0001$). Similarly, in BM from a pt with MDS after 1 cycle of RIG and AZA treatment demonstrated a decrease in association of Pol II with H3K4me2 (67%) and H3K4me3 (28%).

Treatment of MDS-L cells with RIG alone or RIG/AZA failed to induce expansion of $CD34^+$ cells and yielded maximum aldehyde dehydrogenase (ALDH) activity, a marker of primitive hematopoietic stem and progenitor cells (HSCs) (ANOVA, $p=0.006$), but the RIG/VOR induced 1.9-fold expansion of $CD34^+$ cells (ANOVA $p=0.002$). A marked decrease in ALDH activity was observed in AZA or VOR or RIG/VOR, that was inversely proportion to the expansion of $CD34^+$ cells.

In an MDS pt treated with RIG/AZA an expansion of primitive HPSCs expressing low levels of CD34 appeared with disappearance of a highly expressing CD34 subpopulation that co-existed

prior to treatment. Expansion of $CD34^+$ cells led to ≥2 fold increase in pluripotent genes (SOX2, OCT4, NANOG and ZIC3) expression levels in the BM from MDS pts after RIG/AZA treatment and 1.7-34 fold increase in the presence of RIG or RIG/AZA or RIG/VOR in MDS-L. These findings indicate that expression of pluripotency genes is a consequence of epigenetic reprogramming that favors expansion of more primitive HSPCs in a pt.

Conclusion

RIG potentially functions as a chromatin modifying agent, in combination with AZA and may overcome HMA resistance through chromatin remodeling. RIG alone and in combinations also leads to epigenetic reprogramming of HSPC that may manifest in hematological improvements in the clinical setting.

Session topic: 9. Myelodysplastic syndromes - Biology

Keyword(s): MDS, Hypomethylation, histone deacetylase inhibitor, Chromatin structure

A MULTICENTER, OPEN-LABEL, PHASE I CLINICAL STUDY: SAFETY, EFFICACY, AND PHARMACOKINETICS OF ORAL RIGOSERTIB IN JAPANESE PATIENTS WITH RECURRENT/RELAPSED OR REFRACTORY MYELODYSPLASTIC SYNDROMES

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Background

Rigosertib, a novel phosphoinositide 3 kinase pathway inhibitor, induces G2/M arrest leading to the apoptosis of cancer cells and myeloblasts and is safe for and well tolerated by pts with low, intermediate-1, intermediate-2, or high-risk myelodysplastic syndromes (MDS).

Aims

The aims of the study were to assess the safety, efficacy, and pharmacokinetics of oral rigosertib and to determine the recommended dose (RD) for a Phase II clinical study in Japanese pts with recurrent/relapsed or refractory MDS.

Methods

We conducted a multicenter, open-label, Phase I clinical study of oral rigosertib. The key eligibility criteria were as follows: recurrent/relapsed or refractory MDS; age: 20 or older; ECOG PS of 0 to 2; and no major organ dysfunctions. Rigosertib (280 and 560 mg BID) was administered orally in one 21-day cycle (up to cycle 6) that consisted of the 14-day, twice-daily, oral administration term, followed by 7-day monitoring. The primary endpoint was dose-limiting toxicity (DLT). The secondary endpoints were 1) safety as assessed with adverse events (AEs) and laboratory results, 2) efficacy as assessed with the International Working Group 2006 criteria, and 3) pharmacokinetics.

Results

Between March 2013 and November 2014, 6 male and 3 female pts (median age: 70; range 52-80) were enrolled. ECOG PS was 0 in 7 pts and was 1 in 2 pts, and 3 and 6 pts were eventually assigned to the 280 and 560 mg BID arms, respectively. According to the FAB classification, 4, 2, 2, and 1 pts were categorized to RAEB, RARS, RA, and RAEB-t, respectively. The prognostic factor according to IPSS was Int-1 risk in 4 pts (1 and 3 pts in the 280 and 560 mg BID arms, respectively) and was Int-2 in 5 pts (2 and 3 pts in the 280 and 560 mg BID arms, respectively). DLT occurred in 1 pt in the 280 mg BID arm and in 2 pts in the 560 mg BID arm: the former

consisted of type 2 diabetes and grade 4 delirium, and the latter grade 5 urinary tract infection and grade 3 prolonged QT interval. Therefore, the RD for a Phase II clinical study in Japanese pts was determined to be 560 mg BID. On day 11 of treatment, 1 pt in the 560 mg BID arm died of grade 5 urinary infection whose relationship with the investigational drug was rated to “Definite”. The presumed cause of death for this patient was septic shock caused by urinary tract infection. The mean counts of leukocytes, neutrophils, lymphocytes, and reticulocytes in the 280 mg BID arm did not decrease along with increases in the number of cycles delivered but decreased slightly in the 560 mg BID arm. Any changes of note were not found in other hematological items. One case of grade 3 neutropenia developed in the 280 mg BID arm, and 1 case each of grade 3 laboratory abnormalities—increased alanine aminotransferase, increased aspartate aminotransferase, prolonged QT interval, neutropenia, and decreased hemoglobin—occurred in the 560 BID arm. The hematological remission rate was 11.1% (1 marrow CR; 1/9 pts), and the hematological improvement rate was 11.1% (1 HI-P; 1/9 pts). Among the PK parameters, inter-individual variability was observed in the C_{max} and AUC. However, changes suggesting the accumulation of rigosertib during repeated oral administration (e.g., consistent increases in the C_{max} and AUC) were not found.

Conclusion

The present chemotherapy regimen of oral rigosertib was well tolerated. Our study indicates that the RD for a Phase II clinical study is 560 mg BID in Japanese patients with recurrent/relapsed or refractory MDS.

Session topic: 10. Myelodysplastic syndromes - Clinical

Keyword(s): Phase I, Pharmacokinetic, MDS, Clinical Trial

SAFETY, EFFICACY, AND PHARMACOKINETICS OF INTRAVENOUS RIGOSERTIB IN JAPANESE PATIENTS WITH RECURRENT/RELAPSED OR REFRACTORY MYELODYSPLASTIC SYNDROMES (MDS): A MULTICENTER, OPEN-LABEL, PHASE I STUDY

Author(s):
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Abstract: PB1919

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Background

Rigosertib, a novel phosphoinositide 3/polo-like kinase pathway inhibitor, selectively induces the apoptosis of cancer cells and is safe and well tolerated in pts with recurrent/relapsed or refractory MDS.

Aims

We conducted a multicenter, open-label, Phase I study of intravenous rigosertib to evaluate its safety, efficacy, and pharmacokinetics and to determine the recommended dose (RD) for Japanese pts.

Methods

The key eligibility criteria were as follows: recurrent/relapsed or refractory MDS; age: 20 or older; FAB classification (RA, RARS, RAEB, RABE-t, and CMML), excepting patients at IPSS low- or Int-1 risk with respect to RA; ECOG PS of 0 to 2; no major organ dysfunction; and

written informed consent. Rigosertib (1,200 and 1,800 mg daily) was administered intravenously for 72 h, followed by 11-day monitoring in one 14-day cycle. The primary endpoint was dose-limiting toxicity (DLT). The secondary endpoints were 1) safety as assessed with adverse events (AEs) and laboratory results; 2) efficacy as assessed with the International Working Group 2006 criteria; and 3) pharmacokinetics.

Results

Between June 2012 and February 2015, 7 male and 2 female pts (median age: 70; range: 63-84) were enrolled, and 3 and 6 pts were eventually assigned to the 1,200 and 1,800 mg arms, respectively. According to the FAB classification, 6, 2, and 1 pts were categorized to RAEB, RAEB-t, and RA, respectively. There were 3 pts each in the IPSS Int-1, Int-2, and high-risk groups, with 1 and 2 pts in each risk group in the 1,200 and 1,800 mg arms, respectively. The median numbers of delivered cycles in the 1,200 and 1,800 mg arms were 4 (2 to 4) and 2 (1 to 8), respectively. DLT occurred not in the 1,200 mg arm but in the 1,800 mg arm: 5 episodes of ≥grade 3 nonhematologic toxicities in 2 pts. One pt developed 2 episodes of sepsis and meningitis, and the other 3 episodes of hypochloremia, pustular rash, and hyponatremia. Thus, 2 among 6 pts in the 1,800 mg arm developed DLT, which led us to conclude that 1,800 mg/day is the RD for Japanese pts. No deaths occurred during the study period. However, 5 pts died during follow-up, 4 of whom died from primary disease progression. Furthermore, 1 pt died of grade 5 bacterial pneumonitis that was rated to “Unrelated”. In the 1,200 mg arm, 2 cases each of grade 3/4 thrombocytopenia, grade 4 neutropenia, and grade 3/4 leukopenia, as well as 1 case of grade 3 lymphopenia developed. In the 1,800 mg arm, 3 cases of grade 3/4 leukopenia, 2 cases each of grade 3 CD4 lymphopenia, grade 4 thrombocytopenia, and grade 3/4 neutropenia, as well as 1 case each of grade 4 lymphopenia, increased C-reactive protein, erythropenia, and hypochloremia developed. Three cases of SAEs, including grade 4 meningitis, grade 4 sepsis, and grade 3 catheter-related infection, developed in the 1,800 mg arm. Stable disease was obtained in 2 pts in the 1,800 mg arm. Hematological remission, hematological improvement, and cytogenetic response were not obtained in the two arms. The C_{max} values in the 1,200 and 1,800 mg arms were 5.99±1.50 and 6.74±2.39 μg/mL, respectively. The $AUC_{0-\infty}$ values were 314.6±142.7 and 324.8±83.9 μg × hr/mL, respectively.

Conclusion

This Phase I study showed that intravenous rigosertib (1,800 mg daily) for consecutive 72 h was well tolerated, indicating that this is the RD for Japanese pts with MDS similar to a Phase III study in the U.S. Based on these clinical outcomes, Japanese pts with MDS are participating in a global randomized Phase III study to compare rigosertib with physicians’ choice of treatment.

Session topic: 10. Myelodysplastic syndromes - Clinical

Keyword(s): Phase I, Pharmacokinetic, MDS, Clinical Trial