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A Pilot Trial of Lirilumab with or without Azacitidine for patients with Myelodysplastic Syndrome

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Abstract

We report the results of a prospective trial of lirilumab in patients with myelodysplastic syndrome(MDS). A total of 10 patients included. Higher-risk patients received lirilumab plus azacitidine, lower-risk received single agent lirilumab. Two patients achieved CR and 5 achieved marrow CR. Although the small sample size precludes definitive conclusions, the results of this study indicate the efficacy and safety of lirilumab in MDS.

Background—Enhancement of NK cell activity by blocking interactions between killer immunoglobulin-like receptors (KIR) and HLA molecules can improve outcomes in myeloid malignancies. Lirilumab is a human IgG4 monoclonal antibody that blocks KIR/HLA-C interaction. We designed a study to evaluate the safety and efficacy of lirilumab as a single-agent and in combination with azacitidine in patients with myelodysplastic syndrome(MDS).

Methods—Adult patients with MDS who had not received prior hypomethylating-agent included. Lower-risk MDS patients received single agent lirilumab (3mg/kg); higher-risk patients received azacitidine (75mg/m2/day for 7-days) in combination with lirilumab (3mg/kg, on day-7), 28-day cycle. Responses were evaluated according to IWG-2006 criteria.

Results—A total of 10 patients including 8 with higher and 2 with lower-risk enrolled. The median age was 70 years (50-84) and 40% had complex cytogenetics. Baseline molecular mutations included TP53 (n=5), TET2 (n=3) and NRAS (n=2). Patients received a median of 4 (2-13) and 9 (5-14) cycles of treatment with azacitidine plus lirilumab and single-agent lirilumab, respectively. Two patients achieved complete remission (CR), 5 marrow CR and 3 had stable

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Authorship Contributions

FFY and GGM wrote the manuscript. All authors contributed substantially to the conception, acquisition, analysis, and interpretation of the data for the work and approved the final approval of the version to be published.

Disclosure

The authors have stated that they have no conflicts of interest.

disease. The median EFS for the entire cohort was 8 months (95%CI, 4 months to not reached), and the median OS has not yet been reached. Five patients experienced 8 episodes of grade >3 adverse events attributable to study drug, with the most frequent being infection or neutropenic fever (75%).

Conclusion—Lirilumab either as a single as well as in combination with azacitidine has clinical activity in MDS. Further studies are needed to confirm our findings.

Keywords

Myelodysplastic syndrome; anti-KIR therapy; natural killer cells; azacitidine; lirilumab

INTRODUCTION

Myelodysplastic syndrome (MDS) consists of a heterogeneous group of myeloid malignancies characterized by bone marrow failure and increased risk of transformation to acute myelogenous leukemia (AML)[1, 2]. The outcome of patients with MDS is very variable with median survival ranging from over 5 years to less than 6 months[2]. At present, allogeneic hematopoietic cell transplantation (HSCT) is the only treatment that can induce long-term remissions[3, 4]. Such therapy, however, is not applicable to most patients, since the median age at diagnosis exceeds 70 years. The standard frontline therapy for most patients with higher risk MDS is a hypomethylating agent (HMA) such as azacitidine or decitabine[5, 6]. Although HMAs have significant activity in MDS and have been shown to improve survival, majority of patients will either not respond to HMA or lose their response to therapy[7, 8]. There is an urgent need to develop new theraupeutic approaches for the patients with MDS.

Natural killer (NK) cells are essential components of the innate immune system and play a critical role in host immunity against various malignancies, including leukemias [9,10,11]. NK cell function, including cytotoxicity and cytokine release, is governed by a balance between signals received from inhibitory receptors, notably the killer immunoglobulin-like receptors (KIRs) and activating receptors[12]. Several groups have reported on the expression of KIR ligands and receptors in myeloid leukemias[13–15]. Our group recently reported an important influence of activating KIR gene content on progression-free survival in MDS, pointing to a role for NK cells in the immune surveillance of MDS[16].

Lirilumab (IPH2102/BMS-986015) is a fully humanized IgG4 monoclonal antibody that is designed to block the interaction between KIR2DL1/L2/L3 inhibitory receptors and their ligands. By blocking the KIR/HLA-C interaction, it lowers the threshold for activation of NK cells, without directly activating NK cells[17]. Once activated, NK cells release preformed cytotoxic granules into the target cell leading to direct killing of cancer cells. The concurrent release of cytokines and chemokines also results in a micro-environmental milieu that recruits other immune cells[17, 18].

The anti-tumor activity of lirilumab has been demonstrated in xenograft mouse models of solid and hematological malignancies as well as in phase I and pilot phase II clinical trials[19–21]. We hypothesized that lirilumab either as a single agent or in combination with

azacitidine, could have clinical activity in patients with MDS. Therefore, we designed a pilot phase II study to determine the safety and efficacy of lirilumab alone, or in combination with azacitidine, in patients with MDS.

PATIENTS AND METHODS

This study was registered at clinicaltrial.gov as NCT02599649. The study was approved by the institutional review board.

Patients

Adult patients with MDS of any risk or chronic myelomonocytic leukemia (CMML), according to the French-American-British or World Health Organization classification were eligible for this study. The International Prognostic Scoring System (IPSS)[2] was used to classify both patients with MDS or CMML. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate organ function (creatinine, bilirubin, aspartate and alanine aminotransferase levels ≤2.5 times the upper limit of normal). Nursing and pregnant women were excluded. Other exclusions included active and uncontrolled infections, active invasive malignancy or New York Heart Association heart failure class III or IV. Patients could not have received any prior therapy with an immune cell modulating antibody or with HMAs. All patients signed informed consent according to institutional guidelines and in accordance with the Declaration of Helsinki.

Study Design and Treatment

This was a phase II, open label study designed to assess the safety, and efficacy of lirilumab as a single agent or in combination with azacitidine, in patients with MDS. Patients were assigned to 2 cohorts based on their IPSS[2] risk evaluation. Lower-risk MDS patients (low and intermediate-1 by IPSS) received single agent lirilumab at the dose of 3mg/kg in every 28 days. Higher-risk MDS patients (intermediate-2 and high by IPSS) received azacitidine at the dose of 75 mg/m^2 on days 1-7 with lirilumab 3 mg/kg on day 7, in a 28-day cycle. Dose modifications for grade 3-4 toxicities were allowed for azacitidine. Lirilumab dose modification was not allowed.

Efficacy and Safety

Patients were evaluated for clinical response with a bone marrow evaluation and complete blood count on day 28 of course 1 (+/− 3 days) and afterwards every 3 months or as indicated to document response or to decide on therapy administration. Response assessment was performed using the revised 2006 International Working Group (IWG) criteria[22]. Event-free survival (EFS) was defined as the time between the start of therapy and the date of lack of response, loss of response, transformation to AML, or death, whichever occurred first. Overall survival (OS) was defined as the time between the start of therapy and death. Patients who were alive at the last follow-up date were censored in survival analysis. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse events (version 4.0).

Statistical Considerations

A sample size of 20 patients for each cohort was planned. The efficacy and safety analysis included all subjects who completed ≥2 cycles of therapy and at least 1 follow-up assessment. Categorical variables were compared by using Fisher's exact test and continuous variables were compared by using one-way analysis of variance. Survival probabilities were calculated by using the Kaplan-Meier method.

RESULTS

Patient characteristics

In total, 10 patients including 8 with higher-risk and 2 with lower-risk, were enrolled between April 2016 and June 2017 (supplemental Table 1). Baseline demographics and disease characteristics are summarized in Table 1. The median age was 70 years (range, 50-84) and 70% were male. The majority of patients had MDS (n=9, 90%) and 1 had CMML (10%). Seven patients (70%) had 2-3 cytopenias and 5 patients (50%) were transfusion dependent at enrollment. On chromosomal analysis, 5 patients had diploid karyotype (50%), 4 had complex karyotype (40%) and 1 had del (5q) plus del (20q). One patient had received prior therapy for MDS with lenalidomide. All patients had baseline targeted next-generation sequencing (supplemental document). A total of 8 patients (80%) had at least 1 detectable mutation. The most frequently identified mutations included TP53 (n=5, 50%), TET2 (n=3, 30%)and NRAS (n=2, 20%).

Safety

In total 9 (90%) patients experienced at least 1 treatment emergent AEs. Drug related AEs were reported in all patients in the higher-risk and in 1 patient in the lower-risk cohort. Five patients (50%) experienced a total of 8 episodes of grade 3 AEs attributable to study drug, with the most frequent being infection or neutropenic fever (6 out of 8, 75%). Frequently reported AEs for both groups are summarized in Table 3. Treatment related AEs leading to azacitidine dose reductions occurred in 3 patients (38%). None of the patients discontinued the study treatment due to AEs.

Disease response

All patients received at least 2 cycles of treatment and were evaluable for response. Response to therapy and outcome in the total study group are shown in Table 2. The median duration of follow up was 9.5 months (range, 5-21 months). Higher-risk MDS patients received a median of 4 cycles (range, 2-13 cycles) of treatment with lirilumab in combination with azacitidine, and lower-risk patients received a median of 9 cycles (range, 5-14 cycles) of single agent lirilumab. Overall; 2 patients (20%) achieved CR (n=2, 25%; higher-risk cohort), 5 patients (50%) had marrow CR (n=4, 50% and n=1, 50% for higher-risk and lower-risk cohort, respectively) and 3 patients had stable disease (n=2, 25% and n=1, 50% for higher-risk and lower-risk cohort, respectively). The median time to best response was 3 months (range, 1-8 months). Additionally, 40% (4 out of 10, all of them in the higher-risk cohort) of the patients had hematologic improvement and 40% (2 out of 5; n=2, 50% for the higher-risk cohort) achieved complete cytogenetic response. Among the 5

patients with TP53 mutations at baseline, 3 were tested for mutation clearance and one found to have clearance of TP53 mutation, following 1 cycle of treatment with azacitidine and lirilumab. Of the patients who were transfusion dependent at baseline, 40% (2 out of 5; n=2, 50% or the higher-risk cohort) achieved transfusion independence.

Three of the responding patients in the higher-risk cohort subsequently underwent HSCT. The best responses at the time of transplantation were CR (n=2) and marrow CR (n=1). With a median follow up of 9 months following HSCT, all of the transplant recipients remained alive and were in CR.

At the time of analysis, 8 patients were removed from the study. In both treatment groups, the most common reason for study discontinuation was progressive disease (n=4, 40%; among them, 3 progressed to AML and 1 had MDS disease progression), followed by stem cell transplant (n=3, 30%). One patient was removed due to myocarditis with no clear etiology. Two patients, one from each treatment group, are still receiving study drug at the time of the analysis.

Survival

The median EFS for the entire cohort was 8 months (95%CI, 4 months to not reached), and the median OS has not yet been reached. At 1 year 70% of the patients are alive. In total, 3 deaths (30%) occurred during follow-up. All of deaths occurred more than 30 days after the last treatment on study and none of them were attributed to protocol therapy. The most common reason for death was disease progression.

DISCUSSION

To the best of our knowledge, the current study is the first clinical trial using lirilumab in patients with MDS. This study indicates that lirilumab either as a single agent or with azacitidine has clinical activity in patients with MDS. Overall, the CR plus mCR rate in this study was 70% and the median OS has not reached. The treatment was generally tolerated but was associated with relatively high rates of fever and infections that required supportive care.

Although available standard-of-care therapies like azacitidine have demonstrated an ability to improve the outcomes of patients with MDS[5, 6, 23], only a subset of patients responds to these treatments, and prognosis remains poor for patients who have failed to respond or relapsed[7, 24]. Therefore, there is a need for new therapies in MDS.

NK cells constitutively express inhibitory KIRs that bind to HLA class I molecules and prevent NK cell activation toward healthy autologous cells. Evidence in support of NK cell involvement in the anti-tumor response is derived from the hematopoietic cell transplant setting. In patients who underwent T cell-depleted haploidentical cell transplant, a KIR ligand-mismatched donor favored NK cell alloreactivity and was associated with improved relapse-free survival[25–26]. In addition, we recently reported an important role for NK cells and the activating KIR gene content in the immune surveillance of MDS[16]. Based on these

concepts, disrupting KIR-ligand interaction as a means to prevent inhibitory signaling in NK cells to augment the NK cell effect has been a topic of ongoing investigation.

Lirilumab is an anti-KIR antibody that was developed for the treatment of patients with hematologic and solid tumor malignancies. It has been tested in patients with AML who are in CR but ineligible for HSCT[20] and subsequently, in salvage setting in combination with azacitidine[21]. A randomized phase II confirmed the safety of lirilumab in such patients; however the study failed to demonstrate an improvement of relapse-free survival, the primary endpoint[27].

Ongoing clinical trials involving lirilumab mainly focus on identifying synergistic combinations particularly with immune checkpoint inhibitors, such as nivolumab and ipilumumab.

Initially, a sample size of 20 patients for each cohort (higher vs lower risk) was planned, but the enrollment was stopped following the sponsor's decision not to pursue development of lirilumab for myeloid malignancies. There were no safety issues leading to this decision. In the present study, 8 patients with higher-risk MDS received treatment with lirilumab in combination with azacitidine. Of these, 6 patients (75%) had objective response with 2 achieving complete cytogenetic response. Importantly, half of the patients in our study had TP53 mutation, which has been demonstrated to have a negative impact on outcomes in patients with MDS[28–30]. We also note that 3 of these patients proceeded to HSCT. HSCT remains the only currently available curative approach for patients with higher-risk MDS[3, 4]. However, outcomes depend on the tumor burden at the time of HSCT and patients with minimal disease at the time of HSCT have better long-term outcomes[31]. Therefore, the azacitidine-lirilumab combination could also serve as a bridge to potentially curative HSCT in eligible patients.

Of the lower-risk patients included in our study, 1 patient achieved mCR and continued with the study drug. The other patient had stable disease and had disease progression following 5 cycles of lirilumab therapy. Notably, that patient also had TP53 mutation.

It is important to mention that the present study is small, and that comparisons to studies of single agent azacitidine are not possible. The results of the current study are encouraging but need to be verified in larger studies.

In conclusion, the results of this study indicate the efficacy and safety of lirilumab in patients with MDS, especially in combination with azacitidine. Although the small sample size precludes definitive conclusions, these findings also indicate that the combination of NK checkpoint blockade with lirilumab and azacitidine may be useful as a bridge to HSCT in eligible patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice points

- Natural killer (NK) cells are essential components of the innate immune system and play a critical role in host immunity against various malignancies.
- NK cell function is governed by a balance between signals received from inhibitory receptors, notably the killer immunoglobulin-like receptors (KIRs) and activating receptors.
- Blockage of KIR receptors with a fully human monoclonal antibody is known to enhance NK-mediated lysis of tumor cells.
- Lirilumab is a fully humanized IgG4 monoclonal antibody that is designed to block the interaction between KIR2DL1/L2/L3 inhibitory receptors and their ligands.
- This is the first report of efficacy and safety with the anti-KIR lirilumab in patients with MDS.
- Our findings indicate that lirilumab is effective and well tolerated either as a single agent or in combination with AZA, in patients with MDS in the limited population studied.
- Based on these data, further evaluation of lirilumab in patients with MDS is warranted.

Table 1:

Patient Demographics and Baseline Characteristics

Variables	All patients, N=10	Azacitidine + Lirilumab, N=8	Lirilumab, N=2
Age, in years, median (range)	70 (50-84)	70 (50-84)	74 (71-77)
Gender, males, N (%)	7 (70)	6 (75)	1 (50)
ECOG performance status			
0	5 (50)	4 (50)	1 (50)
1	4 (40)	3 (38)	1 (50)
2	1 (10)	1 (12)	
IPSS risk group			
Intermediate-1	2 (20)	0	2 (100)
Intermediate-2	7 (70)	7 (88)	0
High	1 (10)	1 (12)	0
Laboratory values, median (range)			
Hemoglobin g/dl	9.1 (7-13)	9.2 (8-13)	7.9 (6.7-9)
WBC	2.6 (1.6-63)	2.6 (1.6-25)	32 (1.6-63)
ANC	2 (0.6-21)	2 (0.6-14)	10.7 (0.7-21)
Platelet count, 10^9/l	62 (7-237)	44 (7-237)	77 (71-83)
Peripheral blast %	0 (0-13)	0 (0-13)	0
Bone marrow blast %	11 (1-19)	13 (2-19)	4 (1-7)
LDH IU/mL	707 (311-1766)	707 (311-1689)	1077 (389-1766)
Next generation sequencing analysis, N (%)	10 (100)	8 (100)	2 (100)
Epigenetic regulators			
TET2	3 (30)	1 (12)	2 (100)
DNMT3A	1 (10)	1 (12)	0
Chromatin regulation			
ASXL1	1 (10)	0	1 (50)
Cell signalling			
JAK3	1 (10)	1 (12)	0
MPL	1 (10)	0	1 (50)
KRAS	1 (10)	1 (12)	0
NRAS	2 (20)	1 (12)	1 (50)
CBL	1 (10)	1 (12)	0
Tumor suppressor genes			
Tp53	5 (50)	4 (40)	1 (10)
Spliceosome components			
SRSF2	1 (10)	1 (12)	0
Others			
STAG2	1 (10)	1 (12)	0

Variables	All patients, N=10	Azacitidine + Lirilumab, N=8	Lirilumab, N=2
Cytogenetic classification *			
Good			
Normal	5 (50)	4 (50)	1 (50)
del(5q); del(20q)	1 (10)	0	1 (50)
Poor			
Complex	4 (40)	4 (50)	0
PCR based gene sequencing	10 (100)	8 (100)	2 (100)
FLT3-ITD	0	0	0
FLT3-TKD	0	0	0
CEBPA	0	0	0

Abbreviations: ECOG=eastern cooperative oncology group; IPSS=international prognostic scoring system; WBC=white blood cells; ANC=absolute neutrophil count; LDH=lactate dehydrogenase; PCR=polymerase chain reaction.

* Based on IPSS cytogenetic categories: Good (normal, -Y, del(5q), del(20q); Poor: chromosome 7 anomalies, complex (3 or more abnormalities); and Intermediate: all others

Table 2.

Summary of Best Overall Responses and Treatment Outcomes

Response	All patients, N=10	Azacitidine + Lirilumab, N=8	Lirilumab, N=2
Number of treatment cycles, median (range)	4 (2-14)	4 (2-13)	9 (5-14)
Best Overall Response, N (%)			
Complete remission	2 (20)	2 (25)	0
Partial remission	0	0	0
Marrow Complete remission	5 (50)	4 (50)	1 (50)
Stable disease	3 (30)	2 (25)	1 (50)
Failure	0	0	0
Cytogenetic response	2/5 (40)	2/4 (50)	0
Complete	2/5 (40)	2/4 (50)	0
Partial	0	0	0
Disease progression	0	0	0
Hematologic Improvement (HI)	4/10 (40)	4/8 (50)	0/2 (0)
HI-E	2/9 (22)	2/7 (29)	0/2 (0)
HI-P	3/8 (38)	3/6 (50)	0/2 (0)
HI-N	2/4 (50)	2/3 (70)	0/1 (0)

Abbreviations: HI-E=HI with erythroid response; HI-P=HI with platelet response; HI-N=HI with neutrophil response

Table 3.

Non-hematologic Adverse Events

	Grades 1-2, n (%)		Grade >3, n (%)	
Adverse Event*	**Azacitidine + Lirilumab (N=8)**	**Lirilumab (N=2)**	**Azacitidine + Lirilumab (N=8)**	**Lirilumab (N=2)**
Nausea	4 (50)			
Constipation	4 (50)			
Rash	3 (38)		1 (12)	
Infusion reaction	2 (25)			
Fatigue	1 (12)			
Pruritus	1 (12)			
Increased bilirubin	1 (12)		1 (12)	
Infections	1 (12)		3 (38)	1 (50)

*Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0)