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A phase I trial of the anti-KIR antibody IPH2101 and lenalidomide in patients with relapsed/refractory multiple myeloma

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Abstract

PURPOSE—Natural killer (NK) cells may play an important role in the immune response to multiple myeloma (MM); however, MM cells express killer immunoglobulin-like receptor (KIR) ligands to prevent NK cell cytotoxicity. Lenalidomide can expand and activate NK cells in parallel with its direct effects against MM; however, dexamethasone may impair these favorable immunomodulatory properties. IPH2101, a first-in-class anti-inhibitory KIR antibody, has acceptable safety and tolerability in MM as a single agent. The present work sought to characterize lenalidomide and IPH2101 as a novel, steroid-sparing, dual immune therapy for MM.

EXPERIMENTAL DESIGN—A phase I trial enrolled 15 patients in three cohorts. Lenalidomide was administered *per os* at 10mg on cohort 1 and 25mg on cohorts 2 and 3 days 1–21 on a 28-day cycle with IPH2101 given intravenously on day 1 of each cycle at 0.2 mg/kg on cohort 1, 1mg/kg on cohort 2, and 2mg/kg on cohort 3. No corticosteroids were utilized. The primary endpoint was safety, secondary endpoints included clinical activity, pharmacokinetics (PK) and pharmacodynamics (PD).

RESULTS—The biologic endpoint of full KIR occupancy was achieved across the IPH2101 dosing interval. PD and PK of IPH2101 with lenalidomide were similar to data from a prior single agent IPH2101 trial. Five serious adverse events (SAEs) were reported. Five objective responses occurred. No autoimmunity was seen.

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CONCLUSIONS—These findings suggest that lenalidomide in combination with anti-inhibitory KIR therapy warrants further investigation in MM as a steroid-sparing, dual immune therapy. This trial was registered at www.clinicaltrials.gov (reference: NCT01217203).

Keywords

Multiple myeloma; natural killer cells; anti-KIR therapy; lenalidomide

INTRODUCTION

Novel therapies including immunomodulating agents (e.g., thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib) have significantly improved patient outcomes with multiple myeloma (MM)(1). Immunomodulatory agents such as lenalidomide may exert anti-MM efficacy, in part, through expansion and activation of natural killer (NK) cells which have been shown to play an important role in the immune response against MM (2–9). However, MM cells utilize specific immunoevasive strategies to reduce NK cell recognition and cytotoxicity (10–14).

Presently, lenalidomide is administered in combination with dexamethasone which may attenuate its favorable immunomodulatory properties (15,16). Corticosteroids are the backbone of virtually every effective therapy for MM, yet these agents also confer substantial risk of toxicities (e.g., hypertension, glucose intolerance, osteoporosis, and psychiatric effects in addition to immune suppression). A prior study of lenalidomide plus high-dose dexamethasone (40 mg PO days 1–4, 9–12, and 17–20 on a 28-day cycle) versus lenalidomide plus low-dose dexamethasone (40 mg PO days 1, 8, 15, and 22 on a 28-day cycle) in newly diagnosed MM showed that although response rates were higher with high-dose dexamethasone, overall survival was superior and less toxicity was observed with low-dose dexamethasone (17). An effective lenalidomide combination therapy, devoid of corticosteroids, would represent a significant advance in the treatment options for MM (18).

IPH2101 (formerly 1–7F9) is a first-in-class, humanized IgG₄ monoclonal antibody against common inhibitory killer immunoglobulin-like receptors (KIRs) which disrupts inhibitory KIR-ligand interaction to promote NK cell recognition and lysis of tumor cells seeking to recapitulate the effects of KIR-ligand mismatch that mediate NK cell alloreactivity in haplo-identical allogeneic stem cell transplantation (19,20). MM cells upregulate surface expression of HLA class I molecules (which serve as inhibitory KIR ligands) making this receptor-ligand axis a provocative target for NK-cell mediated therapeutics (5). A single-agent, dose-escalation, phase I trial of IPH2101 in relapsed/refractory MM reached the biologic endpoint of full KIR blockade over dosing interval, with correlative evidence of NK cell activation and enhanced function, but without dose-limiting toxicity (21). In that trial, stable disease was observed in 34% of treated patients (21). Preclinical data suggest that the combination of lenalidomide and IPH2101 confer anti-MM effects through complementary mechanisms modulating the NK cell versus MM effect (22). With lenalidomide to augment NK cell function and IPH2101 to release NK cells from inhibition, the present phase I dose-escalation trial of this combination was conducted in patients with relapsed/refractory MM. No corticosteroids were utilized.

MATERIALS AND METHODS

Study objectives

The primary objective of the trial was to determine the safety and tolerability of IPH2101 in combination with lenalidomide by NCI CTC Version 4.0 of May, 2009. The secondary objectives were to evaluate: the anti-MM activity, the pharmacokinetics and pharmacodynamics of IPH2101 in combination with lenalidomide, and to confirm the absence of immunogenicity of IPH2101.

Study population

Adult patients (ages 18 – 80 years) with relapsed/refractory MM according to International Myeloma Working Group (IMWG) definition after one or two prior lines of treatment were eligible for inclusion with: measurable disease, Eastern Cooperative Oncology Group performance status of 0–2, adequate renal (calculated creatinine clearance ≥ 60 ml/min), hepatic (bilirubin $< 1.5 \times$ institutional upper limit of normal, ALT / AST $< 3 \times$ institutional upper limit of normal), and bone marrow function (absolute neutrophil count $> 1 \times 10^9 / l$ and platelet $\geq 75 \times 10^9 / l$ for patients with $< 50\%$ bone marrow plasma cells and $\geq 30 \times 10^9 / l$ for patients with $\geq 50\%$ bone marrow plasma cells). Eligibility also included meeting satisfactory conditions outlined in the mandatory RevAssist® program for lenalidomide dispensing. Patients could have had prior lenalidomide but had to have achieved at least partial response for 6 months and not have discontinued lenalidomide previously due to toxicity or intolerance. Patients with history of autoimmune disease, HIV, chronic hepatitis, or history of allogeneic transplantation were excluded. Concomitant use of corticosteroids was prohibited. The study was approved by Institutional Review Boards before initiation and was conducted in accordance with the Declaration of Helsinki. All subjects provided informed consent prior to participation.

Study design

IPH2101 was administered intravenously on day 1 of a 28-day cycle over three cohorts of escalating doses: 0.2 mg/kg (with 10 mg lenalidomide orally days 1–21), 0.2 mg/kg (with 25 mg lenalidomide), and 1 mg/kg (with 25 mg lenalidomide). A standard 3+3 trial design was utilized with dosing cohorts added sequentially following interim safety and tolerability data review.

Patients were to receive 4 cycles of IPH2101 and lenalidomide and were eligible for an additional 4 cycles pending safety, tolerability and evidence of clinical benefit. Thereafter, patients were maintained on single agent lenalidomide. Dose modifications of IPH2101 were not permitted. Dose modifications for lenalidomide-related grade 3 or 4 hematologic AEs followed standard dose adaptation rules. For other grade 4 adverse events related to lenalidomide, treatment was held and restarted at next lower dose following resolution of toxicity if trial continuation was considered in the patient's best interest by the treating physician.

Dose limiting toxicity (DLT) was defined as any of the following in cycle 1 of treatment: grade 4 neutropenia lasting ≥ 7 days or grade 3 neutropenia with fever $> 38^\circ\text{C}$, grade 4

thrombocytopenia for patients with baseline platelet count $75 \times 10^9 / l$ (or $< 10 \times 10^9 / l$, or with bleeding, for patients with baseline $> 50\%$ bone marrow plasma cells and platelet count $30-75 \times 10^9 / l$). Patients experiencing a lenalidomide related hematologic DLT were able to continue on trial if considered in the patient's best interest by the treating physician and if patient qualified for next cycle of therapy with dose reduction (however, the event was still counted towards establishment of a maximally tolerated dose). Any grade 3 non-hematologic toxicity possibly or probably related to the combination that did not resolve or decrease to grade 2 or less within 3 days was also considered a DLT.

Response criteria

Objective responses were assessed by uniform International Myeloma Working Group (IMWG) criteria and minor response by European Group for Blood and Marrow Transplant (EBMT) criteria. Time to event endpoints (time to progression, progression free survival and duration of response) were defined according to IMWG guidelines.

Correlative studies

Pharmacokinetics (PK) and pharmacodynamics (PD) were analyzed as described previously (21). PK and PD of IPH2101 were assessed in combination with lenalidomide and compared to historical data from a prior single agent IPH2101 trial to assess any effects of concomitant administration of lenalidomide on the PK and PD of IPH2101. Cytokine profiles and lymphocyte subsets were serially analyzed over the course of the trial as described previously (21).

Statistical considerations

Descriptive statistics were used to summarize continuous data and categorical data were summarized by number / percentage of events. Progression-free survival was calculated using the Kaplan-Meier method.

RESULTS

Patient characteristics

In total, 15 patients (10 male, 5 female; median age 60 years, range 39–76) were enrolled between February, 2011 and December, 2013 and received at least 1 dose of IPH2101 and lenalidomide. Cohorts 1 and 3 were expanded to $n = 6$ patients resulting from potential dose limiting toxicities (DLTs) described in detail below. There was an average of 3.5 years (range 1.25 – 10.1) from diagnosis to enrollment on the trial. Ten patients had one prior line of therapy, 5 patients had two prior lines. Twelve had had prior high-dose therapy with autologous stem cell transplantation. Ten had received prior lenalidomide (prior exposure to lenalidomide was mean of 6.8 ± 6.5 months, and time from lenalidomide exposure to first dose of IPH2101 and lenalidomide on study was average of 2 ± 1 year). Patient demographics, disease and prior treatment characteristics are summarized in Table 1.

Treatment, safety and toxicity

Eight patients (53%) completed 4 planned cycles of therapy. 5 patients (33%) completed 8 cycles of therapy of which, 4 went onto maintenance therapy. Four patients (27%) received reduced doses of lenalidomide, mainly related to neutropenia. In total, 46 treatment emergent adverse events (AEs) of grade 3/4 severity were observed in n = 8 patients and considered “possibly” or “probably” related to IPH2101 and/or lenalidomide (summarized in Table 2). Of 5 serious AEs, 3 were “possibly” or “probably” related to IPH2101 and/or lenalidomide. No patients permanently discontinued treatment for safety related to IPH2101.

Potential dose-limiting toxicities (DLTs) were experienced by one patient in cohort 1 and one patient in cohort 3. These two events were similar in nature and timing, characterized by fever and cytokine release on Cycle 1, Day 1 following administration of IPH2101 and lenalidomide. Both patients subsequently developed grade 4 leucopenia and neutropenia which resolved without growth factor support or other intervention within 72 hours. Cohorts 1 and 3 were both expanded without recurrence of the potential DLT. Both patients remained on study and did not experience similar reactions during subsequent cycles of therapy; however, neither experienced an objective response. Both patients with this DLT demonstrated profound increases in pro-inflammatory cytokines (IFN- γ , IL-6, TNF- α and MIP-1 β as shown in Figure 1) following infusion of IPH2101 as compared to other patients in the study. The trial was amended to include anti-pyretic and anti-histamine prophylaxis, and no further infusion-related reactions were observed.

After completion of the study, one patient developed therapy-related myelodysplasia. This patient had previously received lenalidomide / dexamethasone induction therapy followed by intravenous melphalan 200 mg/m² with autologous stem cell transplantation before relapsing and entering cohort 1. The patient received lenalidomide 10 mg / day during 28 months while on study with treatment interruptions transiently for neutropenia.

IPH2101 PK and PD are not affected by co-administration of lenalidomide

As in a prior single-agent trial, the dose of IPH2101 correlated with serum concentration over time (Figure 2A). KIR occupancy was consistent across the 28-day dosing interval for most patients at the 1 mg/kg dose of IPH2101 (Figure 2B). The administered dose of IPH2101 also correlated with the observed proportion of KIR occupancy (Figure 2C). A direct comparison of IPH2101 serum concentrations as a function of dose (Figure 2D) suggests that co-administration of lenalidomide did not significantly affect the PK of IPH2101 in the present study in comparison with data obtained in a prior single agent trial (21).

Immunomodulatory correlates of IPH2101 and lenalidomide

No statistically significant changes were observed in proportions of lymphocyte subsets or expression of markers of activation on lymphocytes over the course of the trial (data not shown).

Evaluation of clinical efficacy

Although safety and tolerability were the primary endpoints of the trial, patients were evaluated for best response to therapy. There were 5 objective responses (Table 3): 2 very good partial responses (VGPR) and 3 partial responses (PR); out of these, objective responses occurred in 3 patients who had received prior lenalidomide / dexamethasone. One patient achieved a minor response (MR) and 6 achieved stable disease. The median time to best response observed (VGPR, PR, or MR) was 2.8 cycles (range 0.9 – 4.8, Figure 3A). The median duration of response was 24 months (95% CI = 2.5 to not reached). The median progression free survival was also 24 months (95% CI = 2.5 to not reached, Figure 3B).

DISCUSSION

NK cells appear to play an important role in the immune response to MM; however the disease utilizes specific strategies to evade NK cell detection and cytotoxicity (23). Among these immunoevasive mechanisms, MM cells may increase expression of inhibitory KIR ligands as the disease progresses (5). KIR-ligand mismatch has been shown to be a potential determinant of outcome in allogeneic stem cell transplantation in MM as in other hematologic malignancies (20,24). Based on these concepts, disrupting KIR-ligand interaction as a means to prevent inhibitory signaling in NK cells to augment the NK cell versus MM effect has been a topic of ongoing investigation. An initial, single-agent, dose-escalation study showed acceptable safety and tolerability with the anti-inhibitory KIR antibody, IPH2101, in patients with MM achieving the biologic endpoint of full KIR occupancy over the dosing interval (21).

Lenalidomide exerts direct anti-MM effects but also appears to confer favorable immunomodulatory effects on NK cells (2–4). Although the addition of dexamethasone to lenalidomide appears to enhance direct anti-MM activity, dexamethasone also appears to suppress lenalidomide's favorable immunomodulatory mechanisms particularly on NK cell function (15,16). Thus, using lenalidomide as a means to augment NK cell number and function and IPH2101 to prevent inhibitory signaling, the present trial may be considered as the first “dual, innate immunotherapy” for MM.

Overall, the combination of lenalidomide and IPH2101 was well tolerated. Infusion-related events observed on cohorts 1 and 3 were abrogated by pre-medication with anti-pyretic and anti-histamine therapy. The PK and PD of IPH2101 did not appear to be affected by co-administration of lenalidomide and the pre-specified biologic endpoint of full KIR occupancy over the 28-day dosing interval was achieved. Objective responses were observed in 33.3% of patients with and without prior lenalidomide exposure, and median PFS was 24 months. A prior study characterizing lenalidomide as a single agent in relapsed/refractory MM demonstrated a relatively similar response rate (26%) to that observed in the present trial; however, median PFS was only 4.9 months with lenalidomide alone (25). Prior trials of lenalidomide plus high-dose dexamethasone in the relapsed/refractory setting showed a 60–61% response rate with median PFS of 11.1 months (26,27). It is important to note that the present study was small, and such comparisons to studies of lenalidomide alone or with dexamethasone are merely speculative in nature.

Therapeutic monoclonal antibodies (mAbs) such as IPH2101 comprise just one dimension (28) of the promising, rapidly expanding field of immunotherapy for MM which also includes NK- and T-cellular therapies (29,30), vaccines (30) and immunomodulating agents, among others. Tumor-directed mAbs (31,32) as well as effector cell-targeted mAbs (21,22,33) provide an opportunity for increasing precision with which to modulate immunity against MM, as well. The optimal combinations as well as the most appropriate clinical setting (e.g., smoldering, induction, maintenance, relapse) remain active areas of ongoing inquiry. The present data inform this process by demonstrating that the combination of anti-KIR blockade with IPH2101 as a release from inhibition with lenalidomide to augment NK cell function appears to be safe and tolerable with preliminary evidence of efficacy. These findings justify further research into combination immune therapies designed to complement one another in enhancing immunity against MM as a therapeutic strategy.

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Statement of Translational Relevance

In addition to directly inducing apoptosis of multiple myeloma (MM) cells, lenalidomide modulates expansion and activation of natural killer (NK) cells. NK cells appear to play an important role in the immune response to MM; however, MM cells utilize NK cell specific immunoevasive strategies, including expression of inhibitory killer immunoglobulin-like receptor (KIR) ligands that prevent NK cell recognition and lysis. IPH2101, a non-depleting, IgG₄ antibody against common inhibitory KIR, was shown to be safe and well tolerated agent in relapsed/refractory MM with evidence of disease stabilization in 34% of patients as a single agent. The present findings suggest that the use of lenalidomide for NK cell stimulation and IPH2101 to release NK cells from inhibitory signaling is safe, tolerable and associated with signs of clinical efficacy. These results justify further research into combinatory, innate immune therapy for MM devoid of corticosteroid use.

Figure 1.

Changes in pro-inflammatory cytokines observed in cycles 1 and 2. The 2 patients who experienced a potential DLT of clinically evident, infusion-related, cytokine release syndrome are marked ("*").

A.

B.

B.

Figure 3.

(A.) Serial changes in individual subject MM biomarkers per cohort. (B.) Progression free survival curve for enrolled subjects in the present trial.

Table 1

Patients (n=15) demographics, disease, and prior treatment characteristics

Demographics	Value
Sex, female, no. (%)	5 (33)
Median age, yr (range)	60 (39–76)
<i>Prior treatments, no of patients (%)</i>	
Corticosteroids	11 (73)
Anthracyclines	5 (33)
Alkylating agents	12 (80)
Bortezomib	11 (73)
Lenalidomide	10 (66)
Thalidomide	5 (33)
Other	4 (27)
Median time, diagnosis to enrollment, y (range)	3.5 (1.3 – 10.1)
International Staging System stage, no., %	
1	8 (53)
2	3 (20)
3	0 (0)
Unknown	4 (27)
Type of M-protein, no of patients (%)	
IgG	6 (40)
IgA	3 (20)
Light chain	6 (40)
Cytogenetics (available on n=11), %	
Standard risk	45
High risk	55

Table 2

Grade 3/4 AEs possibly/probably related to IPH2101 and/or lenalidomide

Category / Event:	Grade:	Events:	N:	Relationship to study agents:	
				IPH2101	lenalidomide
<i>Constitutional:</i>					
Cytokine release syndrome	3	1	1	1	
Infusion reaction	3	1	1	1	1
Febrile neutropenia	3	2	2	2	1
<i>Hematologic:</i>					
Neutropenia	3,4	23	7	9	20
Lymphopenia	3,4	15	3	7	13
Thrombocytopenia	3	1	1		1
<i>Infectious:</i>					
Eye infection	3	1	1		1
<i>Metabolic:</i>					
Lipase elevation	3	1		1	1
Hypophosphatemia	3	1		1	1

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Table 3

Overall best response to therapy

Response	Cohort*			total
	1	2	3	
Objective response:				
- VGPR	1	0	1	2 (13.3%)
- PR	1	1	1	3 (20%)
Minor response:	0	0	1	1 (6.7%)
Stable disease:	3	0	3	6 (40%)
Progressive disease:	1	2	0	3 (20%)

* Cohort 1: 0.2 mg/kg IPH2101+ 10 mg lenalidomide,
Cohort 2: 0.2 mg/kg IPH2101+ 25 mg lenalidomide
Cohort 3: 1 mg/kg IPH2101+ 25 mg lenalidomide