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Phase I study of the anti-CD74 monoclonal antibody milatuzumab (hLL1) in patients with previously treated B-cell lymphomas

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Abstract

Milatuzumab (hLL1), a humanized anti-CD74 monoclonal antibody, has activity in preclinical NHL models. We conducted a phase 1 trial in previously treated B-cell malignancies. Dose escalation included 4 planned dose levels (1.5, 4, 6, and 8 mg/kg) with milatuzumab given twice weekly for 6 weeks. After dose level 1, the schedule was changed to daily (Monday-Friday) for 10 days. Twenty-two patients were treated. The most common possibly-related toxicities were infusion reaction, anemia, lymphopenia, neutropenia, and thrombocytopenia. Three patients experienced dose-limiting toxicity (neutropenia, neutropenia, rash) at dose levels 1, 2, and 4 respectively. Eight patients had stable disease, with no objective responses. The serum half-life of milatuzumab was ~2 hours. In 7 patients, In-111 imaging showed no clear evidence of tumor targeting. The short half-life may reflect CD74 rapid internalization and presence on extratumoral tissues; this antigen sink must be overcome to capitalize on the promising preclinical activity of the drug.

Background

Therapeutic monoclonal antibodies have been a cornerstone in the management of B-cell non-Hodgkin lymphoma (NHL) treatment since the approval of the anti-CD20 antibody rituximab in 1997. Targeting of alternative cell surface antigens (e.g., surface immunoglobulin, CD22, CD30, CD52, CD80) and changes in the production of subsequent generations of anti-CD20 antibodies (e.g., humanization, glycosylation) have met with varying degrees of success but have generally supported the notion that novel antibodies might provide significant therapeutic benefits.¹

CD74, originally described as the cell surface-expressed epitope of the HLA class II-associated invariant chain, is expressed on the surface of normal B cells, T cells, antigen presenting cells, epithelial cells, and endothelial cells, and it plays a role in expression of the class II MHC, antigen loading, regulation of intramembrane proteolysis, and signaling by macrophage migration inhibitory factor (MIF).^{2,3} Its role in differentiation, maturation, proliferation, and survival of B cells, and its supraphysiological expression in B-cell

neoplasms suggest that it may be a good therapeutic target.^{4–6} Under normal circumstances, CD74 is only transiently expressed on the cell surface before being internalized and replaced by newly synthesized CD74.

Milatumuzumab is a humanized IgG1k anti-CD74 monoclonal antibody that demonstrated activity against multiple lymphoma cell lines in preclinical studies and was safely administered to patients with multiple myeloma.^{7,8} As a result of rapid internalization and re-expression of CD74 on the cell surface, up to 10⁷ molecules of milatumuzumab can be taken up by each cell in a 24-hour period.⁹ Milatumuzumab does not result in antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity. Rather, it appears to induce direct antiproliferative effects, suggesting possible additive and non-overlapping effects when combined with other therapeutic monoclonal antibodies.⁵ We report a phase I study of milatumuzumab in patients with previously treated B-cell NHL including chronic lymphocytic leukemia (CLL).

Methods

Study Design

This was a phase I trial with a standard 3+3 dose escalation design. The four planned dose levels of milatumuzumab were 1.5 mg/kg, 4 mg/kg, 6 mg/kg, and 8 mg/kg. Patients were initially separated into NHL and CLL cohorts due to concern for different rates of infusion reactions. The primary objective of the study was to determine maximum tolerated dose of milatumuzumab. Secondary objectives were to assess the toxicity profile and response rates. Additionally, we sought to assess serum pharmacokinetics of milatumuzumab, in vivo biodistribution of In-111 labeled milatumuzumab, and the presence of CD74 on tumor tissue.

Patient Eligibility

Patients with a histologically confirmed diagnosis of recurrent/progressive B-cell NHL or CLL who had received at least one prior chemotherapy regimen and at least one course of rituximab were eligible for the study. Additional requirements included measurable disease (tumor mass >1.5 cm in one dimension for NHL patients and WBC >5,000 in CLL patients), age >18 years, absolute granulocyte count >1500 cells/mm³, platelet count >100,000 cells/mm³, and creatinine <2 x upper limit of normal. Exclusion criteria included known central nervous system involvement, HIV disease, pregnant or nursing females, active treatment with other investigational drugs, known serum anti-human antibodies (HAHA), and life expectancy <3 months.

Treatment

Patients received milatumuzumab by intravenous infusion according to the schedules described below. Based on preclinical rationale, treatment in dose level 1 was administered twice weekly for six weeks (12 total doses). Due to an extremely short plasma half-life and lack of evidence of tumor targeting on nuclear medicine imaging, the protocol was amended to administer treatment daily (Monday-Friday) for two weeks (10 total doses) at subsequent dose levels. After two dose levels were completed with no difference in adverse events between patients with NHL and CLL, the cohorts were combined for the final two dose

levels. Premedication with acetaminophen and diphenhydramine was used before all infusions. After the first patient experienced a grade 2 infusion reaction associated with hypotension and vomiting following the first infusion and again with subsequent infusions premedication with dexamethasone was added as follows: 20 mg IV prior to day 1, 10 mg IV prior to day 2, and 4 mg IV prior to all subsequent infusions.

Toxicity

Toxicity was assessed according to standard CTCAE v3 criteria. Dose-limiting toxicity (DLT) was defined as any treatment-related non-hematologic Grade 3 or 4 toxicity, any Grade 3 or 4 thrombocytopenia or neutropenia, any Grade 2 autoimmune reactions, or Grade 2 allergic events of either asymptomatic bronchospasm or generalized urticaria. Patients who experienced DLT did not receive additional milatuzumab. Dose escalation was done by the standard 3+3 method. The trial started at dose level 1 (1.5 mg/kg/dose). Escalation occurred after 3 patients were treated without DLT according to the statistical plan. If 1 of 3 patients at a dose experienced DLT, then an additional 3 patients were treated at the same dose level before further escalation.

Response

Response was assessed according to standard International Working Group criteria for lymphoma¹⁰ and CLL¹¹.

Pharmacokinetics

For every infusion, blood samples of 5 mL were collected prior to the infusion, 2 hours from the start of the infusion, and 30 minutes following the infusion. After the first injections, blood samples were also taken at 1, 2, and 4 hours. After the last injection only, additional samples were collected on day 6 or 7, and day 13 or 14. Pharmacokinetic studies were performed by measurement of the amount of milatuzumab in the plasma by radioactivity (e.g., In-111 milatuzumab in injection #1) and by enzyme-linked immunosorbent assay (ELISA). The ELISA utilizes an anti-idiotypic antibody to milatuzumab to specifically capture it. Plasma samples for ELISA determination of milatuzumab were sent to the Center for Molecular Medicine and Immunology (Dr. Robert Sharkey, Belleville, New Jersey).

Biodistribution Imaging

At various time points with both infusion schedules and across all dose levels, In-111 labeled milatuzumab was injected to determine the biodistribution. No biodistribution studies were performed in the first patient of each cohort.

Biodistribution imaging studies were performed in selected patients twice during the treatment phase depending on the results of pharmacokinetic studies performed in previous patients in the same dose cohort. In the first dose level, In-111 milatuzumab IgG (~2 mg, 5.0 mCi) was infused on day 1 either prior to initiation of unlabeled milatuzumab or within 30 minutes of completion of the total prescribed dose of unlabeled milatuzumab. Anterior/posterior whole-body gamma camera images were taken post infusion at 2 hours. Up to three more scans took place between 24 and 120 hours post-infusion. Based on lack of evidence of tumor targeting in initial patients, and given the possibility that non-tumor-

related CD74 was binding the radiolabeled antibody, subsequent patients underwent injection of radiolabeled milatuzumab at later time points with the goal of exploring whether non-tumor-related CD74 could be blocked by unlabeled antibody.

All imaging studies were performed on appropriately qualified cameras so that quantitative data could be derived (i.e., to measure the amount of milatuzumab uptake in the tissues, as well as to calculate radiation doses to the organs and tumors). These images were correlated to CT scan findings, the current standard parameter in lymphoma tumor response criteria. The radiation-absorbed doses of In-111 milatuzumab were calculated using the MIRDose software program. For this study, a 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-conjugate of milatuzumab was provided by Immunomedics, Inc.

Results

Subjects

A total of 23 patients were enrolled (CLL=10, follicular=8, DLBCL=3, MCL=1, MZL=1). Patient characteristics are described in Table 1. One patient with CLL was removed before receiving any study treatment due to neutropenia. The median number of prior therapies was 5 and 11 patients were refractory to their most recent therapy.

Disposition

Ten patients (7 NHL, 3 CLL) were treated at dose level 1 (1.5 mg/kg twice weekly x 12 doses). Four patients with NHL received all planned treatments. Two patients were removed from study due to DLT (grade 4 neutropenia) after 1 and 2 infusions. A third patient was removed from study after 9 infusions due to disease progression. Two patients with CLL received all planned doses. One patient with CLL was removed from study after 9 infusions due to disease progression. Six patients (3 NHL, 3 CLL) were treated at dose level 2 (4 mg/kg daily Monday-Friday x 10 doses). All 6 subjects received all planned infusions. Three patients (2 CLL, 1 NHL) were treated at dose level 3 (6 mg/kg daily Monday-Friday x 10 doses) and received all planned infusions. Three patients (2 NHL, 1 CLL) were treated at dose level 4 (8 mg/kg daily Monday-Friday x 10 doses). One subject completed all planned infusions, one subject completed 9/10 infusions, and one subject was removed from study after 5 infusions due to DLT (grade 3 rash). The study was stopped at the highest planned dose level by the investigators based on limited evidence of clinical activity.

Toxicity

Treatment-emergent hematologic and non-hematologic toxicity (occurring in at least two subjects) independent of association are described in Tables 2 and 3, respectively. The most common possibly treatment-related toxicities of any grade included infusion reaction, anemia, lymphopenia, neutropenia, thrombocytopenia, hypocalcemia, herpes labialis, insomnia, hypoalbuminemia, and rash. Infusion reactions, including fever, rigors, nausea, vomiting, and hypertension were common but low grade. Although infusion reactions became less frequent/severe with subsequent infusions, dexamethasone was required prior to every dose or the infusion reactions worsened. Rash appeared to be more significant at higher dose levels. Insomnia and anxiety were likely related to chronic corticosteroid use.

The most common treatment-related grade 3–4 toxicities included neutropenia (9%), thrombocytopenia (5%), and rash (5%). Both patients that experienced rash were treated at dose level 4 and no rash was experienced at any other dose level. Three patients experienced dose-limiting toxicity: grade 3 rash (one patient with NHL at dose level 4) and grade 4 neutropenia (one patient with CLL and one patient with NHL treated at dose level 1).

Efficacy

Eight patients had stable disease following treatment but no patients achieved complete or partial response. Among patients with CLL, the WBC count fell from an average pre-treatment count of 91×10^9 cells/L to a nadir of 32×10^9 cells/L but the duration of clinical benefit (time to progression (TTP), death, or subsequent therapy) was short. The median TTP was 1 month, and only two patients had a TTP of 3 months, both treated at dose level 2 and both with relatively low risk disease (IPI 2 in one patient, Rai stage 2 in one patient).

Pharmacokinetics

Milatumzumab was cleared very quickly from the blood after every injection, regardless of injection sequence or dose (i.e., twice weekly or daily, dose level). The serum half-life of milatumzumab was ~2 hours with more than 90% of the product cleared by the next day. There was a linear increase in peak plasma concentration (C_{max}) found in the first sample at the end of the infusion on day 1 as a consequence of increase in dose level. Additionally, there was some evidence of a higher concentration in successive peak and/or trough values during the course of treatment, particularly at higher dose levels. However, there was little evidence that changing from the twice weekly to the daily schedule was able to achieve saturation of binding sites sufficient to result in significant accumulation of the antibody in the plasma. See Figure 1 for a representative example. In one CLL patient CLL with a baseline WBC count of 61×10^9 cells/L and a nadir WBC count of 3.2×10^9 cells/L, there was some evidence of accumulation, suggesting a possible decrease in milatumzumab binding sites though this observation was not universal.

Biodistribution

In the 7 patients that underwent biodistribution imaging, In-111 imaging showed rapid antibody clearance with localization to the spleen and liver but absence of uptake in sites of tumor-related adenopathy at any dose level. The apparent absence of tumor targeting was noted regardless of whether radiolabeled antibody was administered before or after administration of unlabeled antibody. Similar results were seen regardless of whether radiolabeled was administered on day 1 or day 6. (Figure 2).

Immunohistochemistry for CD74

Immunohistochemistry demonstrated strong expression of CD74 on all patient tumor tissue samples (NHL) and cell blocks (CLL) with no discernible difference between the histological subtypes.

Discussion

CD74 represents a rational target for therapeutic monoclonal antibodies due to its high expression on the surface of malignant B cells. Moreover the rapid internalization and re-expression of newly synthesized CD74 makes it an excellent target for antibody drug conjugates carrying a toxic payload. We found that single-agent, unconjugated milatuzumab could be safely administered to patients with previously treated B-cell malignancies and that aside from grade 1–2 infusion reactions there was no clear pattern of adverse reactions. Although we did not observe any clinical responses to milatuzumab in this clinical trial, there was some evidence of activity as demonstrated by a fall in the circulating white blood cell count observed in patients with chronic lymphocytic leukemia. Given the small patient numbers and the heterogeneity of patients treated at each dose level it is difficult to determine whether there might be a dose-response relationship. Unfortunately, the duration of benefit was quite limited, suggesting that alternative dosing strategies, combinations, or antibody drug conjugates might be required to capitalize on the potential positive aspects of the target antigen.

The results of this phase I trial are interesting for what they suggest: A large amount of CD74 exists in circulating blood or vascular tissue. This phenomenon has been referred to as an antigen sink in the context of other therapeutic monoclonal antibodies, and the term appears particularly relevant here. Evidence for the antigen sink is provided by the pharmacokinetic analysis, the biodistribution nuclear medicine studies, and the adverse event profile. We found that milatuzumab could be safely administered to patients with B-cell malignancies as long as appropriate premedication with dexamethasone was provided. Infusion reactions were the most commonly reported adverse event but were primarily grade 1–2 in severity. Unlike anti-CD20 antibodies, which result in fairly rapid depletion of circulating CD20-expressing B-lymphocytes, milatuzumab-related infusion reactions continued to occur beyond the first dose, resulting in an ongoing requirement for dexamethasone premedication. This is consistent with the presence of an antigen sink that either could not be saturated with the doses of antibody we were using or with rapid re-expression of the antigen on accessible tissues between infusions.

Interestingly, the apparent dose-dependency of rash, seen in two of three patients treated at the highest dose level, might suggest that the antigen sink could be saturated, at least transiently. The rash did not appear to be related to infusion reactions, which occurred at all dose levels. Nor was it likely related to hypersensitivity, which also might be expected to occur at all dose levels. One possible explanation is the presence of CD74 in the skin (perhaps in the context of cutaneous professional antigen presenting cells) that was accessible after partial saturation of the vascular antigen sink. Given small number of patients that were treated at the highest dose level and that experienced rash it will likely be necessary to wait for future trials to confirm our observation.

The biodistribution imaging failed to demonstrate localization of radiolabeled milatuzumab in involved lymph nodes despite the universal expression of CD74 on malignant cells from all patients. We found that whether radiolabeled milatuzumab was administered before or after the first dose of unlabeled milatuzumab there was no change in distribution imaging,

suggesting that unlabeled milatuzumab was not blocking CD74 on tumor cells but rather was insufficient to saturate the antigen sink present elsewhere. The localization to liver and spleen relative to adenopathy may be explained in several ways. One possibility is that the liver and spleen contain significantly more tumor cells than the lymph nodes and therefore took up the bulk of the radiolabeled antibody. Another possibility is that the liver and spleen contain a significant number of non-tumor cells expressing CD74 (e.g., antigen presenting cells). A third possibility, which is recognized in indium-111-labeled white blood cell scans, is the tropism of the indium-111 label in the reticuloendothelial system, potentially overwhelming the imaging of tumor-associated antigen.¹²

The linear increase in maximal plasma concentration (C_{max}) of milatuzumab seen across dose levels indicates that there are not an infinite number of easily accessible receptors and that antibody saturation may be feasible by increasing the dose further. However, because the concentration of antibody in the blood continued to decrease at an exceptionally fast rate despite the increases across dose levels, it is likely that following rapid internalization of antigen-antibody complexes, surface CD74 is re-expressed rather quickly, allowing for additional binding of more antibody, resulting in the sharp drop in the blood levels. Moreover, there is no evidence that a more frequent dosing regimen at the doses tested was able to achieve saturation of the binding sites responsible for the antibody's rapid removal from the plasma. These data are consistent with the observation that infusion reactions continued to occur with each infusion in the absence of sufficient premedication. Collectively with the biodistribution data, the PK data suggest that a significant antigen sink outside of the tumor cells exists.

In conclusion, despite the attractive properties of CD74 as a target, there remain considerable challenges to the development of therapeutic monoclonal antibodies. Specifically, the presence of an overwhelming antigen sink will need to be addressed. Strategies currently under evaluation to target CD74 include liposomal formulations¹³, antibody drug conjugates¹⁴, and bispecific antibodies¹⁵.

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Figure 1.

Pharmacokinetics. A representative example of the pharmacokinetic profile of milatuzumab in a patient with chronic lymphocytic leukemia treated daily (Monday-Friday) for 10 doses at 4 mg/kg. On day 1, plasma samples were collected prior to the infusion, 2 hours from the start of the infusion (30 minutes post-infusion; i.e., infusion time was 90 minutes), and at 1, 2, and 4 hours post-infusion. The C_{max} was seen in the 30 minute post-infusion sample. Additional PK samples were taken pre-infusion and 30 minutes following infusion on days 2–10 as well as days 14, 15, 16, and 18.

Figure 2. Biodistribution. Whole body gamma camera images from a patient with CLL and thoracic/abdominal adenopathy treated at dose level 2. In-111-DOTA-hLL1 IgG (~2 mg, 5.0 mCi) was injected 30 minutes after termination of the infusion of the total prescribed dose of unlabeled milatuzumab. The anterior/posterior images were taken 2 hours post infusion on day 6 (left two images) and day 10 (right two images).

Table 1

Patient Characteristics

Disease		Disease	
NHL	13	CLL	10
DLBCL	3		
FL	8		
MCL	1		
MZL	1		
Age		Age	
Median	61	Median	61
Range	53–76	Range	42–75
Ann Arbor Stage		Rai Stage	
I–II	11	1	2
III–IV	2	2	3
		3	1
		4	3
Elevated LDH	4		
WHO PS		WBC	
0	8	Median	61
1	4	Range	13–231
2	1		
IPI		ZAP-70positive	8
Low	3	CD38	4
Low-Int	7	17p–	1
High-Int	2	13q–	5
High	1	12+	1
		11q–	3
		6q–	0
Median # of prior treatments	4	Median # of prior treatments	6
Response to last treatment		Response to last treatment	
CR	2	CR	1
PR	3	PR	4
SD	1	SD	2
PD	6	PD	2

Table 2

Hematologic Toxicity

Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Total N (%)
Anemia	5 (22)	3 (13)	1 (4)	1 (4)	10 (43)
Thrombocytopenia	2 (9)	2 (9)	1 (4)	2 (9)	7 (30)
Neutropenia	2 (9)	2 (9)	1 (4)	1 (4)	6 (26)
Lymphopenia	1 (4)	2 (9)	1 (4)		4 (17)

Table 3

Non-Hematologic Toxicity

Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Total N (%)
Infusion reaction	10	4			14
Hypocalcemia	3 (13)	1 (4)	1 (4)		5 (22)
Fatigue	5 (22)				5 (22)
Infection	1 (4)	1 (4)	2 (9)		4 (17)
Hypoalbuminemia	4 (17)				4 (17)
Herpes labialis	3 (13)				3 (13)
Peripheral neuropathy	3 (13)				3 (13)
Hyperglycemia	3 (13)				3 (13)
Insomnia	3 (13)				3 (13)
Rash	1 (4)		1 (4)		2 (9)
Anxiety	2 (9)				2 (9)
Hyponatremia	2 (9)				2 (9)