Preliminary Tolerability Assessment of Naxitamab (Humanized anti-GD2 Monoclonal Antibody) Therapy in a Phase 2 Osteosarcoma Trial.

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Abstract

Background: The high prevalence of GD2 positivity in osteosarcoma (OS), and clinical activity of anti-GD2 therapy in pediatric solid tumors, prompted an ongoing phase 2 clinical trial of naxitamab (Hu3F8) in relapsed OS. Naxitamab is a fully humanized anti-GD2 monoclonal antibody with improved pharmacokinetics and increased cytotoxic activity. Early phase pediatric trials of naxitamab demonstrated tolerability and clinical activity. However, the toxicity and tolerability profiles of naxitamab therapy in comparably older OS patients remain undescribed.
Methods: OS patients with recurrent disease and in > 2nd complete remission were eligible for this single institution phase II trial of naxitamab in combination with GM-CSF. Patients must have adequate organ function and performance status, and could have previously received anti-GD2 therapy. Enrolled patients received naxitamab in the outpatient setting for 3 days augmented with GM-CSF constituting 1 cycle administered every 3-4 weeks for a maximum of 5 cycles.
Results: Twenty-seven patients have been enrolled to date with a median age at enrollment of 15.7 years (range 8.8-29.5). Grade 3/4 toxicities were observed in 81.5% (N=22 Grade 3, N=3 Grade 4) of patients but were all clinically manageable. Toxicities were as previously reported for naxitamab and included pain, hypo- and hypertension, fever, nausea, urticaria, and transaminase elevation. No long term or delayed toxicities have been observed. A majority of patients were able to receive therapy in an outpatient setting (78%, N=21). Human antihuman antibody (HAHA) positivity developed in 37% (N=10) of patients with 60% (N=6/10) occurring after 1 cycle of naxitamab, significantly higher than observed in neuroblastoma (9%).
Conclusions: Despite the higher incidence of treatment-related toxicity, naxitamab can be safely and tolerably administered to osteosarcoma patients in an outpatient setting and with a manageable toxicity profile. Determining the clinical impact of naxitamab on disease control and prognostic significance of HAHA positivity in OS is ongoing.

Background

The prognosis for relapsed or metastatic osteosarcoma (OS) remains poor, and there are limited therapies for relapsed or progressive disease[1]. GD-2, a membrane-bound adhesion molecule, is expressed in >80% of OS[2,3]. Anti-GD-2 based immunotherapy in the treatment of pediatric solid tumors, notably neuroblastoma (NB), has resulted in significant improvements in disease control and survival[4,5]. Pre-clinical studies suggest anti-GD-2 antibodies inhibit OS cell lines[6]. Naxitamab (Hu3F8) is a fully humanized monoclonal antibody directed against GD-2. In contrast to predecessor anti-GD-2 antibodies (14.G2a, dinutuximab/ch14.18), naxitamab is distinguished by improved pharmacokinetics resulting in increased target affinity, antibody-dependent (ADCC), complement mediated cytotoxicity (CMC), and direct cytotoxicity on tumor cells[7,8]. Granulocyte-macrophage colony stimulating factor (GM-CSF) has been effectively used as an adjuvant with monoclonal antibody therapy in minimal residual disease[4,5,9-11].

A single institution phase I study of naxitamab in combination with GM-CSF in relapsed/refractory NB (NCT01757626) at Memorial Sloan Kettering (MSK) has been completed[9]. No unanticipated, delayed or long-term toxic side effects were observed facilitating the safe administration of this combination in the outpatient setting. A Children's Oncology Group (COG) phase II trial (AOST1421, NCT02484443) of the chimeric anti-GD2 antibody dinutuximab (ch14.18) with GM-CSF in patients with recurrent osteosarcoma also demonstrated no excessive toxicities[12].

In two phase I protocols with naxitamab that OS patients were eligible (NCT01419834, NCT01662804), 40% of OS patients (N=2/5) developed HAHA, none with previous antibody exposure.

Given preclinical and early signals of transient disease control in OS patients treated on phase I studies of naxitamab, a phase II trial of naxitamab + GM-CSF is ongoing to evaluate the therapeutic role of this combination in relapsed OS. This unplanned interim analysis presents preliminary data describing the toxicity profile of naxitamab + GM-CSF and HAHA positivity rates in patients with relapsed OS rendered radiographically free of disease with surgery.

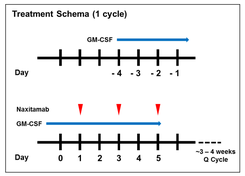
Methods

Overall Study Design: Phase II prospective, non-randomized clinical trial to assess the efficacy of naxitamab + GM-CSF in patients with recurrent OS who have been rendered radiographically free of disease following surgery. Accrual goal of 39 patients.

Inclusion Criteria:
- Patients with OS in ≥ 2nd complete remission
- Age > 1 year and ≤ 40 years
- Must be ≥ 3 weeks from last cytotoxic, immune, or radiation therapy. More than 1 week from major surgery
- Adequate performance status, organ and hematopoietic function

Exclusion Criteria:
- Patients with OS in 1st complete remission
- Presence of overt metastatic disease at any site
- Active life-threatening infection

Treatment Overview:
One cycle consists of 3 days of naxitamab (2.4 mg/kg/dose) given on Days 1, 3, and 5 with 10 days of GM-CSF (250 mcg/m²/day for Days -4 to Day 0, and increased to 500 mcg/m²/day for Days 1 - 5). Cycles are repeated at ~3-4 week intervals for a maximum of 5 cycles. Naxitamab is administered intravenously (IV) through a peripheral or centrally-inserted venous catheter and given over ~30 minutes.



Pretreatment medications are administered to mitigate pain and allergic reactions as per institutional guidelines. HAHA titers are obtained 10 days after the last dose of naxitamab. If HAHA titer becomes positive (defined as >1300 Elisa units/mL), cycles are deferred until HAHA levels are negative. Repeat HAHA levels are done every 2-4 weeks from positive testing. No simultaneous anti-cancer therapy is permitted while on study. GM-CSF is held if ANC >20,000/uL.

Primary Objective: Determine the event-free survival (EFS) at 12 months from the time of study enrollment for all patients.

Secondary Objectives:
- Determine overall survival from the time of study entry for all patients
- Determine time to recurrence from study entry for all patients
- Describe the toxicities associated with protocol therapy

Exploratory Objectives: Estimate the prevalence of HAHA positivity for treated patients.

Disease Monitoring: Pre-treatment scans including CT of the chest, CT or MRI of the primary site (if clinically indicated or appropriate), and bone scan or PET imaging are performed. On therapy imaging will be performed prior to the 3rd cycle, after the last dose of naxitamab in the 5th cycle, followed by off therapy surveillance imaging.

Toxicity Monitoring:
All observed adverse events are recorded for Cycle 1. After Cycle 1, only Grade 2 unexpected adverse events considered possibly, probably, or definitely related to protocol therapy and adverse events >/= Grade 3 are recorded. Adverse events are graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).

Results

A total of 27 patients have been enrolled to date and evaluable for toxicity (**Table 1**). All patients received conventional MAP (Methotrexate/ Adriamycin/cisPlatin) chemotherapy followed by surgical resection of tumor. The median age at enrollment is 15.7 years (range 8.8 – 29.5 years) with a majority of patients initially presenting with localized disease, but experiencing subsequent distant pulmonary relapse. In contrast to prior OS studies evaluating adjuvant therapy in relapsed disease (NCT00066365, NCT01757626), this study allows enrollment of patients with extra-pulmonary recurrence as long as the disease has been fully resected or demonstrated to no longer represent active disease.

Table 1. Patient Characteristics

Current Enrollment	27
Gender	
Male	19 (70%)
Female	8 (30%)
Race	
White	19 (70%)
Black	3 (11%)
Asian	2 (7 %)
Other	1 (5%)
Not Reported/Refused to Answer	2 (7%)
Age at Initial Diagnosis (Years)	
Mean	14.4
Median	13.7
Range	7.1 - 27.9
Age at Enrollment (Years)	
Mean	17.1
Median	15.7
Range	8.8 - 29.5
Extent of Disease at Diagnosis	
Localized	20 (74%)
Metastatic	7 (26%)
Site of Relapse	
Unilateral Lung	14 (52%)
Bilateral Lung	7 (26%)
Primary Site/Local Recurrence	3 (11%)
Non-Lung Distant Recurrence	3 (11%)
Prior Therapy	
Chemotherapy	27 (100%)
Surgery	27 (100%)
Radiation	2 (7%)

Results

We observed Grade 3 toxicity in a larger proportion of patients (81%) and Grade 4 in 3 patients (11%). However, all Grade 3 events were clinically manageable and did not generally require hospitalization. Three patients were withdrawn from study for toxicity (recurrent blood pressure lability, severe pain and fevers) after receipt of 1 – 3 cycles of naxitamab. Although Grade 3-4 toxicities did not appear to occur with greater frequency in older patients enrolled on study (median age with Grade 3-4 toxicity 16.5 years old), patients who required hospitalization for treatment-related adverse events (for blood pressure management and monitoring) were older (median age of hospitalized patients 20.9 years old). A summary of adverse events related to therapy are summarized in **Table 2**, and specific toxicities detailed in **Table 3**. No long-term or delayed toxicities and no deaths related to therapy have been observed to date. A majority of patients received all protocol therapy in an outpatient setting (78%, N=21) supporting the feasibility of therapy administration in an outpatient setting.

HAHA positivity results in therapy delay. We observed a higher rate of HAHA positivity following Cycle 1 (37%, N=10/27), a rate higher than previously described for NB patients treated with naxitamab (9%)[9]. The prognostic significance of HAHA positivity in OS remains unclear. HAHA positivity rates are summarized in **Table 4**.

Table 2. Summary of Adverse Events Related to Therapy

Total Number of Adverse Events	218
Grade 1	97
Grade 2	71
Grade 3	47
Grade 4	3
Grade 1-2	168
Grade 3-4	50
Patients Evaluable for Toxicity	27 (100%)
# Patients with Grade 3 Tox	22 (81%)
# Patients with Grade 4 Tox	3 (11%)
# Patients with No Grade 3-4 Tox	5 (19%)
Mean age with Grade 3-4 Tox (Years)	16.9
Median age with Grade 3-4 Tox (Years)	16.5
Mean Age with Grade 4 Tox	19.2
Median Age with Grade 4 Tox	15.2
Mean Age with No Tox (Years)	18.2
Median Age with No Tox (Years)	14.8
Mean Age of Hospitalized Pts (Years)	21.9
Median Age of Hospitalized Pts (Years)	20.9

Abbreviations: Pts: Patients, Tox: Toxicity, # or No: Number

Table 3. Treatment-Related Toxicities*

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Abdominal Pain	2	4		
Acute Respiratory Distress Syndrome				1
Alanine Aminotransferase (ALT) Increase	2			
Alkaline Phosphatase Increase		1		
Allergic Reaction	1	2	1	
Amylase Increase	2			
Anaphylaxis			1	
Anemia	3	1		
Anorexia		1		
Anxiety	1	2		
Apnea			1	
Back Pain	1			
Blurred Vision		1		
Chills			1	
Constipation	2	3		
Cough	1	2		
Depression	1			
Diarrhea	2	1		
Dyspepsia		1		
Dyspnea		7	1	
Edema - Face	1			
Erythema Multiforme	1			
Fatigue	1	3		
Fever	7	4	1	
Headache	1			
Hot Flashes	1			
Hyperglycemia	2			1
Hyperkalemia	1			
Hypermagnesemia			1	
Hypernatremia	1			
Hypertension		2	5	
Hypoalbuminemia	1			
Hypocalcemia		2	1	
Hypokalemia				1
Hypomagnesemia	2			
Hyponatremia			2	
Hypophosphatemia	1	2	1	
Hypotension	1	2	7	
Hypoxia			1	
Injection Site Reaction	2			
INR Increased		1		
Irritability		1		
Laryngospasm		1		
Lethargy		1		
Lipase Increase		1	1	
Lymphocyte Decrease	1	1	2	
Myalgia	1			
Mydriasis - Bilateral	1	1		
Nausea	4	4	1	
Neutrophil Decrease		1	1	
Non-cardiac Chest Pain	1	1		
Pain	27	7	9	
Pain in Extremity	1	1		
Pancreatitis			1	
Paresthesia		1		
Peripheral Motor Neuropathy	1			
Peripheral Sensory Neuropathy	1	1		
Platelet Decrease	1			
Poor Oral Intake	1			
Pruritus	3			
Rash Maculopapular			1	
Sinus Tachycardia	1	1	1	
Stridor			1	
Swollen Lip		1		
Urinary Urgency	1			
Urticaria	5	2	2	
Vomiting	4	1	2	
Wheezing	2	2		
WBC Decrease			1	

* Number of occurrences for each toxicity is listed by toxicity grade.

Table 4. Development of HAHA

Total Number of HAHA Positivity	10 (37%)
HAHA Positivity after Cycle 1	6
Mean # of Cycles Prior to HAHA Positivity	1.6
Median # of Cycles Prior to HAHA Positivity	1

Abbreviations: HAHA: Human anti-human antibody, #: Number

Conclusions

Naxitamab in combination with GM-CSF can be safely administered in an outpatient setting despite the incidence of adverse effects associated with therapy. No long term or unanticipated toxicities were observed. A higher prevalence of HAHA positivity has been observed in our OS patient cohort and its prognostic significance remains unclear. The clinical impact of naxitamab + GM-CSF on disease control in relapsed osteosarcoma is ongoing with future plans to expand enrollment of patients at additional centers in the US.

Disclosure

MSK has institutional financial interests related to this research in the form of intellectual property rights and equity interests in Y-mAbs Therapeutics, the company licensing the intellectual property from MSK. The authors of this study have no financial interest in Y-mAbs Therapeutics or other conflicts to disclose as relates to this study.

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