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Phase 1b Study of IGF-Methotrexate Conjugate in the Treatment of High-grade Myelodysplastic Syndromes

HASSAN B. ALKHATEEB[1], MRINAL M. PATNAIK[1], AREF AL-KALI[1], DARCI L. ZBLEWSKI[1], SAMANTHA WALLERICH[1], HUGH MCTAVISH[2] and ARKADIUSZ Z. DUDEK[2,3]

[1]*Department of Medicine, Division of Hematology and Oncology, Mayo Clinic, Rochester, MN, U.S.A.;*
[2]*IGF Oncology, LLC, Saint Paul, MN, U.S.A.;*
[3]*Regions Cancer Care Center, HealthPartners Institute, Minneapolis, MN, U.S.A.*

Abstract. *Background/Aim: The insulin-like growth factor type 1 receptor (IGF-1R) is overexpressed in myelodysplastic syndrome (MDS) cells, and 765IGF-Methotrexate (IGF-MTX) is a conjugate of methotrexate and a variant of insulin-like growth factor-1 (IGF-1) designed to selectively target cancer cells through binding to IGF-1R. The aim of this study was to determine whether IGF-MTX would be effective to treat MDS. Patients and Methods: In this phase I clinical trial, two patients with high grade MDS or oligoblastic acute myeloid leukemia (O-AML) that had failed standard therapy were treated with IGF-MTX. Results: No dose-limiting toxicity was observed. Both patients had stable or improved cell counts and CD34+ myelodysplastic cell counts and exceeded their life expectancy (both alive at 1.9 years despite a life expectancy of less than 6 months). Bone marrow blast counts decreased from 22% to 5% in one patient, and from 17% to 16% in the other. Conclusion: In conclusion, IGF-MTX at 0.20 μM equivalents per kg was well tolerated, caused no cytopenia, and produced stable disease and extension of life.*

Myelodysplastic syndrome (MDS) is a heterogenous hematological neoplasm with limited treatment options and with variable clinical outcomes. The Revised International Prognostic Scoring System (IPSS-R) defines five risk groups from very low to very high with median overall survival (OS) ranging from 10 years to only 14 months, respectively (1). For eligible individuals with high-grade MDS, allogeneic stem cell transplant is a goal and bridging with hypomethylating agent therapy is commonly used. For transplant-ineligible patients, hypomethylating agents are the only available treatment option. After failure of hypomethylating agents to control disease progression to worsening cytopenias or acute myeloid leukemia (AML), there is no standard therapy (2). Median survival after progression on hypomethylating agents is less than 6 months (3).

The insulin-like growth factor type 1 receptor (IGF-1R) is a transmembrane hetero-tetramer tyrosine kinase whose intracellular kinase domain is 84% homologous to that of the insulin receptor (IR) (4). Binding of its ligands, insulin-like growth factor-1 (IGF-1) and IGF-2, induces biological actions after conformational changes of the receptor, followed by activation of both PI3K/AKT/mTOR and MAPK/Erk-1/2 pathways. IGF-1R activation also promotes malignant cells progression by stimulating glycolysis and protein synthesis, while reducing tumor sensitivity to hypoxia through influencing angiogenesis regulation (5).

IGF-1R has been shown to be significantly overexpressed in malignant bone marrow nucleated cells in MDS and AML patients as compared to healthy controls (6). Clonal cells in MDS markedly overexpressed IGF-1R in comparison to corresponding normal nucleated bone marrow cells in the same individuals (78% *vs.* 14%, $p<0.0001$) (7).

IGF-Methotrexate (IGF-MTX) is a novel conjugate of methotrexate (MTX) and 765IGF, a variant of IGF-1 with high affinity for IGF-1R and reduced affinity for soluble IGF binding proteins (8). *In vivo* studies have confirmed tumor control at a dose 6-fold lower than that of free MTX (8).

AML cells have been shown to be sensitive to methotrexate *in vitro*. The concentration for 50% inhibition of cell growth (IC_{50}) for methotrexate was reported to be 10 nM for the HL-60 cell line (9). IGF-MTX inhibits AML cell lines; HL-60, HL-60/S4, and Kasumi-1 with an IC_{50} ranging between 458-668 nEq/l, and the MDS cell line, MDS-L with an IC_{50} of 400 nEq/l (unpublished data). Therefore, MDS, a neoplasm where IGF-1R is overexpressed, could be a potential target for IGF-MTX.

Correspondence to: Hugh McTavish, Ph.D., IGF Oncology, LLC, 7460 Pinehurst Road, Saint Paul, MN 55115, U.S.A. Tel: +1 6514920283, e-mail: hmctavish@igfoncology.com

Key Words: IGF-1R, IGF-MTX, phase 1 study, myelodysplastic syndrome, chronic myelomonocytic leukemia, oligoblastic acute myeloid leukemia.

A phase I clinical trial of IGF-MTX in patients with solid tumors and hematologic malignancies that expressed IGF-1R found that IGF-MTX at a dose of up to 0.8 μEq/kg was well tolerated without any serious adverse events and without any cytopenias in any patient at any dose level (10). Lack of the side effect of cytopenias also makes IGF-MTX attractive for MDS, where patients have cytopenias as a consequence of their disease.

The primary objective of this study was to determine the safety and tolerability of 765IGF-MTX in previously treated high-grade MDS or oligoblastic acute myeloid leukemia (O-AML). The secondary objectives were to evaluate efficacy. This study was registered at ClinicalTrials.gov (identifier: NCT03175978).

Patients and Methods

Patients. Enrolled patients had a diagnosis of high-grade MDS or O-AML that had failed standard therapy. Main eligibility criteria were as follows: a) Eastern Cooperative Group Oncology (ECOG) performance status of 2 or less (on a scale from 0 to 5); b) platelet count >10×10^9/l; c) adequate hepatic and renal function. Main exclusion criteria included active extramedullary disease, central nervous system (CNS) involvement, pleural effusion or ascites, ≥grade 3 peripheral neuropathy, active infection, myocardial infarction within 6 months prior to enrollment, uncontrolled diabetes mellitus, and known immediate or delayed hypersensitivity reaction to drugs chemically related to IGF or MTX. All patients gave written informed consent before enrollment. The study was approved by the Mayo Clinic Institutional Review Board (IRB#: 17-003541).

Treatment plan. 765IGF-MTX was given at the assigned dose as a 90-min IV infusion in 250 ml of 5% dextrose on days 1, 8, and 15 of a four-week treatment cycle. 765IGF-MTX was supplied by IGF Oncology, LLC (St. Paul, MN, USA).

Study design. Dose finding component: A total of five incremental dose levels (0.20, 0.40, 0.80, 1.6, 2.5 μEq/kg) were planned. One μEq is equivalent to one micromole of methotrexate groups; IGF-MTX has approximately 8 MTX groups covalently attached to each 765IGF protein molecule. The maximum tolerated dose (MTD) was defined as the highest dose associated with DLT in less than 33% of patients treated.

The study design allowed using cohorts of size 1 for the initial doses and expanding to cohorts of size 3 once any grade 2 or higher toxicity was observed that was considered related to the study drug (except for alopecia, nausea, or diarrhea). Additional patient cohorts were not to be enrolled until 1 of 1 (with no grade 2 toxicity), 3 of 3, 5 of 6, or 7 of 9 patients at the current dose level completed all planned treatment for cycle 1 (defined as 3 doses of 765IGF-MTX without DLT and were able to start cycle 2 with no more than a 2-week delay). A DLT was defined as one of the following treatment-related events occurring during cycle 1: a) grade 4 or greater treatment-related hematologic toxicity for >7 days during the first cycle (28 days) of therapy, b) grade 3 or greater treatment-related clinical non-hematological toxicity (excluding ≥grade 3 nausea, vomiting, or diarrhea without maximal medical intervention and/or prophylaxis) during the first cycle (28 days) of therapy, c) febrile neutropenia during the first cycle (28 days) of therapy, d) platelets less than 10×10^9/l with clinically significant bleeding during the first cycle of therapy.

Evaluation of toxicity and response. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 were used to evaluate symptoms and toxicity assessment on day 1, day 8, and day 15 of each treatment cycle. Assessment of clinical benefit was performed by investigators at the end of cycle 1 and confirmed with bone marrow studies as per MDS- (11), CMML-, or O-AML- (12) specific response criteria done at the end of cycles 2, 4, and 6 (*i.e.*, at 8, 16, and 24 weeks, each +/– 7 days) and at the discretion of the physician thereafter.

Presence of CD34+ cells in the blood and bone marrow aspirate via flow cytometry. When bone marrow aspirates were collected from patients, a fresh portion of the bone marrow aspirate was kept at room temperature and shipped on the day of collection in an insulated container at room temperature to Charles River, Inc., for testing of CD34 expression by flow cytometry, the next day. Whole blood samples were also tested for CD34 by flow cytometry by Charles River, Inc. (Reno, NV, USA).

Statistical analysis. Descriptive statistics were used to describe response rates.

Results

Patient characteristics. Two patients were enrolled in the trial between February 21, 2018 and February 28, 2018 and were given IGF-MTX at 0.20 μEq/kg. The study was suspended to further accrual on September 2019 due to financial challenges of the sponsor IGF Oncology, LLC.

The first patient (Patient 101) was a 79-year-old man who had a diagnosis of MDS starting in 2013. Subsequently he received 43 cycles of azacitidine starting May 2013 and finishing in November 2016, because of disease progression. Thereafter, he was treated with decitabine from November 2016 till February 2018, when disease progressed after 15 cycles. At the start of this study, his ECOG performance status was 1 and his MDS disease evolved to O-AML with 22% blasts in the bone marrow. With adverse bone marrow cytogenetics that were 46, XY, t (1;11) (p32;q23)c[20][20] as defined by European LeukemiaNet (13), his predicted OS was 0.8 years.

The second patient (Patient 102) was an 82-year-old man who had an initial diagnosis of MDS in 2015. The initial treatment for MDS was azacitidine starting in April 2015 and finishing after 20 cycles of therapy in November 2016 because of disease progression. Subsequently, he was treated with 8 cycles of decitabine from November 2016 until February 2018. ECOG at the time of accrual was 1. Bone marrow cytogenetics were normal: 46, XY [20][20]. His disease evolved to MDS with excess blasts -2 (MDS-EB-2) with 17% blasts in the bone marrow with high IPSS-R score (=6) and predicted OS of 1.6 years.

Table I. *Hematologic responses to IGF-MTX in patient 101.*

Subject ID	Visit	WBC (10^9/l)	RBC (10^{12}/l)	Hgb (g/dl)	Platelet count (10^9/l)	Neutrophils (10^9/l)	Lymphocytes (10^9/l)	Monocytes (10^9/l)
101	Screening/Baseline	0.8	1.92	7.3	12	0.04	0.71	0.03
101	Cycle 1 - Day 1	0.9	2.28	8.3	27	0.05	0.79	0.03
101	Cycle 1 - Day 8	0.9	2.24	8.1	32	0.09	0.77	0.04
101	Cycle 1 - Day 15	1.2	2.14	7.8	31	0.33	0.79	0.08
101	Cycle 2 - Day 1	1.3	2.42	8.8	26	0.47	0.71	0.12
101	Cycle 2 - Day 8	1.5	2.32	8.7	21	0.74	0.66	0.11
101	Cycle 2 - Day 15	1.8	2.38	8.9	24	0.75	0.87	0.11
101	Cycle 3 - Day 1	1.1	2.04	7.7	17	0.33	0.65	0.08
101	Cycle 3 - Day 8	1.1	2.35	8.6	12	0.27	0.69	0.09
101	Cycle 3 - Day 15	1.2	2.22	8.2	20	0.25	0.86	0.06
101	Cycle 4 - Day 1	1.0	2.28	8.2	10	0.22	0.73	0.05
101	Cycle 4 - Day 8	1.0	2.30	8.4	27	0.17	0.76	0.05
101	Cycle 4 - Day 15	1.0	2.53	8.9	34	0.17	0.78	0.06
101	Cycle 5 - Day 1	0.8	2.23	8.0	15	0.16	0.57	0.04
101	Cycle 5 - Day 8	1.0	2.56	8.7	36	0.14	0.81	0.04
101	Cycle 5 - Day 15	1.0	2.29	7.9	12	0.16	0.82	0.03
101	Cycle 6 - Day 1	1.1	2.35	7.8	20	0.16	0.89	0.06
101	Cycle 6 - Day 8	1.0	2.19	7.4	9	0.14	0.75	0.05
101	Cycle 6 - Day 15	1.4	2.55	8.2	14	0.16	0.79	0.06
101	Cycle 7 - Day 1	0.8	2.01	6.7	32	0.12	0.58	0.06
101	Cycle 7 - Day 8	1.0	2.33	7.7	11	0.04	0.94	0.05
101	Cycle 7 - Day 15	1.0	2.54	8.4	16	0.15	0.74	0.06
101	Cycle 8 - Day 1	0.9	2.77	9.2	23	0.12	0.67	0.06
101	Cycle 8 - Day 8	1.0	2.69	8.8	9	0.13	0.81	0.04
101	Cycle 8 - Day 15	1.1	2.51	8.3	17	0.13	0.88	0.05
101	Cycle 9 - Day 1	0.9	2.04	6.9	19	0.11	0.73	0.04
101	Cycle 9 - Day 8	1.0	2.76	9.0	37	0.13	0.78	0.04
101	Cycle 9 - Day 15	0.7	2.18	7.2	13	0.33	0.33	0.04
101	Cycle 10 - Day 1	1.0	2.15	7.2	23	0.46	0.44	0.07

Hgb: Hemoglobin; IGF-MTX: 765IGF-Methotrexate; RBC: red blood cell; WBC: white blood cell.

Because both patients had disease progression on hypomethylating agents, their expected overall survival at baseline was less than that based just on IPSS-R score and was less than 6 months for both (3).

IGF-MTX administration. Only dose level 0.20 μeq/kg of 765IGF-MTX was tested, which was the lowest dose level planned in this study. A total of 16 treatment cycles were administered during the trial. No DLT was observed at this initial dose level. Patient 101 withdrew from the study after 10 cycles because of non-drug-related febrile neutropenia. Patient 102 completed 5 cycles of therapy and initiated 6th cycle but decided to withdraw from the study because of grade 2 peripheral sensory neuropathy.

Toxicity. There was one possible treatment-related grade 3 syncopal episode in Patient 102 after day 1 of cycle 6. There was no hypoglycemia, diaphoresis, tunnel vision, vertigo, tongue biting, nor incontinence associated with this event. Encephalography, CT scan of head, serial electrocardiography, and transthoracic echocardiogram were performed without a pathologic diagnosis found. The principal investigator concluded it was a syncopal event due to orthostatic hypotension related to recent initiation of losartan therapy for hypertension. There was one episode of grade 3 lymphopenia and one episode of grade 3 anemia possibly attributed to IGF-MTX on subject 101 during cycle 9. There was one possible treatment-related grade 2 peripheral motor and sensory peripheral neuropathy that led to Patient 102's withdrawal from the study. There was one grade 1 possibly treatment-related non-cardiac chest pain reported by Patient 102. No treatment-related deaths occurred.

Response. Patient 101 initiated treatment with 22% bone marrow leukemic blasts; after 2 cycles of therapy blast count had decreased to 5%, then increased to 31% after 4 cycles, and then stabilized down to 27% and 22%, after 6 and 8 cycles, respectively.

Starting neutrophil count was 0.04×10^9/l, Hgb level 7.3 g/dl and platelet count 12×10^9/l. Best response in neutrophil

Table II. *Hematologic responses to IGF-MTX in patient 102.*

Subject ID	Visit	WBC (10^9/l)	RBC (10^{12}/l)	Hgb (g/dl)	Platelet count (10^9/l)	Neutrophils (10^9/l)	Lymphocytes (10^9/l)	Monocytes (10^9/l)
102	Screening/Baseline	0.8	2.72	9.7	85	0.38	0.38	0.03
102	Cycle 1 - Day 1	4.4	3.40	12.2	95	1.71	2.37	0.26
102	Cycle 1 - Day 8	3.8	3.41	12.0	78	1.61	1.90	0.21
102	Cycle 1 - Day 15	2.4	3.11	10.8	66	0.90	1.37	0.10
102	Cycle 2 - Day 1	2.8	3.10	11.0	56	1.02	1.61	0.13
102	Cycle 2 - Day 8	2.4	2.85	10.1	44	1.03	1.16	0.13
102	Cycle 2 - Day 15	2.9	2.79	9.9	39	1.29	1.40	0.12
102	Cycle 3 - Day 1	1.9	2.74	9.9	42	0.96	0.87	0.06
102	Cycle 3 - Day 8	1.9	2.67	9.6	38	0.73	1.01	0.06
102	Cycle 3 - Day 15	1.9	2.57	9.6	45	0.87	0.93	0.05
102	Cycle 4 - Day 1	2.0	2.75	10.1	58	0.74	1.13	0.05
102	Cycle 4 - Day 8	1.7	2.73	10.1	53	0.60	0.96	0.06
102	Cycle 4 - Day 15	1.7	2.70	10.1	51	0.69	0.91	0.05
102	Cycle 5 - Day 1	1.7	2.73	10.0	48	0.67	0.93	0.05
102	Cycle 5 - Day 8	2.0	2.61	9.7	42	0.61	1.33	0.05
102	Cycle 5 - Day 15	1.8	2.49	9.2	42	0.59	1.06	0.07
102	Cycle 6 - Day 1	1.5	2.33	8.5	40	0.68	0.75	0.04
102	Cycle 6 - Day 8	1.7	2.04	7.3	37	0.86	0.73	0.05
102	Day-30 Follow-Up	1.9	2.53	8.9	39	0.82	0.92	0.08

Hgb: Hemoglobin; IGF-MTX: 765IGF-Methotrexate; RBC: red blood cell; WBC: white blood cell.

was an increase to 0.75×10^9/l, best response in Hgb was an increase to 9.2 g/dl, and best response in platelet count was an increase to 37×10^9/l (Table I). This patient obtained complete response in the marrow (11).

Patient 102 started with 17% leukemic blasts in bone marrow that remained stable at 17% and 16% after 2 and 4 cycles of therapy, respectively.

Starting neutrophil count was 0.38×10^9/l, Hgb level 9.7 g/dl and platelet count 85×10^9/l. These counts improved to a neutrophil count of 1.71×10^9/l, Hgb level of 12.2 g/dl and platelet count of 95×10^9/l, likely from recovery from the cytopenic effects of decitabine. The following peripheral blood counts were stable (Table II). This patient obtained stable disease for more than 5 months (11).

Presence of CD34+ cells in the blood and bone marrow aspirate during treatment. Both patients had blood and bone marrow aspirate analyzed for the presence of CD34+ cells. CD34 marker is present on early hematopoietic precursors and on myelodysplastic cells (14). The CD34+ cell counts in Table III illustrate decreasing numbers of myelodysplastic cells in the peripheral blood and bone marrow aspirate in both patients.

Survival. Based on being high or very high-risk patients who had progressed on hypomethylating agents, both patients had predicted survival of less than 6 months (3). But both patients were alive at January 31, 2020, 1.9 years after starting IGF-MTX.

Table III. *CD34+ expression in the peripheral blood and bone marrow aspirate.*

	Screening	Week 8	Week 16	Week 24
Bone marrow aspirate				
Patient 101	7.4%	4.5%	12.4%	8.6%
Patient 102	NA	23.5%	15.6%	NA
Peripheral blood				
Patient 101	1.1%		2.5%	1%
Patient 102	2.3%		1.2%	
Healthy control	0.1%			

Discussion

Based on preclinical data showing high expression of IGF-1R on MDS cells and myeloid leukemia (6, 7, 14), *in vitro* data showing cytotoxicity at low concentrations of IGF-MTX against MDS and AML cells (unpublished), and the lack of clinical cytopenia caused by IGF-MTX (10), we initiated this phase I study of IGF-MTX in refractory MDS, CMML, and O-AML. Here, we present initial safety data of IGF-MTX in patients with MDS/O-AML showing no concerns about safety and no negative impact on cytopenia. In addition, although we had concerns of a possible effect of IGF-MTX on erythropoiesis that could be mediated by high expression of IGF-1R on erythroid precursors expressing CD235a (14), we did not see a negative impact

Table IV. *Responses to IGF-MTX in week 8 of therapy.*

	Subject 101		Subject 102		
	Baseline	8 weeks	Baseline	8 weeks	Normal range
Bone marrow parameter					
Bone marrow blast %	22	5	17	17	0-5
Hematology parameters					
Leukocytes $\times 10^9$/l	0.8	1.8	0.8	2.9	4.5-11
Red blood cell count $\times 10^{12}$/l	1.92	2.38	2.72	2.79	4.1-5.5
Hemoglobin (g/dl)	7.3	8.9	9.7	9.9	12-16
Hematocrit %	20.5	25.4	28.1	28.5	37-47
Platelets $\times 10^9$/l	12	24	85	39	150-450
Neutrophils $\times 10^9$/l	0.04	0.75	0.38	1.29	2-7
Lymphocytes $\times 10^9$/l	0.71	0.87	0.38	1.40	1-3
Monocytes $\times 10^9$/l	0.03	0.11	0.03	0.12	0.2-1
Eosinophils $\times 10^9$/l	0.03	0.03	0.03	0.04	0.02-0.5

of this drug on the level of hemoglobin. On the contrary, in both patients, we saw increases in red cell count. Table IV summarizes responses in the bone marrow and peripheral blood in week 8 after initiation of therapy. It is significant to note that both patients had improvement in absolute neutrophil count from severe neutropenia to moderate (Patient 101) or mild neutropenia (Patient 102) that protected them from a severe infection during the first 2 cycles of therapy.

Patient 101 had O-AML with adverse cytogenetics and a predicted OS of 0.8 years, while patient 102 had high risk MDS with a predicted survival of 1.6 years based on the IPSS-R scores; however, based on being high or very high risk patients who had progressed on hypomethylating agents, both had a predicted survival of less than 6 months (3). Both patients were alive on January 31, 2020, 1.9 years after starting IGF-MTX.

In summary, we have noted an intriguing activity of IGF-MTX in refractory MDS that warrants completion of trial and further testing.

Conflicts of Interest

Hugh McTavish and Arkadiusz Z. Dudek are officers of and own stock in IGF Oncology, LLC, which owns the rights to IGF-MTX. No other author has a conflict of interest in relation to this study.

Authors' Contributions

AZD wrote the first draft of the manuscript. HM, AZD, MMP, and AA-K designed the clinical protocol, with assistance from DLZ and SW. MMP was the initial principal investigator and HBA later became the principal investigator. HBA, MMP, AA-K, HM, and AZD analyzed the data. All Authors reviewed and participated in revising the manuscript.

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