

## **A Phase I Biological Study of MG98, an Oligodeoxynucleotide Antisense to DNA Methyltransferase 1, in Patients with High-Risk Myelodysplasia and Acute Myeloid Leukemia**

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**Abstract Purpose:** Epigenetic silencing via aberrant promoter DNA hypermethylation of normal genes has been described as a leukemogenic mechanism in myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML). We hypothesized that MG98, an oligonucleotide antisense to DNA methyltransferase 1 (*DNMT1*), could reverse malignant phenotypes by down-regulating *DNMT1* and inducing reexpression of hypermethylated genes. This phase I study was conducted to determine a biologically effective dose and describe the safety of MG98 in MDS/AML.

**Experimental Design:** Twenty-three patients with MDS ( $n = 11$ ) and AML ( $n = 12$ ) were enrolled. Biologically effective dose was defined as the dose at which  $\geq 50\%$  of patients experienced  $>50\%$  reduction in *DNMT1* expression with acceptable toxicity. Escalating doses of MG98 were administered according to two schedules (2-hour i.v. bolus followed by 5-day continuous i.v. infusion every 14 days, or 14-day continuous i.v. infusion every 21 days).

**Results:** *DNMT1* down-regulation was observed in 8 patients. However, biologically effective dose was not reached. Reexpression of target genes (*P15*, *WIT1*, and *ER*) was observed in 12 patients but did not correlate with *DNMT1* down-regulation. Escalation was stopped due to dose-limiting toxicities (bone pain, nausea, and fever). No objective clinical response was observed. Disease stabilization occurred in 6 (26%) patients.

**Conclusions:** No pharmacodynamic or clinical activity was observed at MG98 doses and schedules administered. Despite this, pursuing *DNMT1* down-regulation remains a sound approach for targeting aberrant epigenetics in AML/MDS. Future studies with different formulation and/or doses and schedules will be required to ensure efficient MG98 intracellular uptake and fully evaluate its therapeutic potential.

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by progressive cytopenias and, often, progression to acute myeloid leukemia (AML; refs. 1, 2). Both MDS and AML present with the highest incidence in older patients, where other comorbid conditions

may significantly affect the ability to receive aggressive therapies with curative intent (i.e., aggressive cytotoxic chemotherapy and/or hematopoietic stem cell transplant; refs. 3, 4). Therefore, alternative therapies with reduced toxicity for these disorders are needed.

A potential pathogenic mechanism common to both MDS and AML is epigenetic silencing via DNA promoter hypermethylation of genes pivotal to normal hematopoiesis (5–12). DNA hypermethylation occurs by an enzymatic addition of a methyl (CH<sub>3</sub>) group at the carbon 5 position of cytosine in the context of the dinucleotide sequence 5'-cytosine-guanosine (CpG) in gene promoter regions and is mediated by the DNA methyltransferase (DNMT) family of enzymes (13). DNMT1 is the most abundant of these isoenzymes and preferentially methylates hemimethylated DNA strands, thereby replicating and conserving existing aberrant methylation patterns. DNMT3A and DNMT3B are, however, responsible for establishing *de novo* methylation (13).

As recent studies suggest that overexpression of DNMT1 occurs in AML patients with aberrant hypermethylation of multiple genes, including the cell cycle regulator p15, which is in turn associated with poor prognosis (8, 9, 12, 14), we

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hypothesized that aberrant hypermethylation can be decreased, and disease response induced, by directly down-regulating DNMT1 expression.

MG98 is a second-generation chemistry 2'-O-CH<sub>3</sub>-substituted phosphorothioate oligodeoxynucleotide antisense molecule designed to hybridize to the 3' untranslated region of the human DNMT1 mRNA. Antisense compounds bind to mRNA by Watson-Crick base pairing and induce target down-regulation through inhibition of mRNA nuclear export and translation, alteration of mRNA stability, and activation of endonucleases (e.g., RNase H) that degrade the mRNA/antisense duplex (15). Although DNMT1 inhibition has successfully been achieved with nucleoside analogues such as decitabine and azacitidine, the advantage of antisense compounds like MG98 over these oligonucleotides lies within their potentially more selective inhibition of the target enzyme production and reduced toxicities (e.g., myelosuppression) than what is observed with such hypomethylating agents.

Herein, we report a phase I study done to determine the biologically effective dose of single agent MG98 based on reductions of target *DNMT1* mRNA in patients with advanced MDS and refractory/relapsed AML.

## Patients and Methods

**Eligibility criteria and study design.** This study enrolled patients (at least 18 years of age) with relapsed/refractory AML or MDS or untreated with poor-risk AML who were not candidates for aggressive therapy with curative intent (i.e., stem cell transplantation). MDS patients with intermediate 1, intermediate 2, or high-risk MDS by International Prognostic Scoring System were eligible (16). Patients were also required to have nonproliferative disease with stable WBC counts (i.e.,  $<40 \times 10^3/\mu\text{L}$ ) that had not increased by  $>20\%$  in the preceding week. Control of WBC with hydroxyurea was permitted before starting therapy and in the first week of therapy as clinically indicated. Left ventricular ejection fraction of at least 45%, Eastern Cooperative Oncology Group performance status of  $\leq 2$ , creatinine  $<2.0$  mg/dL, alanine aminotransferase/aspartate aminotransferase  $\leq 3$  times the upper limit of normal, and total bilirubin  $\leq 1.5$  times upper limit of normal (unless due to Gilbert's disease) were also required. Protocol was approved by the appropriate Institutional Review Boards, and informed consent was obtained from all patients before study entry.

Patients were treated with two different schedules of MG98. In cohort 1, MG98 was administered i.v. via a central line as a 2-h i.v. bolus infusion (240 mg/m<sup>2</sup> in dose level 1, 360 mg/m<sup>2</sup> in dose level 2) followed by a 5-d continuous i.v. infusion of 80 mg/m<sup>2</sup>/d every 14 d. After the initial cohort 1 analysis of *DNMT1* mRNA, any reduction in *DNMT1* mRNA was observed on day 5, not on day 1. Therefore, the 2-h bolus was unlikely to significantly contribute to reductions in the target. Subsequently, the protocol was amended to test a 14-d continuous infusion designed to remove the 2-h bolus, increase the duration of infusion, and decrease the drug-free interval while intending to minimize toxicity. As such in cohort 2, MG98 was administered as a continuous i.v. infusion of 100 mg/m<sup>2</sup>/d for 14 d every 21 d (dose level 3).

The primary end point was determination of a biologically effective dose defined as the dose level where at least 50% of patients had  $>50\%$  reduction in *DNMT1* mRNA levels in bone marrow on completion of MG98 administration compared with baseline and  $\leq 2$  patients experienced a dose-limiting toxicity. The intent was to enroll 10 patients at each dose level. However, if it was deemed impossible to achieve the target biologically effective dose in 5 of 10 patients by continuing to enroll at that dose level, accrual was stopped if at least 6 patients had

been enrolled and fewer than two dose-limiting toxicities were observed. Supportive care including transfusion support, antibiotics, and/or antivirals was administered at the discretion of the treating physician.

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 2.0. Dose-limiting toxicity was defined as nonhematologic toxicity of grade  $\geq 3$  (with the exception of fatigue); irreversible grade 2 nonhematologic toxicity; for AML patients or MDS patients with severe preexisting cytopenias (platelets  $<75 \times 10^3/\mu\text{L}$ , neutrophils  $<2 \times 10^3/\mu\text{L}$ ), failure to recover blood counts to 75% of baseline in the absence of disease progression by day 56; or for MDS patients, grade 4 cytopenias persisting more than 5 d if baseline values were normal. Clinical responses were assessed per the recommendations of the respective International Working Groups (17–19).

**Pharmacokinetic analysis.** Sampling for pharmacokinetic analysis of plasma levels of MG98 was done on day 1 (pretreatment and during the 120-min infusion at 30, 60, and 110 min) and day 5 (before the end of continuous infusion and 30, 60 min, 2, 4, and 24 h after the completion of the infusion) for patients treated on cohort 1, and on day 1 (pretreatment and 6 h after start of the infusion), day 7 (10 min before the end of first bag), day 14 (10 min before the end of infusion and during infusion washout at 30, 60 min, 2, 3, 4, and 6 h), and day 35 (10 min before the end of infusion) for enrollees on cohort 2. Plasma samples were assayed by Ricerca Bioscience using a validated liquid chromatography-tandem mass spectrometry method developed with a dynamic range of 0.05 to 10  $\mu\text{g}/\text{mL}$  for MG98 and its metabolites N-1 and N-2 as previously described (20). Plasma pharmacokinetic parameters were calculated from plasma concentration-time data using noncompartmental methods by WinNonLin version 3.3 (Pharsight).

**Pharmacodynamic studies.** To define the biologically effective dose, changes in *DNMT1* expression levels were evaluated before MG98 treatment and on completion of the infusion (day 5 for cohort 1 and day 14 for cohort 2). Total cellular RNA was isolated from bone marrow mononuclear cells, and cDNA synthesized as previously described (21, 22). Each cDNA sample was then used as a template for reverse transcription-PCR amplification runs in duplicate on the ABI Prism 7700 Sequence Detection System (Applied Biosystems) using forward primer (AGCCCCGTAGAGTGGGAATGG), reverse primer (TGGGCGT-GCGAGGTTT), and probe (FAM-AGATGCCAACAGCCCCCCCAA-TAMRA). Primers and probes for *DNMT1* were validated in cell lines (A549, T24, Kasumi-1, and K562) treated with increasing doses of MG98 and mismatched oligonucleotide, and reductions confirmed by Northern blotting. The comparative cycle threshold ( $C_T$ ) method was used to determine the expression levels of *DNMT1* relative to 18S levels used as an internal control. Normalized *DNMT1* transcript levels were calculated using the mean  $\Delta C_T$  [ $\mu(\Delta C_T)$ ] from two replicates for each sample and expressed as  $2^{\mu(\Delta C_T)}$ . *DNMT1* transcript levels, determined at the completion of MG98 infusion, were expressed as percentage of pretreatment *DNMT1* transcript levels.

Using the same approach, samples were also examined for reexpression of the commonly hypermethylated genes *ER*, *WIT-1*, and *p15*. Primer and probe sets used included *ER* forward primer (AAGCTATGTTTGTCTCCTAACTTGC), *ER* reverse primer (CCAC-CATGCCCTCTACACATT), *ER* probe (FAM-TTGGACAGGAACCAGGG-MGB), *WIT-1* forward primer (TCACCCAGCGGCCG), *WIT-1* reverse primer (TGACCGACCGCAGCG), *WIT-1* probe (FAM-ACAACGTAAACACCC-MGB), *p15* forward primer (ATCCCAACGGAGTCA-ACCG), *p15* reverse primer (CGTGCCCATCATCATGA), *p15* probe (FAM-TTCGGGAGGCGCGC GATA-TAMRA), 18S forward primer (CGGCTACCACATCCAAGGAA), 18S reverse primer (GCTGGAAT-TACCGCGCT), and 18S probe (JOE-TGCTGGCACCAGACTTGCCC-TAC-TAMRA).

**Statistical analysis.** Descriptive statistics to include means, medians, SDs, and frequencies were computed for all pharmacokinetic and pharmacodynamic variables.

**Table 1.** Patient clinical characteristics

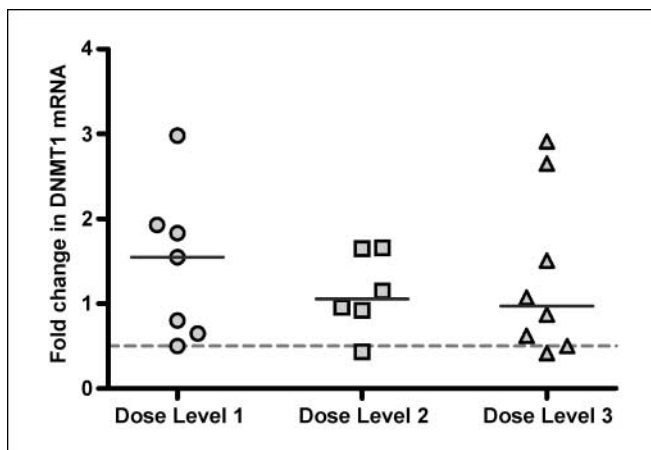
	Total (N = 23)
Sex	
Female, n (%)	8 (35)
Age, y	
Median	67
Range	60-83
Diagnosis, n (%)	
AML	12 (52)
MDS	11 (48)
MDS IPSS score, n (%)	
Intermediate 1	5 (45)
Intermediate 2	5 (45)
High	1 (10)
ECOG performance status, n (%)	
0	9 (39)
1	13 (57)
2	1 (4)
Time from diagnosis to first dose, wk	
Median	38
Range	5-357
Prior treatment, n (%)	
None	4 (17)
Hydroxyurea only	2 (9)
ESA only	1 (4)
Combination chemotherapy	13 (57)
No. prior chemotherapy regimens	
Median	2
Range	1-5
Bone marrow blasts at screening visit	
Median	17
Range	1-96

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; ESA, erythropoiesis-stimulating agents.

**Results**

**Patient characteristics and treatment.** A total of 23 patients with either AML (relapsed/refractory *n* = 9; untreated *n* = 3) or MDS (*n* = 11) from the Ohio State University or the University of Chicago were enrolled on this study. Baseline clinical characteristics are detailed in Table 1 and data on the number of administered MG98 cycles are given in Table 2.

**Pharmacodynamic studies.** The primary objective of the study was to determine a biologically effective dose, defined as a dose level at which at least 50% of patients had >50% reduction in *DNMT1* mRNA on completion of MG98 admi-



**Fig. 1.** Fold changes in *DNMT1* mRNA levels (with median) in bone marrow mononuclear cells after completion of MG98 infusion (day 5 in dose levels 1 and 2, day 14 in dose level 3). Dotted line, goal reduction for defined biologically effective dose.

nistration compared with untreated baseline. The quantitative reverse transcription-PCR results are summarized in Fig. 1. Three patients (one in each dose level) had inadequate sample and were therefore not evaluable with respect to biologically effective dose. On the first dose level, seven patients had samples assessable at the end of MG98 infusion on day 5 (median change from untreated baseline, +55%; range, -50% to +198%). Of these, only one patient had ≥50% reduction in *DNMT1* transcript. Of the seven patients treated on dose level 2, six patients had assessable samples (median change from untreated baseline, +5%; range, -57% to +66%). Of these, only one patient had ≥50% reduction in *DNMT1* transcript. Nine patients received treatment on dose level 3, and eight had assessable samples (median change from untreated baseline, -3%; range, -58% to +191%). Of these, only two had ≥50% reduction in *DNMT1* transcript.

Concurrent with assessment of *DNMT1* levels, we measured changes in expression of three genes known to be frequently methylated in hematopoietic malignancies. *ER*, *p15*, and *WIT-1* were assessed before treatment and after completion of MG98 infusion (day 5 for schedule 1 and day 14 for schedule 2). Twelve patients had evidence of gene reexpression (greater than +100% change from baseline) in at least one of the three targets tested. Median percentage changes in gene expression compared with baseline for *ER*, *p15*, and *WIT-1* were +2% (range, -69.1% to 190.2%), +2.6% (range, -96.6% to 3,510%), and

**Table 2.** MG98 exposure by dose level

	Dose level 1 (n = 8)	Dose level 2 (n = 7)	Dose level 3 (n = 9)
No. cycles			
1	8	5	8
2		2	
3			1
Total dose (mg/m <sup>2</sup> )			
Median	1,523	3,039	2,188
Range	637-2,577	743-6,080	1,400-7,000
Dose intensity (mg/m <sup>2</sup> /wk)			
Median	320	380	467
Range	293-320	380-380	350-467

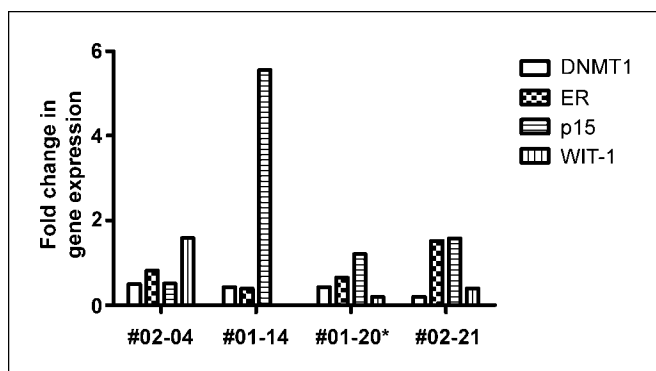


Fig. 2. Gene expression patterns in bone marrow mononuclear cells in patients with down-regulation of *DNMT1* after completion of initial MG98 infusion. \*, patient with stable disease.

+40.4% (range, -94.2% to 36,305%), respectively. Down-regulation of *DNMT1* did not correlate with gene reexpression. Of the four patients with >50% reduction in *DNMT1* transcript following MG98 treatment, only one (#01-14) had evidence of *p15* reexpression (Fig. 2).

**Toxicities.** The number of courses and cumulative dose received are summarized in Table 2. The adverse event pro-

file reported across the dose levels in this trial was similar to that reported in other clinical trials with MG98 (20, 23, 24). Compiled grade 3 and 4 adverse events, including those commonly observed in patients with MDS and AML and therefore non-dose limiting, are detailed in Table 3. Fatigue and fever were the most frequent treatment-related adverse events. More than 50% of patients reported having fatigue possibly related to MG98 therapy. Two patients discontinued therapy due to treatment-related adverse events: one due to grade 3 fatigue and one secondary to grade 3 leukopenia, epistaxis, and syncope. Dose-limiting toxicities (i.e., adverse events considered directly attributable to the drug), were observed in four patients on dose level 3 and included grade 3 bone pain with no dose delays or reductions; grade 3 nausea and vomiting requiring a hospitalization and dose delay; grade 3 fever, catheter-related infection, and hypotension leading to hospitalization; and grade 3 neutropenia with infection, syncope, and epistaxis resulting in hospitalization and removal from study. No deaths attributable to MG98 were observed, and there were no deaths on study. Reversible grade 3 hepatic dysfunction was seen in only one patient (elevated alanine aminotransferase on dose level 1, and the patient continued on study on resolution). Although a mild reversible elevation in creatinine was

**Table 3.** Compiled grade 3 and 4 adverse event

	AML (n = 12)		MDS (n = 11)		All patients (N = 23)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Blood/bone marrow*						
Anemia	3	0	5	0	8	0
Leukopenia	0	0	3	0	3	0
Lymphopenia	1	0	1	0	2	0
Neutropenia	2	1	0	0	2	1
Thrombocytopenia	1	0	1	1	2	1
Constitutional						
Fatigue	0	0	2	0	2	0
Fever †	1	0	0	0	1	0
Infection	3	1	2	0	5	1
Cardiovascular						
Hemorrhage	1	0	0	0	1	0
Hypertension	1	0	0	0	1	0
Hypotension	1	0	0	0	1	0
Syncope	1	0	0	0	1	0
Digestive system						
Diarrhea	1	0	0	0	1	0
Gingivitis	1	0	0	0	1	0
Ileus	1	0	0	0	1	0
Nausea †	1	0	1	0	2	0
Vomiting	1	0	1	0	2	0
Metabolic						
AST	0	0	1	0	1	0
Musculoskeletal						
Bone pain †	0	0	1	0	1	0
Pain						
Abdominal	1	0	0	0	1	0
Neck	0	0	1	0	1	0
Pulmonary						
Dyspnea	1	0	1	0	2	0
Epistaxis	2	0	0	0	2	0

Abbreviation: AST, aspartate aminotransferase.

\*Only in patients without grade 3 or 4 baseline cytopenias.

†Dose-limiting toxicities.



**Table 4.** Relevant pharmacokinetic parameters of MG98 (mean  $\pm$  SD) in all treated patients

Parameter	Dose level 1 (n = 8)	Dose level 2 (n = 7)	Dose level 3 (n = 7)
$C_{max}$ ( $\mu$ g/mL)	34.0 $\pm$ 9.57	60.5 $\pm$ 14.5	—
$T_{max}$ (h)	1.9 $\pm$ 0.1	1.8 $\pm$ 0	—
$C_{ss}$ ( $\mu$ g/mL)	0.462 $\pm$ 0.362	0.720 $\pm$ 0.309	1.07 $\pm$ 0.531
$t_{1/2}$ (h)	1.2 $\pm$ 0.5	1.0 $\pm$ 0.2	1.7 $\pm$ 0.4

noted in one patient, no severe renal events or coagulopathies were observed.

**Pharmacokinetics.** Plasma samples were assayed for all patients treated. Table 4 summarizes relevant pharmacokinetic parameters. MG98 showed a relatively short plasma decay with a half-life of 1.0 to 1.7 hours across the treatment levels. A steady-state concentration ( $C_{ss}$ ) of 1.07  $\mu$ g/mL was achieved with a 14-day 100 mg/m<sup>2</sup>/d infusion rate. Concentrations of N-1 and N-2 shortened metabolites were negligible (<7%) compared with MG98 concentrations.

**Clinical response.** No patient met the objective criteria for clinical response with MG98 therapy. Six of 11 MDS patients had disease stabilization of brief duration as their best response to therapy, including one in dose level 1, two in dose level 2, and three in dose level 3. Of the eight patients who had an at least 50% reduction in *DNMT1* mRNA for at least one time point, only two had stabilization of disease. There was no correlation between patients having stable disease and reduction of *DNMT1* mRNA levels.

## Discussion

Based on the therapeutic potential for hypomethylating agents in advanced hematologic malignancies, we examined the toxicity, pharmacokinetics, pharmacodynamics, and clinical response of patients with AML or MDS treated on a phase I study of MG98. We hypothesized that targeting *DNMT1* by MG98 would result in down-regulation of *DNMT1* and a reversal of aberrant hypermethylation in AML and MDS, thereby leading to therapeutic benefit.

The primary end point of this study was defined by a reduction in *DNMT1* mRNA expression in an attempt to validate the hypothesis that MG98 exerts a specific pharmacologic effect on its designated target. Although reductions in *DNMT1* were observed in select patients, this study failed to identify a biologically effective dose in the dose levels tested, and toxicity prohibited further dose escalation. No objective

responses were observed in this study at any dose level. Reexpression in the commonly hypermethylated genes, *ER*, *WIT-1*, and *P15*, was variable and did not correlate with changes in *DNMT1*, raising the possibility that these changes may not be directly related to MG98 administration.

The lack of MG98 biological and clinical efficacy in this study could be related to several distinct causes. First, one could ask whether biologically effective drug levels were indeed achieved. We showed dose-dependent plasma levels of MG98 ~3 times higher than the IC<sub>50</sub> reported to reduce *DNMT1* *in vitro*. In spite of this, we did not observe a clear dose-dependent reduction in *DNMT1* mRNA, although the median levels in *DNMT1* compared with baseline seemed to decrease with MG98 treatment at higher doses (Fig. 1). Lack of correlation of plasma levels with target down-regulation, and furthermore, disease response, has also been noted with other antisense therapies. Because target down-regulation might be dependent on achievement of robust intracellular drug levels, future studies with MG98 should determine whether biologically active drug levels can be achieved in both plasma and intracellular compartment and whether this correlates with target modulation.

Similar to other studies with MG98, the most common toxicities were fatigue and fever, and asthenia that led to patient withdrawal from the study (20, 23, 24), which prevented us from further escalating MG98 that may have produced greater target down-regulation. This toxicity profile is similar to that observed with other phosphothiorate compounds, where improvements in tolerability were described once different administration schedules were adopted (20–24). Nevertheless, it may be that modification of the schedule of administration alone will not greatly enhance the therapeutic efficacy of MG98. Combination therapy using other chemotherapeutics may provide the best opportunity to see the added benefit of this cytostatic agent in the context of its proposed mechanism of action, the reexpression of tumor suppressor genes aberrantly silenced by hypermethylation.

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