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Effect of the Ginger Derivative, 6-Shogaol, on Ferritin Levels in Patients With Low to Intermediate-1-Risk Myelodysplastic Syndrome-A Small, Investigative Study

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Abstract

Background: Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders characterized by dysplastic and ineffective hematopoiesis and peripheral cytopenias. Elevated serum ferritin (SF) is often observed in nontransfused, lower risk MDS. It has been reported that ineffective erythropoiesis enhances iron absorption in MDS through downregulation of hepcidin and its prohormones such that SF rises. **Aim:** To determine the effect of 6-shogaol, a dehydration derivative of ginger, known to have hepatoprotective and chemotherapeutic activity, on 6 early-stage, transfusion-independent patients with MDS, 3 of whom had raised levels of SF. **Method:** Six patients with MDS with low or intermediate-1 subtypes, as defined by the International Prognostic Scoring System (IPSS), were recruited into the study and were administered 1 gel capsule daily containing 20 mg ginger extract standardized for 20% 6-shogaol. Blood and urine samples were collected and various markers monitored at regular intervals. **Results:** 6-shogaol caused a decrease in SF levels in 3 of 6 patients with early MDS (50%) whose SF levels were elevated at the start of the study. Our findings suggest upregulation of hepcidin and its prohormones, possibly through an improvement in liver function. **Discussion:** In light of the encouraging results in this small, investigative study, we are planning a larger study to confirm the beneficial effect of 6-shogaol in patients with raised ferritin levels due to ineffective erythropoiesis.

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ABSTRACT

BACKGROUND: Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders characterized by dysplastic and ineffective hematopoiesis and peripheral cytopenias. Elevated serum ferritin (SF) is often observed in nontransfused, lower risk MDS. It has been reported that ineffective erythropoiesis enhances iron absorption in MDS through downregulation of hepcidin and its prohormones such that SF rises.

AIM: To determine the effect of 6-shogaol, a dehydration derivative of ginger, known to have hepatoprotective and chemotherapeutic activity, on 6 early-stage, transfusion-independent patients with MDS, 3 of whom had raised levels of SF.

METHOD: Six patients with MDS with low or intermediate-1 subtypes, as defined by the International Prognostic Scoring System (IPSS), were recruited into the study and were administered 1 gel capsule daily containing 20 mg ginger extract standardized for 20% 6-shogaol. Blood and urine samples were collected and various markers monitored at regular intervals.

RESULTS: 6-shogaol caused a decrease in SF levels in 3 of 6 patients with early MDS (50%) whose SF levels were elevated at the start of the study. Our findings suggest upregulation of hepcidin and its prohormones, possibly through an improvement in liver function.

DISCUSSION: In light of the encouraging results in this small, investigative study, we are planning a larger study to confirm the beneficial effect of 6-shogaol in patients with raised ferritin levels due to ineffective erythropoiesis.

KEYWORDS: Myelodysplasia, ginger, 6-shogaol, ferritin, liver-function

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Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders characterized by dysplastic and ineffective hematopoiesis and peripheral cytopenias. The natural history of MDS is variable, ranging from the indolent condition spanning years, to a form rapidly progressing to acute myelogenous leukemia.¹ The disease predominates in an elderly population, the median age being approximately 70 years. Many of these patients also have numerous comorbid conditions which make the use of natural compounds, with little or no toxicity, highly desirable in the lower risk MDS, defined by the International Prognostic Scoring System (IPSS) as low or intermediate-1 (Int-1) subtypes.

Elevated serum ferritin (SF) is often observed in nontransfused, patients with lower risk MDS. Kikuchi et al² evaluated baseline SF levels in nontransfused patients with MDS and found that the SF level was significantly higher in patients with MDS compared with healthy controls. They also found that the SF level of patients with higher risk MDS was significantly higher than that of the patients with lower

risk MDS. These authors suggest that baseline SF level may be an independent prognostic factor for overall survival and leukemia-free survival (LFS) in patients with MDS as the LFS was significantly shorter in the high SF group than in the low SF group. High SF at diagnosis (>500 ng/mL) was significantly associated with future development of transfusion dependency.

The liver polypeptide hepcidin plays a pivotal role in iron homeostasis. In macrophages, it accelerates the degradation of the transmembrane iron exporter ferroportin messenger RNA. In intestinal epithelial cells, it is believed to downregulate divalent metal transporter 1, which is involved in the transfer of iron across the intestinal wall.³ It has been reported that ineffective erythropoiesis enhances iron absorption in MDS through downregulation of hepcidin and its prohormones such that SF rises.⁴

Plants of the ginger family have been credited with hepatoprotective activity.^{5,6} The substance called [6]-gingerol is the main active compound in ginger root and the



one that gives ginger its distinctive flavor. Shogaols are the dehydration products of gingerols during storage or thermal processing. Hepatoprotective effects of 6-shogaol have been found in animal studies against ethanol, carbon tetrachloride, diclofenac, and acetaminophen-induced hepatotoxicity. Zhuang et al⁶ identified that shogaol in ginger-derived nanoparticles specifically targets hepatocytes and plays a role in the induction of nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 transcriptionally controls the gene expression of many cytoprotective enzymes and plays an important role in protecting liver against insults. A study by Alquasoumi et al⁵ showed that pretreatment of rats with 6-shogaol for 6 days exhibited a significant protective effect on diclofenac sodium-induced hepatic injury by reduction in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase compared with controls. Their results showed that 6-shogaol prevented diclofenac sodium (DFS)-induced acute hepatotoxicity by protecting serum marker enzymes, bilirubin, and antioxidant activity.

Based on the above findings, we have conducted a small, investigative study to evaluate the effect of 6-shogaol in 6 early stages, transfusion-independent patients with MDS, 3 of whom had raised levels of SF.

Methods

Six patients with low or Int-1-risk MDS, as defined by the IPSS, were recruited into the study. The study was performed in the Department of Endocrinology at St George Hospital, Sydney, and informed consent was obtained from each patient before recruitment. Patients were administered 1 gel capsule daily containing 20 mg ginger extract standardized for 20% 6-shogaol. Blood samples were drawn at baseline and at 2-monthly intervals for a period of 6 months (initial study—i). Based on the decrease in SF levels shown in 3 of 6 patients with elevated SF and the improvement in liver function markers shown in 1 patient, the study was repeated on 2 of 3 patients for a further 6 months (repeat study—r) with a washout period of 3 months between the initial study and the repeat study. Markers monitored for the initial study (i) included full blood count, serum chemistry, liver function, reticulocyte count, Coombs test, and serum iron studies. Markers monitored for the repeat study (r) included full blood count, serum chemistry, liver function, and the add-on tests for 24-hour urine iron excretion and serum hepcidin levels.

Hepcidin was measured in serum using a highly precise and validated liquid chromatography method, incorporating online extraction and coupled with tandem mass spectrometry.⁷

Results

There were 4 men and 2 women with an average age of 70 years in the study (Table 1). The mean disease duration

was 5.6 years. Of the 6 patients, 5 patients (83%) completed the 6-month initial study. One patient (no. 5) stopped the initial study at month 4 and was lost to follow-up. Two patients, due to their decrease in SF levels (nos 1 and 3) in the initial study, were entered into the repeat study with a washout period of 3 months, and both these patients completed the 6-month repeat study, ie, a total of 12 months shogaol therapy. None of the patients were treated with anything other than the 6-shogaol during the study period and none displayed ill effects from the 6-shogaol.

In the study, 4 of 6 (67%) patients were anemic at baseline and all had variable cytopenias (Table 1). There was no change in cell counts over the course of the initial or repeat study period.

Of the 6 patients, 3 (50%—nos 1, 3, 5) had elevated SF levels at baseline (Table 1). No sign of infection or inflammation was found in any of these patients. Patient no. 1 had a high alcohol intake which may have also contributed to his significantly high SF. All 3 patients showed a >40% decrease in SF by the end of the initial study period (Table 1). Patients 1 and 3 repeated the study, with a 3-month washout period between the initial study and the repeat study. In patient 1, the decreased SF remained stable during the 3 month washout period. Once shogaol therapy was recommenced, SF continued to decrease from baseline by the end of the repeat study (51% decrease from baseline in initial study and 58% decrease from baseline by the end of the repeat study; Figure 1). Urinary iron excretion was measured in the 2 patients participating in the repeat study and there was no effect of the 6-shogaol on urinary iron excretion.

In addition to significantly elevated SF at baseline (2195 µg/L—normal: 30–300 µg/L), patient no. 1 had significantly elevated liver function enzymes (γ -glutamyl transferase [GGT], ALT, and AST) at baseline which was most likely associated with his high alcohol intake and he did not decrease his alcohol intake (his intake remained constant during the year that he participated in both the initial and the repeat studies). All 3 liver function enzymes (GGT, ALT, and AST) decreased during the 12 months on shogaol therapy with ALT and AST falling (53% and 40%, respectively) to within normal range (Table 2). The decrease in SF and liver function enzymes seen in patient no. 1 was accompanied by an increase in serum hepcidin in the repeat study (12.3–19.3 ng/mL—an increase in 57% from the start to the end of the repeat study; Table 2).

Table 2 shows the decrease in SF levels and liver function enzymes in patient no. 1 over both the initial study period (i) and the repeat study period (r) (SF decreased by 58% from initial baseline, GGT decreased by 19% from initial baseline, ALT decreased by 53% from initial baseline, AST decreased by 40% from initial baseline). Serum hepcidin levels were measured in the repeat study, and the table shows a 57% increase from repeat baseline.

Table 1. Hematologic parameters, WHO type, and iron studies of the 6 early patients with MDS at the start of the initial study (SOS) and the end of the initial study (EOS).

PATIENT NO.	AGE/SEX	WHO-TYPE MDS		Hb (128-175 G/L)	WCC (4-11 × 10 ⁹ /L)	NEUT. (2-7.5 × 10 ⁹ /L)	PLTLTS (150-450 × 10 ⁹ /L)	RETIC. (20-100 × 10 ⁹)	IRON (5-30 μMOL/L)	TIBC (46-70 μMOL/L)	FERRITIN (30-300 μG/L)	% SATURATION (10%-45%)
1	54/M	RCMD	SOS	151	3.6	1.76	29	95	28	56	2195	50
			EOS	151	4.1	2.43	38	93	35.9	58	1071	62
2	64/M	RCMD	SOS	95	5.1	2.31	214	24	28	37	222	76
			EOS	93	4.6	2.1	195	22	24	58	275	58
3	72/M	RCMD	SOS	108	2.9	1.48	114	76	22.4	50	709	45
			EOS	101	1.7	0.67	94	61	29.4	48	387	61
4	72/F	CMML-1	SOS	152	6.8	1.2	133	38	21.8	NA	94	36
			EOS	137	9.5	2.7	148	52	10.5	NA	122	19
5	85/M	RCMD	SOS	94	6.5	3.27	193	165	10.7	48	336	22
			EOS	125	4.5	2.05	79	122	16.8	56	117	30
6	75/F	RARS	SOS	91	5.4	2.61	467	32	29.5	44	198	67
			EOS	88	5	2.18	464	34	35.7	44	227	81

Abbreviations: EOS, end of study; Hb, hemoglobin; neut., neutrophils; pltlts, platelets; RARS, refractory anemia with ringed sideroblast; RCC, red cell count; RCMD, refractory cytopenia with multilineage dysplasia; retic., reticulocytes; SOS, start of study; TIBC, total iron-binding capacity; WCC, white cell count; WHO, World Health Organization.

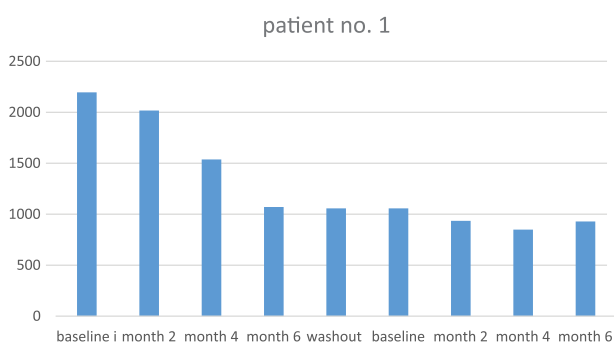


Figure 1. Serum ferritin (SF) levels of patient no. 1 during the initial (i) study, washout period and the repeat (r) study. The decrease in SF levels in patient no. 1 over 6-month period of initial study, stabilization during the washout period, and further decrease over 6-month repeat study period. Patient no. 1 showed a 58% decrease in SF levels from initial baseline.

Patient no. 3 had a 45% decrease in SF from baseline to 6 months in the initial study (709–387 μg/L). During the 3-month washout period, his SF levels increased (to 664 μg/L). Reintroduction of shogaol once again led to a decrease in SF (to 390 μg/L; Figure 2). This decrease in SF remained at 45% from baseline in the repeat study. The decrease in SF was accompanied by an increase in serum hepcidin in the repeat study (19 ng/mL at start of repeat study to 42.2 ng/mL at end of repeat study). Liver function enzymes in this patient were within normal range during both the initial and repeat studies.

Discussion

The patients with lower risk MDS, whose disease is monitored on a “watch and wait” basis, represent the ideal conditions to test the role of nontoxic natural compounds. The rationale for using 6-shogaol in this small, investigative study is that both the ginger-derived 6-gingerol and 6-shogaol show anticarcinogenic, hepatoprotective, and anti-inflammatory activities.^{8–10} 6-Shogaol has been found to have much stronger growth inhibitory effects than 6-gingerol on H1299 human lung cancer cells and HCT-116 human colon cancer cells.¹¹

Although the 6-shogaol had no effect on cell counts, the results of our study show that 6-shogaol caused a decrease in SF levels in 3 of 6 patients with early MDS (50%) whose SF levels were elevated at the start of the study.

The decrease in SF level was reproduced in repeat studies in 2 patients. Neither had changed his dietary habits and urinary iron excretion remained normal during the study periods. The decrease in SF was accompanied by an increase in serum hepcidin level in both patients. A decrease in elevated liver function enzymes was seen in patient 1 with a history of excess alcohol consumption, in keeping with probable hepatoprotective activity of 6-shogaol.^{5,6}

Our findings suggest upregulation of hepcidin and its pro-hormones, with the resultant decrease in SF level attributable to decreased absorption of dietary iron. The improvement in liver function in patient 1 may reflect less cellular damage, as has been shown in animal studies by Zhuang and Alqasoumi.^{5,6}

Table 2. Patient no. 1—SF and liver function enzyme values during the initial (i) and repeat (r) study (ie, 12-month study period) and hepcidin levels in repeat study.

	BSL. (I)	M2 (I)	M4 (I)	M6 (I)	BSL (R)	M2	M4 (R)	M6 (R)	% CH. FR. BSL.
Ferritin (30-300 µg/L)	2195	2017	1537	1071	1057	935	967	929	-58
GGT (5-50 U/L)	151	132	132	137	117	116	110	123	-19
ALT (5-40 U/L)	80	81	59	43	54	49	39	38	-53
AST (10-40 U/L)	70	73	51	48	48	47	37	42	-40
Iron (5-30 µmol/L)	28	17.6	35.7	35.9	39.8	25.5	43.4	27.9	0
TIBC (46-70 µmol/L)	56	58	54	58	60	56	54	56	0
% srr (10%-45%)	50	30	66	62	66	46	80	50	0
Hepcidin (16-288 ng/mL)					12.3	16.8	8.3	19.3	57

Abbreviations: % ch. fr. bsl., percentage change from baseline; % srr, percentage saturation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bsl., baseline; GGT, γ -glutamyl transferase; TIBC, total iron-binding capacity.

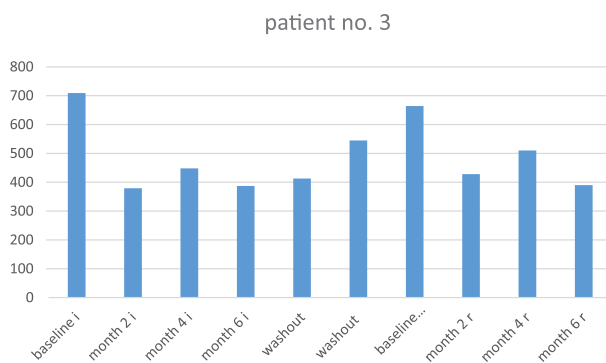


Figure 2. Serum ferritin (SF) levels of patient no. 3 during the initial study (i), washout period, and the repeat (r) study. The decrease in SF levels in patient no. 3 over 6-month period of initial study, an increase in SF during the washout period, and further decrease over 6-month repeat study period. Patient no. 3 showed a 45% decrease in SF levels from initial baseline.

In light of the encouraging results in this small, investigative study, we are planning a larger study to confirm the beneficial effect of 6-shogaol in patients with MDS with raised SF due to ineffective erythropoiesis.

Author Contributions

TG: consulted with patients, issued product, monitored follow-up visits and wrote up the resulting study.

THD: consulted on study methodology and assisted with analysis of results.

AM: recruited patients, consulted on study methodology, monitored follow-up visits, assisted with analysis of results and study write-up.

RR: recruited study patients, monitored follow-up visits.

VB: provided study concept and product.

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