Leukemia Research 34 (2010) 1151–1157

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Multicenter phase II trial of vitamin K_2 monotherapy and vitamin K_2 plus 1α-hydroxyvitamin D_3 combination therapy for low-risk myelodysplastic syndromes

Nobu Akiyama[a,g], Keisuke Miyazawa[b], Yoshinobu Kanda[c,g], Kaoru Tohyama[d,h], Mitsuhiro Omine[e,i], Kinuko Mitani[f,g,h], Kazuma Ohyashiki[b,g,h,*]

[a] Department of Internal Medicine, Teikyo University, Tokyo, Japan
[b] First Department of Internal Medicine, Tokyo 160-0023, Japan
[c] Department of Internal Medicine, Ohmiya Medical Center, Jichi Medical University, Saitama, Japan
[d] Department of Clinical Laboratory Medicine, Kawasaki Medical University, Okayama, Japan
[e] Department of Hematology, Showa University, Kanagawa School of Medicine, Japan
[f] Department of Hematology, Dokkyo Medical University School of Medicine, Tochigi, Japan
[g] Japan Hematology-Oncology Clinical Study Group (J-HOCS), Japan
[h] Japanese Research Committee for Research on Epoch-making Therapy for Myelodysplastic Syndrome, Japan
[i] Japanese Research Committee for Measures for Intractable Diseases, Japan

ARTICLE INFO

Article history:
Received 29 August 2009
Received in revised form 13 February 2010
Accepted 9 April 2010
Available online 1 June 2010

Keywords:
Myelodysplastic syndromes
Vitamin K_2
Vitamin D_3

ABSTRACT

We performed an open-labeled single-arm prospective phase II clinical trial of vitamin K_2 (menatetrenone: VK2) monotherapy and VK2 plus 1α-hydroxyvitamin D_3 (alfacalcidol: VD3) combination therapy for myelodysplastic syndromes (MDS) with refractory anemia and refractory cytopenia with multilineage dysplasia, having either low or intermediate-1 risks of the IPSS. The overall response rate to VK2 monotherapy (45 mg/day) after 16 weeks was 13% (5/38) including 4 cases with improvement of both anemia and thrombocytopenia and 1 case with thrombocytopenia. We then enrolled and evaluated 20 out of 33 VK2-monotherapy non-responders for VK2 plus VD3 (0.75 μg/day) combination therapy. The overall response rate at 16 weeks after initiation of VK2 plus VD3 was 30% (6/20). HI for hemoglobin (Hb) was observed in 6 out of 11 patients (55%) and for thrombocytopenia in 3 out of 11 patients (27%), respectively. No HI was observed for neutropenia in VK2 monotherapy and VK2 plus VD3 combination therapy. It was suggested that IPSS scores and absolute neutrophil counts positively correlated, and Hb levels inversely correlated with the response to VK2 plus VD3 combination therapy. Our study demonstrated that VK2 plus VD3 combination therapy appears to be promising for improvement of anemia and thrombocytopenia with low/intermediate-1 MDS.

1. Introduction

Myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by dysplastic features of hematopoietic and blood cells, cytopenias caused by ineffective hematopoiesis, and a variable risk of progression to acute myeloid leukemia (AML) due to accumulation of genetic abnormalities [1]. The treatment options available to patients with MDS are largely based upon the patient's age and prognosis as determined by the International Prognostic Scoring System (IPSS) [2]. For patients in the low to intermediate-1 by IPSS score categorized as "low-risk MDS", the goal of treatment is to improve ineffective hematopoiesis while providing the appropriate supportive care. The US National Comprehensive Cancer Network MDS recommendations are that therapies for the patients with low-risk with clinically significant cytopenias should be stratified into several groups, for example lenalidomide for del(5q), erythropoietin (Epo) for patients with low serum Epo [3]. DNA-hypomethylating agents as azacitidine or decitabine are also recommended for non-responders to these treatments. However, these therapeutic effects are not satisfactory for every patient and other options for low-risk MDS, especially elderly MDS patients, are still required [4].

Vitamin Ks are known to act as cofactors for γ-carboxylation of vitamin K-dependent coagulation factors. Menatetrenone, a vitamin K_2 analog, is approved as an active agent for osteoporosis in Japan [5,6]. As a coenzyme of γ-carboxylase, it promotes osteogen-

* Corresponding author at: First Department of Internal Medicine, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.
Tel.: +81 3 3342 6111x5895; fax: +81 3 5381 6651.
E-mail address: ohyashik@rr.iij4u.or.jp (K. Ohyashiki).

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doi:10.1016/j.leukres.2010.04.006

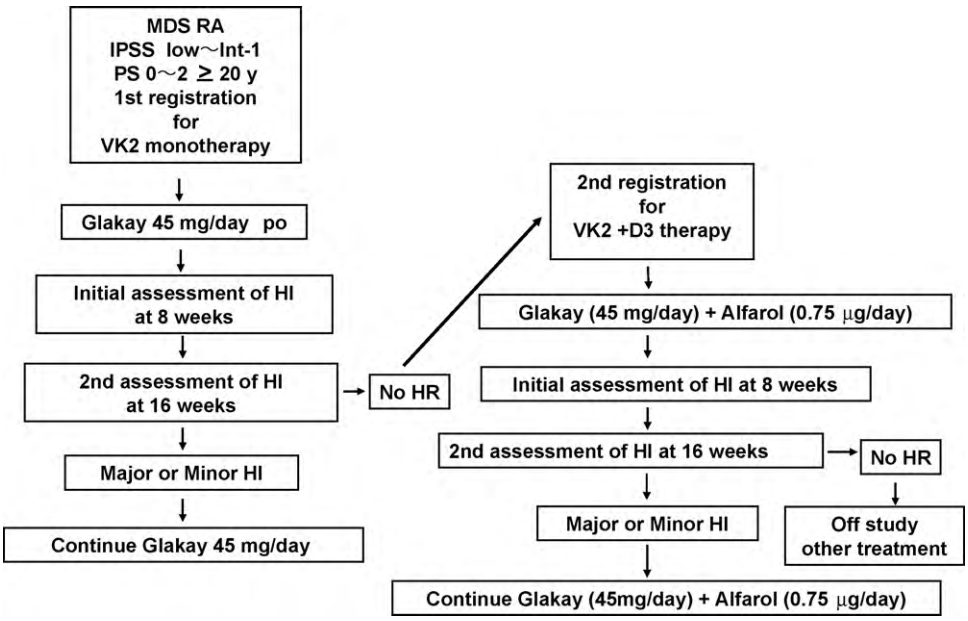

Fig. 1. Treatment strategy for VK2 monotherapy or VK2 plus VD3 combination therapy.

esis through γ-carboxylation of glutamate residues in osteocalcin. The safety of long term administration of menatetrenone has been well established [5,6]. The efficacy of oral menatetrenone therapy in RA and other types of MDS has been reported in Japan [7–10]. Regarding with the effect for improvement of cytopenias in clinical trials including pilot studies, the response varies 20–75%, and toxicity is tolerable [8–10]. The underlying mechanism of improvement of cytopenias by vitamin K_2 (VK2) remains to be cleared. However, VK2 has been reported to induce apoptosis and differentiation in some leukemic cell lines *in vitro* [11–13]. VK2 was also reported to improve hematopoietic supportive functions of the stromal cell lines established from MDS patients [14].

The active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 inhibits the proliferation and induces the differentiation of normal and leukemic myeloid cells *in vitro* [15]. There are reports demonstrating that vitamin D_3 analogs such as alfacalcidol (1α-hydroxyvitamin D_3), calcifediol (25-hydroxyvitamin D) and calcitriol (1α,25-dihydroxyvitamin D_3) have some therapeutic effects in patients with MDS [15–19]. Mellibovsky et al. reported that treatment with calcifediol showed some hematological improvements in 10 out of 14 MDS patients with low/intermediate risk [18]. Motomura et al. reported that alfacalcidol prevents the progression of MDS to overt leukemia under the effect of differentiation capacity from blasts to monocytes [19]. However, these therapeutic effects of VD3 analogs in MDS were controversial [20,21]. The therapeutic serum concentrations of these VD3 analogs based on *in vitro* studies were supposed to be practically difficult to achieve because of hypercalcaemia *in vivo*, a well known dose-limiting toxicity of vitamin D_3 (VD3) [21]. It is noteworthy that combination of VK2 plus either 22-oxa-1,25-dihydroxyvitamin D_3

Table 1
Characteristics of evaluable patients for VK2 monotherapy and VK2 plus VD3 combination therapy.

	VK2 monotherapy ($n=38$)			VK2 + VD3 combination therapy ($n=20$)		
Age	Median: 65 years, range: 23–84			Median: 65 years, range: 27–81		
Sex	Male 20	Female 18		Male 10	Female 10	
WHO classification	RA 27	RCMD 11		RA 16	RCMD 4	
IPSS	0 13	0.5 19	1 5	0 7	0.5 8	1 5
Hb	Average: 8.99 ± 3.03 g/dl <10 g/dl 24	10 g/dl≦ 14		Average: 9.47 ± 3.16 g/dl <10 g/dl 11	10 g/dl≦ 9	
PLT	Average: 118,900 ± 121,000/μl <100,000/μl 24	100,000/μl≦ 14		Average: 133,500 ± 149,400/μl <100,000/μl 11	100,000/μl≦ 9	
ANC	Average: 1,426 ± 1,013.5/μl <1500/μl 25	1500/μl≦ 13		Average: 1082.5 ± 746.8/μl <1500/μl 14	1500/μl≦ 6	
Transfusion dependency	RBC 10	PLT 6		RBC 2	PLT 3	
Cytogenetics	Normal 26	Abnormal 11	Unknown 1	Normal 13	Abnormal 7	Unknown 0