**Brief report**

Treatment of myelodysplastic syndromes with valproic acid alone or in combination with all-trans retinoic acid

Andrea Kuendgen, Corinna Strupp, Manuel Aivado, Alf Bernhardt, Barbara Hildebrandt, Rainer Haas, Ulrich Germing, and Norbert Gattermann

Valproic acid (VPA) has been shown to inhibit histone deacetylase activity and to synergize with all-trans retinoic acid (ATRA) in the differentiation induction of acute myelogenous leukemia (AML) blasts in vitro. We treated 18 patients with myelodysplastic syndromes (MDS) and AML secondary to MDS (sAML/MDS) with VPA monotherapy (serum concentrations 346-693 μM [50-100 μg/mL]). Five patients received VPA and ATRA (80 mg/m²/d, days 1-7, every other week). Response according to international working group (IWG) criteria was observed in 8 patients (44%) on VPA monotherapy, including 1 partial remission. Median response duration was 4 months (range, 3-9 months). Four of 5 patients relapsing were treated with VPA + ATRA, 2 of them responding again. Among 5 patients receiving VPA + ATRA from the start, none responded according to IWG criteria, but 1 patient with sAML/MDS achieved a marked reduction in peripheral and marrow blasts. Thus, VPA is of therapeutic benefit for patients with MDS, and ATRA may be effective when added later. (Blood. 2004;104:1266-1269)

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**Introduction**

Valproic acid (VPA) is a short-chain fatty acid (SCFA) that has been used as an anticonvulsant for 30 years. Recently, the drug has been discovered to have additional properties. There is growing evidence that VPA, like other SCFAs, affects the growth and differentiation of a variety of malignant cells in vitro.1,2 Tumor cell differentiation induced by VPA is coupled with its capability to inhibit histone deacetylation.3,4 Histone acetylation status, which is controlled by histone acetylases (HATs) and deacetylases (HDACs), plays a key role in the regulation of gene transcription. Altered activity of HDACs in malignant cells leads to decreased histone acetylation and, in turn, silencing of tumor suppressor genes. This is because highly charged hypoacetylated histones bind tightly to DNA, preventing transcription factors from gaining access to the affected genes. Acetylation instead neutralizes the positive charge and generates an open, easily accessible DNA conformation, facilitating re-expression of the tumor suppressor genes.5-8

VPA is capable of inducing differentiation as well as apoptosis in leukemic cell lines in vitro, and this differentiating effect is enhanced by all-trans retinoic acid (ATRA).9-12 Because VPA is orally applicable, reaches stable serum concentrations, and has a low toxicity profile, we tried to harness its differentiation-promoting effects for the treatment of patients with myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) secondary to MDS (sAML/MDS).

**Study design**

Between February 2002 and August 2003, 23 patients with MDS and sAML/MDS were treated after written informed consent had been obtained. The study protocol was approved by the ethics committee of the Medical Faculty of Heinrich-Heine-University, Düsseldorf, Germany. Clinical characteristics of the patients are given in Table 1. VPA was administered to reach serum concentrations between 346 and 693 μM (50 and 100 μg/mL), which is the therapeutic range for treatment of seizures. These concentrations have been shown to inhibit histone deacetylase activity in vitro1,4 and to exert an effect on fetal hemoglobin synthesis in vivo, indicating HDAC inhibition.15 Hematologic toxicities of VPA are mainly observed at serum valproate levels greater than 693 μM (100 μg/mL).16,17 ATRA was given at a dosage of 80 mg/m²/d in 2 divided doses, days 1 to 7, every other week.18 If neither significant side effects nor disease progression occurred, treatment was continued. Eighteen patients were started on VPA monotherapy, with addition of ATRA planned for patients who did not respond or who relapsed. In an attempt to enhance responses, 5 patients were treated with VPA + ATRA from the start, using the same dosages. Serum VPA concentrations were measured with a commercially available fluorescence polarization immunoassay (Abbott, Wiesbaden, Germany). Treatment response was assessed according to international working group (IWG) criteria.19

**Results and discussion**

Median treatment duration was 6 months (range, 2-23 months) for VPA and 3 months (range, 1-18 months) for ATRA. All patients had serum VPA concentrations within the target range and completed at least 2 months of treatment. Median dosage was 1250 mg (range, 900-2550 mg). According to IWG criteria, 8 patients (44%) on VPA monotherapy responded to treatment (nos. 3, 10, 11, 13, 14, 16, 21, 23), with a median time to response of 30 days (range, 14-38 days).

We observed hematologic improvement in 7 patients, namely 2 major erythroid (MaR-E), 2 minor erythroid (MiR-E), 1 major...
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Study group 1 indicates VPA monotherapy; study group 2, VPA + ATRA; WHO, World Health Organization; IPSS, International Prognostic Scoring System; RAEB, refractory anemia with excess of blasts; Int, intermediate; Epo, erythropoietin; SD, stable disease; —, not applicable; PD, progressive disease; RCM, refractory cytopenia with multilineage dysplasia; MaR-N, major neutrophil response; RCM with RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; 2-CDA, 2-chlorodeoxyadenosine; ATG, antithymocyte globulin; G-SCF, granulocyte colony-stimulating factor; MR-E, minor erythroid response; NA, not applicable; PR, partial remission; MaR-P, major platelet response; MaR-E, major erythroid response; MTC, mitoxantrone, topotecan, cyclophosphamide; FTI, famesyltransferase inhibitor; CMML, chronic myelomonocytic leukemia; PSA, pure sideroblastic anemia.

*Temporary rise in platelet count (≤ 2 months).
†Reduction in blast count.
‡Treatment ongoing.
§Response ongoing.
neutrophil (MaR-N), and 2 major platelet responses (MaR-P; Figure 1), as well as partial remission (PR) in 1 patient (Figure 1). Among the responding patients, 3 have ongoing responses (4, 4, and 9 months, respectively). Five patients relapsed after a median of 4 months (range, 3-5 months), and 4 of these patients were switched to VPA + ATRA, with 2 responding for another 11 and 16 months, respectively, at the time of this writing.

Four patients showed stable disease, with a median duration of treatment of 5 months. Six patients had progressive disease. Of the nonresponding patients, 6 (2 SD, 4 PD) were changed to VPA + ATRA, without success.

In the group of 5 patients treated with VPA + ATRA from the start, we observed no response according to IWG criteria. Still, 1 patient (no. 12) with sAML/MDS showed clearance of peripheral blasts (27%), and a decrease in bone marrow blasts (45% to 10%). Another patient had stable disease for 3 months, while 3 cases were classified as progressive disease.

Regarding prognostic groups, all 3 patients belonging to the low-risk category according to the International Prognostic Scoring System (IPSS) showed a major response. In contrast, only one of the high-risk patients had a (minor) response. Still, among 9 patients with elevated blast count in the marrow, 3 (33%) achieved a significant reduction of peripheral and marrow blasts.

Looking for other variables with prognostic relevance, we found that the frequency of red cell transfusions prior to VPA treatment was significantly lower in responders than in nonresponders (P = .026). Response to VPA was not associated with age (P = .397), sex (P = .278), pretreatment platelet count (P = .244), bone marrow blast count (P = .453), or dosage of VPA (P = .624). The frequency of chromosomal aberrations was not different (P = .879), but 3 of 4 responders with cytogenetic abnormalities had a low-risk karyotype (–Y). None of the patients with complex karyotype responded.

Considering potential confounding factors, it is noteworthy that 2 responders had concomitant erythropoietin treatment. They had been receiving Epo for 7 and 18 months, respectively, making a late response to Epo unlikely. However, a synergism, perhaps by inhibition of apoptosis, cannot be excluded. In 2 patients who had been receiving thalidomide for 2.5 and 4 months, respectively, before starting VPA, a delayed thalidomide response cannot be excluded, although only one such case among 83 patients has been reported by Raza et al.

Response to VPA monotherapy was better than response to first-line combination with ATRA. A possible explanation might be that HDAC inhibition is needed to relieve repression of retinoic acid signaling pathways. Therefore, pretreatment with VPA may be necessary for a synergistic effect of both drugs.

Side effects were mild. Only one patient discontinued VPA because of vertigo and tremor. A few patients had fatigue (≤ grade 2). Thrombocytopenia (< 50% of initial platelet count) occurred in 8 patients and appeared to be attributable to study medication in 2 patients (nos. 10 and 4). Both patients had received VPA + ATRA, and platelet counts normalized when treatment was discontinued. In all other patients thrombocytopenia was more likely a result of progressive disease. Intermittent ATRA treatment was well tolerated. Grades 1 to 2 hyperkeratosis and cheilitis were observed in 2 patients.

To our knowledge, this is the first report on valproic acid alone or in combination with ATRA for the treatment of MDS. Gore et al conducted 2 trials of the structurally related HDAC inhibitor phenylbutyrate in patients with MDS and AML, achieving responses in 4 of 27 and 2 of 23 patients, respectively. Of interest, plasma concentrations of phenylbutyrate, achieved at the maximum tolerated dose level, were lower than targeted on the basis of in vitro studies. On the basis of the relatively small numbers of patients treated, response to phenylbutyrate appears to be less frequent than response to VPA.

Although VPA must be considered a first-generation HDAC inhibitor, it has the advantage of oral applicability, stable serum concentrations, and a low toxicity profile. From our study we conclude that oral treatment with valproic acid is well tolerated and achieves a response rate of approximately 40% in patients with MDS. Because VPA is also a promising drug for combination regimens with cytotoxic or demethylating agents, future studies may concentrate on using such combinations to increase the rate and duration of responses.

**Acknowledgment**

We thank Prof Aul, Duisburg, Germany, for providing clinical data.

**References**


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