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Case report

Valproic acid for the treatment of low-risk myelodysplastic syndromes: A case report and a review of the literature

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ABSTRACT

Myelodysplastic syndromes are heterogeneous myeloid neoplasms ranging from indolent conditions with a near-normal life expectancy to forms approaching acute myeloid leukemia. Here we report a 51-year-old woman with depression and severe obesity who was diagnosed with an International Prognostic Scoring System low-risk myelodysplastic syndrome, presenting mainly with thrombocytopenia, treated with escalating dose of valproic acid as a single agent. After two years of treatment her platelet count is almost normal and the tolerance to therapy is good. It is already known that valproic acid could be used in high-risk myelodysplastic syndromes and acute myeloid leukemia, mainly in association with other drugs, but its role in low-risk myelodysplastic syndrome is not well established yet.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders associated with worsening cytopenias and leading to reduced survival and a compromised quality of life.[1,2] Treatment for MDS patients with low-risk disease generally requires the management of the patient's symptomatic anemia with its attendant fatigue.[3] Patients with severe thrombocytopenia (rarely the only cytopenia) also require supportive management. The prevalence of thrombocytopenia $< 100 \times 10^9$/l in MDS ranges from 33% to 76%.[4–6] Severe thrombocytopenia is generally managed with platelet (PLT) transfusion support (at levels $\leq 10 \times 10^9$ or $\leq 20 \times 10^9$/l for clinical bleeding). Peri-operative platelet transfusion support is often needed for patients with even higher PLT counts due to their frequent thrombocytopathy.

There is no consensus about how to treat isolated thrombocytopenia in MDS patients and several drugs are under investigation.

Romiplostim is an Fc-fusion protein that augments thrombopoiesis by binding to and activating the thrombopoietin receptor.[7] It is approved for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Romiplostim is under investigation for thrombocytopenia in patients with International Prognostic Scoring System (IPSS)[8] low-risk or intermediate 1-risk MDS who are not currently receiving disease-modifying treatment and in patients who have MDS with grade 3 or 4 treatment-related thrombocytopenia. Few phase II clinical trials have demonstrated the efficacy of romiplostim for increasing PLT levels and decreasing thrombocytopenic adverse events either alone or in combination with hypomethylating agents.[9–11]

The novel nonpeptide thrombopoietin receptor agonist eltrombopag was approved also for treatment of patients with chronic idiopathic thrombocytopenic purpura (ITP) in the United States and in Europe. Eltrombopag has been shown to effectively elevate PLT numbers and reduce thrombocytopenia-related complications in patients with chronic ITP or hepatitis C.[12,13] This drug is now under investigation for thrombocytopenia in low-risk MDS.[14,15]

Valproic acid is another drug which has shown an antileukemic activity mainly when used in association and in high-risk MDS and AML.[16–18]

Its current use in low-risk MDS is neither clear nor well established (Table 1 shows an overview of the published studies).

2. Case study

A 51-years-old woman came to our attention on February 2010 for decreased PLT count (PLT 39×10^9/L) and an increase in the mean corpuscular volume (MCV) without anemia (Hb 12.6 g/dL, MCV 104.3 fL) or leukopenia (WBC 5.06×10^9/L, neutrophils 3.50×10^9/L) which were discovered by chance after a routine check of the complete blood cell (CBC) count. Anti-PLT I and D antibodies were absent. Physical examination did not show splenomegaly, showed a severe obesity (body mass index = 33),

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Table 1
Overview of the studies on the use of VA in MDS.

Author	Cohort	Treatment schedule	Response rate
Siitonen et al. Haematologica 2007	MDS/CMML	VA dose escalation in 2 weeks→[VA] 500–700 mcmol/L+13-cis-retinoid acid 10 mg twice a day+Vitamin D_3 1 mcg once a day	16% HI
Ryningen et al. Leukemia Research 2008	AML	VA dose escalation i.v. for 5 day (then oral therapy until the appearance of side effects), after 5 days given orally+ATRA 22.5 mg twice a day for 14 days every 3 months +Theoplylline→[theophylline] 50–100 mcM	41% HI
Voso et al. Cancer Research 2009	MDS/AML	VA dose escalation→[VA] > 50 mcg/mL+5-aza 75 mg/m^2 daily for 7 days (repeated once every 28 days)	30% (CR+PR)
Cimino et al. Cancer Research 2006	AML	VA dose escalation→[VA] 50–110 mcg/mL+ATRA 22.5 mg twice a day (since VA is in range or since day 14 from VA start)	25% HI
Kuendgen et al. Blood 2004	MDS/AML	VA dose escalation→[VA] 50–100 mcg/mL+ATRA 40 mg twice a day for 7 days every other week	24% HI
Pilatrino et al. Cancer 2005	MDS/AML	VA dose escalation→[VA] 45–100 mcg/mL+ATRA 45 mg once a day (since VA is in range)	"Clinical benefit" 30%
Kuendgen et al. Clinical Epigenetics 2012	MDS/AML	VA dose escalation→[VA] 80–110 mcg/mL+5-aza 100 mg/m^2 daily for 5 days (repeated once every 28 days)	37% (CR+PR)

MDS: myelodysplastic syndrome, AML: acute myeloid leukemia, ATRA: all trans retinoic acid, 5-aza: 5-azacitidine, HI: hematological improvement, CR: complete remission, PR: partial remission, i.v.: intra vein.

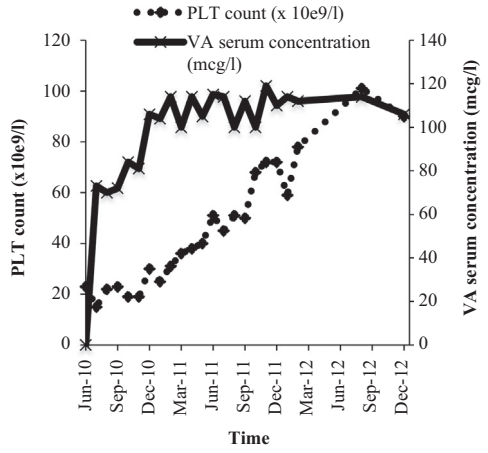

Fig. 1. PLT count trend during the treatment with Valproic Acid (according to VA serum concentration).

the patient was previously diagnosed with a depression treated with risperidone. Since this was suggestive for a MDS, on 25th of February 2010 a bone marrow (BM) evaluation was performed; the BM aspirate was not evaluable, while the trephine showed a cellularity of 30%, an erythroid slow maturation with an increase of haemosiderin, small and medium size of the megakaryocytes precursors and no abnormality or maturation defects of the myeloid progenitors, myeloid blasts were less than 5%, no sign of bone marrow fibrosis. Cytogenetic was normal. The patient was eventually diagnosed with a IPSS low and WPSS very low risk MDS; considering her comorbidities, and the absence of a sibling donor she was considered noneligible for allogeneic stem cell transplantation; the patient also refused to be enrolled in a clinical trial for the use of eltrombopag in low risk MDS. As the patient never reported any bleeding, the final decision was to adopt a watch and wait strategy and the thrombocytopenia remained stable until May 2010 (40×10^9/L). On June 2010 PLT count started to decrease and we decided, after having properly informed the patient, to start valproic acid starting 200 mg per day with a weekly assessment of serum valproic acid concentration (normal range in our laboratory: 50–100 mcg/L); the decision to start from such a low valproic acid dosage was made based on our limited experience with this drug. There was a progressive increase in drug dosage up to 1200 mg per day on November 2010 (with this dosage valproic acid serum concentration permanently raised up to 70 mcg/L). The PLT count stayed stable around 20×10^9/L until December 2010. Since January 2011 the serum level of valproic acid moved to the upper normal limit (100 mcg/L) and PLT increased up to 30×10^9/L in January and up to 40×10^9/L in April, 50×10^9/L in June, 60×10^9/L in September when she had to decrease the dosage down to 1000 mg per day due to tremor and sleepiness. In November PLT count was 72×10^9/L. She is currently under treatment with valproic acid 1000 mg per day and her PLT count is constantly higher than 90×10^9/L (Fig. 1 shows the trend of PLT count according to VA serum concentration).

3. Discussion

Here we report a case of a low-risk MDS with just one cytopenia successfully treated with valproic acid (12 months of hematological response). According to National Comprehensive Cancer Network (NCCN) guidelines, the treatment for clinically relevant neutropenia or thrombocytopenia ranges from hypomethylating agents (not approved in Italy for this setting of patients) to allogeneic stem cell transplantation or immunosuppressive treatment for nonresponders to hypomethylating drugs. Still the best choice is to include them in clinical trials.

Valproic acid is a potent inhibitor of histone deacetylases (HDAC). It can modify the structure of chromatin allowing recruitment of transcription factors to restore epigenetically suppressed genes.[19] Valproic acid has been shown to possess antiproliferative activity and to overcome the differentiation block in leukemia blast cells.[20,21] Valproic acid concentrations consistent with normal clinical dosage are believed to achieve the inhibition of HDAC.[20,22]

In 2004 Kuendgen et al. observed a response, according to international working group (IWG) criteria[23], in 8 patients (both high-risk MDS and AML) (44%) on Valproic acid monotherapy, including 1 partial remission and median response duration was 4 months (range 3–9 months).[24] Later on, the same group confirmed their results in the same setting of patients and found that all trans retinoic acid (ATRA) could add some benefits in valproic acid nonresponders.[25] Almost the same observations were made by an Italian group in 2005; they observed a clinical benefit in 30% of their patients (high-risk MDS and AML) treated with a combination of both valproic acid and ATRA.[26] The association HDAC inhibitors and hypomethylating agents was also used in IPSS high risk MDS and in AML patients and 30% of patients obtained a remission (complete and partial) suggesting, according to the authors, that valproic acid could enhance azacitidine efficacy.[18] The

same drug association was used by a German group and confirmed the results shown by Voso et al..[27]

In conclusion, we have reported a case of a low-risk MDS patient who was successfully treated with escalating doses of valproic acid and showed a good response; this therapy was safe (no grade 3 or 4 toxicity), effective, feasible, and inexpensive. Clinical randomised trials are needed to confirm the antileukemic activity of this drug (in combination with others, e.g. hypomethylating agents) in high-risk MDS and AML and to extend its use to low-risk disease. The identification of cytogenetic and molecular features able to predict the response to valproic acid would be useful as well.

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