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Review Article

Thrombocytopenia in Patients with Myelodysplastic Syndromes: Still an Unsolved Problem

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Abstract. The myelodysplastic syndromes (MDS) are a group of clonal bone marrow (BM) stem cell disorders, characterized by ineffective hematopoiesis, peripheral cytopenias, and hematologic cellular dysfunction, as well as potential transformation to acute leukemia.
Thrombocytopenia is common in MDS and is associated with bleeding complications, occasionally life-threatening. Low platelet count (PLT), as well declining PLT also serves as a prognostic marker. Understanding thrombopoiesis led to the cloning of thrombopoietin, resulting in the development of platelet stimulating agents, thrombomimetics, romiplostim and eltrombopag.
Both agents have been shown to increase PLT, decrease the need for platelet transfusions and reduce the number of bleeding episodes, with a reasonable tolerance. They are already approved for immune thrombocytopenia and thrombocytopenia related to liver disease.
Romiplostim and eltrombopag have proven efficacy in lower- and higher-risk MDS with thrombocytopenia, as monotherapy, as well as a part of a combination, either with lenalidomide, and mainly combined with hypomethylating agents. However, safety concerns have been raised: while several trials have been completed with no evidence of disease progression, others have been early terminated due to an increased number of BM blasts and possible leukemic transformation in treated-patients. The jury is still out regarding this safety concern, although recent publications are more encouraging.

Keywords: Myelodysplastic Syndrome, Thrombocythopenia, Thrombomimetics.

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Introduction. The myelodysplastic syndromes (MDS) are a group of clonal bone marrow (BM) stem cell disorders, characterized by ineffective hematopoiesis, peripheral cytopenias, and hematologic cellular dysfunction, as well as potential transformation to acute leukemia.[1,2,3] The clinical course is variable and the main clinical manifestations are related to the cytopenias: anemia with the related symptoms, leukopenia with an increased incidence of infections, and thrombocytopenia with a risk of bleeding. MDS is usually a disease of the elderly, with 74 as the median age of diagnosis, and overall survival (OS) ranging from 4.6 years in patients with lower-risk disease[4] to less than two years for the patients with higher-risk disease.[2,5]

Thrombocytopenia, defined as platelet count (PLT) less than $100x10^9$/L, occurs in 40-65% of patients with MDS.[6] It is more common in the elderly and in patients with higher–risk disease. Severe thrombocytopenia, PLT< $30x10^9$/L occurs in 7.1% of MDS patients.[7] The Low PLT, as well as the PLT dysfunction,[8] is associated with bleeding in 19% of MDS patients,[9] and bleeding is the cause of death in 10%-20% of MDS patients.[6,10]

The differential diagnosis of MDS with isolated thrombocytopenia from immune thrombocytopenia (ITP) might be sometimes difficult. The involvement of other lineages, as well as the use of additional markers, might help in distinguishing between both disorders and establishing the diagnosis of MDS. The use of flowcytometry, and applying the Ogata score,[11] as well as molecular analysis and detection of MDS typical signatures, might help.[12]

Low PLT is also considered an independent prognostic factor and has been introduced into the prognostic classification systems,[4,12,13] since it is believed to reflect the BM function and reserve. Recently, Itzykson et al[14] have shown that not only PLT at presentation but also the rapidly decreasing platelet count (kinetics) might indicate a poor prognosis.

In addition to BM failure as a cause of thrombocytopenia, one has to take into consideration that PLT may decline due to some of the treatments administered to these patients, such as lenalidomide[15,16] and hypomethylating agents (HMA), azacitidine[17] and decitabine.[18]

Until recently, PLT transfusions have been the only available treatment for clinically significant thrombocytopenia.[2] More than 33% of patients require PLT transfusions at some point in their treatment.[9] However, PLT transfusions might carry the risk of infection transmission (being a biological product), and might also be associated with a risk of alloimmunization, and a short effect. Thus, more effective therapy is needed**.**

Thrombopoiesis and Thrombomimetic Agents. It has been more than a hundred years since James Homer Wright proposed that BM megakaryocytes are responsible for PLT production.[19] Production of PLT involves hematopoietic stem cells, megakaryocytes, their differentiation, BM microenvironment and hematopoietic cytokines. In 1958 Kelemen et al. described the humoral substance responsible for PLT production, thrombopoietin (TPO, THPO).[20] In 1994, three research groups simultaneously cloned and identified thrombopoietin.[21] TPO is a hormone produced in several organs, including the liver, kidney, skeletal muscle, and mainly by the BM stroma. The hormone acts on megakaryocyte progenitors to enhance their proliferation and survival.[22] TPO interacts with the surface receptor, c-mpl, a member of the hematopoietic growth factor receptor superfamily.[23] TPO has also been reported to have an effect on other lineages as well, at least in murine systems.[24,25]

The TPO cloning opened new avenues for treatment of MDS-related and other types of thrombocytopenia. A successful treatment is characterized by increasing PLT, and/or reducing the need for PLT transfusions and/or minimizing significant bleeding episodes, with a reasonable tolerance. The first generation drug, the recombinant human TPO mimicked TPO function by activating thrombopoietin receptor (TPOR). Despite encouraging preliminary results,[26] the development of these agents was stopped when they were found to be associated with stimulation of antibodies that cross-reacted with endogenous TPO, eventually leading to severe thrombocytopenia.[27] The next step was the development of non-peptide TPO mimetics or peptide TPO mimetics, thrombopoietin receptor agonists (TPO-RA), that do not share epitopes with endogenous TPO, the second-generation TPO mimetics, romiplostim and eltrombopag.

The two agents have been successfully tested in several types of thrombocytopenia, and have been approved in Europe and the US, for the treatment of adults with thrombocytopenia related to aplastic anemia, chronic ITP and liver disease.[28] Both agents have good short- and long-term safety profiles and reasonable tolerance.[29,30] The common adverse effects are fatigue, diarrhea, and headache.[28] Other potential adverse effects are a risk for thrombotic complications, cytogenetic abnormalities, BM fibrosis, rebound thrombocytopenia, hepatic abnormalities, cataracts, and development of cross-reactive antibodies.

Romiplostim (Nplate®, Amgen) is a homodimer of a single-chain peptide consisting of the human IgG1-Fc region linked to a TPOR binding domain.[31] Romiplostim binds the extracellular

domain of the TPOR and competes with TPO for this binding site. It is administered as a weekly subcutaneous (SC) injection. Single intravenous or SC injection in healthy people showed a dose-responsive PLT production with an apparently linear relationship between PLT response and dose and a peak PLT on days 12 to 16.

In the first phase I/II clinical trial (**Table 1**), 44 patients with lower-risk MDS and thrombocytopenia, (PLT<50x10^9/L), romiplostim monotherapy increased PLT in four dosing regimens (300, 700, 1000, and 1500 µg).[32] Finally, 700 µg was suggested to be the optimal dose. A durable PLT response (eight consecutive weeks independent of PLT transfusions) was achieved in 19 of 41 patients (46%). Those who achieved PLT response required fewer transfusions. However, two patients had an increase in BM blast count and progressed to AML, and other four patients experienced a transient increase in BM blast percentage. The results of this study, although encouraging, raised concerns about a possible association with leukemic progression.[32]

This was followed by a phase II study, in which 250 patients with low- or intermediate-1- risk MDS were randomized to receive romiplostim or placebo.[33] The number of clinically significant bleeding events (CSBE) was smaller in the romiplostim group. CSBE per patients had a hazard ratio for romiplostim: placebo of 0.83. PLT response rates were also higher in the romiplostim group (36.5%) versus the placebo group (3.6%). Unfortunately, the trial was early terminated due to concerns about increased rates of AML in the romiplostim group (6% vs 4.6%). Survival rates were similar among the two groups. Recently, Kantarjian et al.,[34] have updated the study results, reporting a 5-year long-term prognosis of the patients who continued the follow-up. According to this report, both previously romiplostim-treated and placebo-treated patients had a similar leukemic transformation rate (12 vs 11%, HR 1.06) and mortality (56% vs 54%, HR 1.03).[34,35] However, as we noted in our commentary,[36] caution is still required in interpreting these data, since the patients in the romiplostim group had not been receiving romiplostim since 2011, and thus the report summarizes long-term prognosis of patients treated for a relatively short period. We still lack the safety data on monotherapy romiplostim administration for a long time.

Another study was designed to determine optimum scheduling of romiplostim in 28 low-risk MDS patients.

Patients were randomized to receive 750µg,

Table 1. Summary-Thrombomimetics in MDS-related thrombocytopenia

Authors	Ref #	Agent	Phase	MDS type	# Pts	Results	Safety	Comments
Kantarjian	32	Romi	I/II	LR	44	46% PLT Red P-Tr	2 AML 4 Bl-inc	Safety concerns
Giagounidis	33	Romi	II	Low/ Int-1	250	CSBE 0.8 36% PLT	AML 6% vs 4.6%	Early terminated
Sekeres	37	Romi	I/II	LR	28	65% PLT 61% P-tr	2 Bl-inc	750 mic/wk SC-dose
Prica	38	Romi	Meta		384	Bleed RR 0.8 P-tr RR 0.7	No AML risk	
Kantarjian	40	Romi+ Aza	II	Low/Int-1	40	CSTE 71%, 62%	2 AML	Not significant
Greenberg	41	Romi + DAC	II	Low/Int-1	29	Bleed 27% PLT 22%	No safety concerns	
Wang	42	Romi + Len	II		54	CSTE 29% vs 67%	2 Bl-inc	
Oliva	46	Elt	II	Low/ Int-1	90	47% PLT	No safety concerns	
Platzbecker	47	Elt	I/II	HR + AML	98	38% P-tr	No safety concerns	
Mittelman	48	Elt	II	HR + AML	145	CRTE 54%	No safety concerns	
Svensson	50	Elt + Aza	Pilot	Int2/ HR	12	9/12 PLT	No safety concern	
Dickinson	51	Elt + Aza	III	Int1/Int-2/HR	356	Futile	12% AML	Early terminated

Legends: Romi – Romiplostim; LR/Int-1/Int-2/HR – MDS subtypes (low, intermediate and high-risk); PLT – platelet count increase (in % of patients); P-tr – decreased (reduced) need for platelet transfusions (in % of patients); Bleed- bleeding events; Bl-inc – increased blast % in treated patients; Aza-azacitidine; DAC – decitabine (dacogen); Len-lenalidomide; CSTE – clinically significant thrombocytopenic events; CRTE – clinically relevant thrombocytopenic events.

weekly SC, biweekly SC, or biweekly IV. Of the patients who completed 8 weeks of treatment, PLT response and reduced PLT transfusions were achieved in 65% and 61% of the patients, respectively.[37] Duration of response was twice as long in the weekly vs biweekly administration. Two patients did have an increase in blast percentage. No neutralizing antibodies were found. The authors recommended 750µg per week SC as the standard dose.

A meta-analysis summarizing data from five TPO-RA trials with 384 patients, reported a relative risk (RR) of 0.84 for bleeding and 0.69 for PLT transfusion rate with romiplostim compared with placebo.[38] The risk of AML progression was not increased. In an attempt to develop a predictive model for the response to romiplostim, based on a cohort of 250 patients, factors such as low levels of TPO, and less than 6 PLT transfusions were found to predict better response to the drug.[39]

Given the high incidence of decreasing PLT in MDS patients treated with HMA and/or lenalidomide, TPO-RA were investigated in these patients. In a small study (n=40), SC weekly romiplostim, 500µg, 750µg, or placebo was administered to azacitidine (AZA)-treated MDS patients. The clinically significant thrombocytopenic events (CSTE) in the placebo, romiplostim 750 and romiplostim 500 groups occurred in 85%, 71% and 62% of the patients respectively, but the results were not statistically significant.[40] No neutralizing antibodies were detected. Two patients in the romiplostim arm and one in the placebo arm progressed to AML.

In a study with 29 low- or intermediate-1 risk MDS patients receiving decitabine, patients were randomized to receive romiplostim or placebo. Bleeding events occurred in 43% of placebo and 27% of romiplostim treated patients. PLT response was higher in the romiplostim group as well (33% vs 21%). Disease progression did not seem to be associated with romiplostim in this study since a similar percentage in each group progressed to AML.[41]

A phase II study with 54 lenalidomide - treated MDS patients, assessed whether concurrent romiplostim could alleviate the drug-related thrombocytopenia.[42] Clinically significant thrombocytopenic events (CSTE) were reported in 67% in the placebo group and 29% in the romiplostim group. Romiplostim-treated patients also required fewer PLT transfusions. Two patients were found to have an increase in BM blasts >20% during the treatment.

Eltrombopag (Revolade ®, Novartis), is an oral, small-molecule, nonpeptide TPO-RA.[43] Eltrombopag does not have structural or sequence homology to endogenous TPO, which eliminates the risk of cross-reactive antibody development. Furthermore, unlike endogenous TPO, eltrombopag binds the transmembrane domain of TPOR, thus, does not compete with TPO for receptor binding. As a result, eltrombopag may enhance endogenous TPO function rather than substitute it. In addition to the effect on megakaryocyte proliferation and differentiation, eltrombopag was found to have in vitro anti-leukemic effect, via intracellular iron depletion.[44,45]

Oliva et al.,[46] reported their experience with eltrombopag monotherapy in patients with low- and intermediate-1-risk MDS and severe thrombocytopenia ($PLT<30x10^9/L$) with refractory or relapsed disease. Ninety patients were enrolled and randomized to eltrombopag vs placebo in this prospective phase 2 trial. Eltrombopag was safe and induced PLT response in 47% vs 3% (eltrombopag vs placebo). The assessment of long-term safety and efficacy of eltrombopag and its effect on OS (phase 2 part of the study) is still ongoing.

In another multicenter, randomized, placebo-controlled, double-blind, phase 1/2 trial, eltrombopag monotherapy or placebo was administered to 98 patients with advanced myelodysplastic syndromes or AML.[47]

Eltrombopag increased rates of PLT and red blood cell transfusion independence compared with placebo (38% vs 21% and 20% vs 6%, respectively) and was well tolerated, with no new safety concerns.

We recently published the encouraging results of the part 1 and 2 of the ASPIRE trial.[48,49] In this phase II, placebo-controlled trial, 145 patients with higher-risk MDS and AML were randomized 2:1 to receive eltrombopag monotherapy or placebo. In part 1 of the study, 4 out of 17 treated patients experienced increased PLT and ten patients benefited from reduced PLT transfusion needs. In part 2, the primary endpoint, the number of clinically relevant thrombocytopenic events

(CRTEs) was observed in 54% of eltrombopag treated patients compared with 69% in the placebo group. No safety concerns were raised in this trial, and OS was not significantly different between the two groups.

Eltrombopag as a part of an anti-MDS combination therapy has been investigated as well. In a small pilot study, 9 of 12 AZA-treated patients maintained or improved their PLT.[50] Up to 200 mg qd was tolerated in this study. Importantly, no increase in blast count or other serious adverse effects could be implicated to eltrombopag.

Finally, the preliminary results of the interesting SUPPORT study were presented.[51] In this phase 3 trial, 356 patients with Int-1, Int-2 and high-risk MDS and thrombocytopenia (PLT<75x10^9/L) were all treated with AZA and randomized 1:1 to eltrombopag or placebo. The study was early terminated due to futility. Eltrombopag given concomitantly with AZA was inferior to placebo/AZA-treated. Surprisingly, eltrombopag/AZA-treated increased the number of required PLT transfusions. Actually, 16% eltrombopag and 31% placebo patients were platelet transfusion- independent during the first four cycles of AZA. The eltrombopag/AZA group also had higher rates of febrile neutropenia. Although there was no difference in overall deaths rates between the two groups, the number of patients transforming to acute leukemia was higher in the eltrombopag/AZA group*:* 12% versus 6% in the placebo/AZA group. A complete assessment of disease progression, including AML progression at the time of study termination, is still in progress. We suggested that there might be some interaction between AZA and eltrombopag that could account for the worsening clinical outcomes.

Summary and Conclusions. Thrombocytopenia is common in MDS and still presents a challenge. Understanding of thrombopoiesis biology enabled the cloning of thrombopoietin, which led to the development of pharmacological agents, romiplostim and eltrombopag. Both agents are still investigated in several clinical setups, including MDS-related thrombocytopenia. In MDS, these two agents have been shown to increase the platelet count, decrease the need for platelet transfusions and reduce the number of clinically significant bleeding episodes, with a reasonable tolerance. However, the response rate, as well as its duration, is still modest, and concerns have been raised regarding potential disease progression and leukemic transformation. Recent data are encouraging and predict a solution for the safety concerns, but further research is still needed on the way to solve this serious problem of MDS-related thrombocytopenia completely. A recent meta-analysis further supports these conclusions, stating that no comparison between both agents have been performed, and further research is mandatory to answer the open question.[52]

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