Trends in Clinical Investigation for Myelodysplastic Syndromes

Thomas Prebet, Amer Zeidan

Abstract

Myelodysplastic syndrome (MDS) paradigms have been dramatically changed over the last 10 years by major breakthroughs on both pathophysiologic and therapeutic aspects. It is currently a field of intense clinical investigation as new challenges have emerged in both low-risk and high-risk populations. In low-risk MDS, long-term control of anemia is a major issue, and second-line treatments after failure of erythropoiesis-stimulating agents are warranted. Several promising therapies are available, and there are many open questions on how to select the most adapted agent and/or sequence of agents in a specific individual. For high-risk MDS patients, improvement of frontline treatment (namely hypomethylating agents) and identification of valid treatments for relapsed/refractory patients are of paramount importance. This review attempts to define these challenges, summarize the results of the most recent and promising investigational strategies in the field, and to describe the future directions.

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Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of bone marrow neoplasms characterized by ineffective hematopoiesis, peripheral blood cytopenias, and a significant risk of progression to acute myeloid leukemia (AML).[1] This general definition of MDS was initially described more than 20 years ago but is still valid, even if refined. What has changed over the last 10 years is our understanding of the underlying mechanisms,[2,3] and, more importantly for our patients, the leverage that we have on the symptoms and evolution of the disease.[4] Three drugs, azacitidine,[5,6] decitabine,[7,8] and lenalidomide,[9,10] have been registered in the United States for the treatment of MDS and represent clinically significant advances for patients with MDS. However, results are still not optimal in terms of both the proportion of responding patients and the duration of response. None of these drugs could be considered a curative approach, and allogeneic hematopoietic stem cell transplantation remains the only opportunity of cure for a limited fraction of our patient population.[11] Moreover, there is no registered drug for relapsed/refractory patients, and the outcome of this group of patients is poor when treated with best supportive care or conventional approaches.[12,13] Thus, there is still a significant unmet medical need for patients with MDS, and more work is underway in order to develop new strategies for these patients (Figure 1).

In this review, we present the current challenges related to the treatment of lower- and higher-risk MDS and the current promising investigational approaches, and finally, we discuss the future directions of development.

Innovative Approaches for Lower-Risk Disease

Patients classified as lower-risk MDS according to the International Prognostic Scoring System (IPSS),[14] the World Health Organization classification-based Prognostic Scoring System,[15] or the revised IPSS[16] have a low probability of evolution to AML, and, while they can have a relatively prolonged survival, they typically suffer from complications of chronic cytopenias. Anemia is the most frequently observed cytopenia and is present at some degree in 70% of patients with MDS at diagnosis. Virtually every patient with MDS will need a red blood cell transfusion during the course of the disease, and 40% to 50% of the patients will be chronically transfused.[17] The severity of anemia and the requirement of blood products have both been linked to an impaired quality of life and a shortened survival, independently of the other factors usually affecting outcome.[15] The sustained and prolonged correction of anemia is therefore one of the most relevant endpoints in low-risk MDS. Substantial evidence supports the use of high-dose erythropoiesis-stimulating agents (ESAs) for patients with MDS with anemia, despite the lack of conclusive evidence from

Section of Hematology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT

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Address for correspondence: Thomas Prebet, MD, PhD, Section of Hematology, Department of Internal Medicine, Yale School of Medicine, 300 Georges St, Room 786, New Haven, CT 06511
E-mail contact: thomas.prebet@yale.edu

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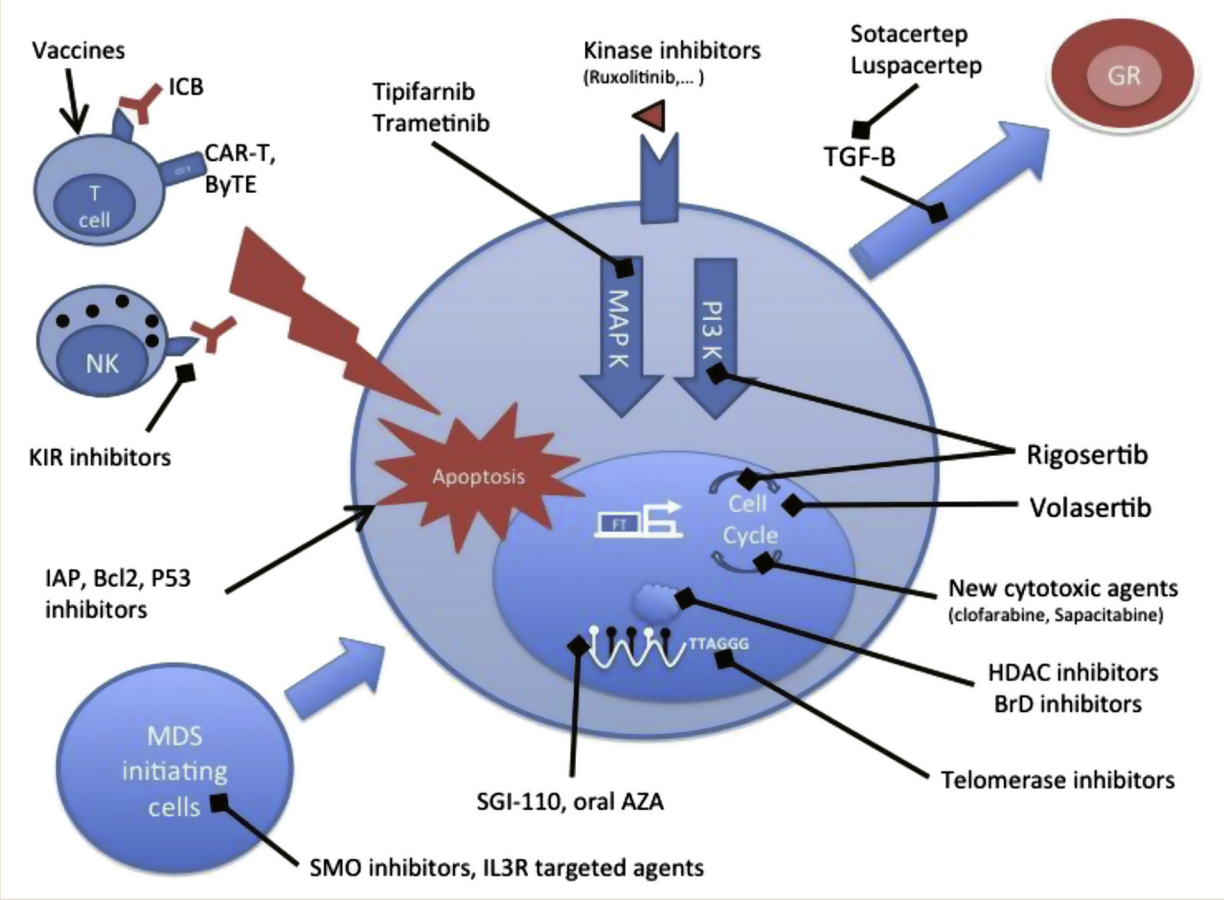
Figure 1 Investigational Approaches for Myelodysplastic Syndromes



Abbreviations: AZA = azacitidine; BrD = bromoDomain; ByTE = bispecific antibody; CAR-T = chimeric antigen receptor T cell; GR = red blood cell; ICB = immune checkpoint blockade; KIR = killer inhibitory receptor; MAPK = mitogen-activated protein kinases; MDS = myelodysplastic syndromes; NK = natural killer cell; SMO = smoothened; TF = transcription factor; TGF-B = transforming growth factor beta.

randomized clinical trials that ESAs prolong survival. Nonetheless, most scientific boards and clinical guidelines recommend the use of ESAs as frontline treatment for patients with lower-risk MDS.[18] Patients with high serum erythropoietin and a high transfusion burden before initiation of ESA have a low probability of response, and therefore should be considered for alternative upfront strategies.[18] The overall response rate for unselected patients is approximately 50% to 65%, and response duration is estimated to be 24 to 36 months. For patients in whom ESAs fail, the expected survival could be short, as low as 24 months for patients with ESA refractoriness or failure within the first 6 months of initiation of therapy.[19] In this situation, there is no standard approach, with the exception of lenalidomide for patients harboring a 5q deletion (del5q). The results of lenalidomide in patients who are ESA-resistant non-del5q are significantly more modest, with a 20% to 25% response rate for a duration of 12 to 18 months,[20-22] but the US Food and Drug Administration and the European Medicines Agency are currently evaluating the drug for approval in this indication. Use of subcutaneous azacitidine could also be potentially interesting, with a fairly similar response rate.[23]

Revisiting Hypomethylating Agents (HMAs)

The revisitation of HMAs directly connects with one of the promising actual approaches is the use of oral azacitidine in these settings.[24,25] The oral formulation is more adapted to ambulatory settings and, interestingly, the incidence of azacitidine-induced cytopenias seems more limited. On a mechanistic standpoint, methylation studies have shown that oral azacitidine was able to trigger demethylation in a lesser magnitude, compared with subcutaneous infusion. However, the favorable toxicity profile had enabled switching from a classic 7-day schedule to a more prolonged 14- or 21-day schedule, which is currently used in phase III trials, with several studies pointing out the potential benefit of a prolonged exposure to HMAs in MDS.[7,26] In the preliminary results of the phase III study, 30% to 40% of patients achieved red blood cell transfusion dependency.[24]

Transforming Growth Factor (TGF)-Beta Inhibitors

There is a multitude of new agents dedicated to low-risk MDS, as shown in Table 1. One of the more promising and mature approaches is the targeting of terminal erythropoiesis with