Review Article

Emerging Therapies for the Myelodysplastic Syndromes

Jonathan Canaani[*]

Hematology Division, Chaim Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel

ABSTRACT

Despite considerable advances in our understanding of the molecular and epigenetic underpinnings of the myelodysplastic syndromes (MDS), this diverse group of myeloid neoplasms remains a significant clinical challenge. Considerable barriers to timely development of effective therapy include the diverse molecular landscape encountered in MDS patients, the difficulty in translating specific molecular aberration into a clinically meaningful animal model, as well as challenges in patient recruitment into clinical trials. These speak to the need to discover efficacious novel therapeutic targets which would in turn translate into improved patient outcomes in terms of both survival and quality of life. In this review, we outline recently published data pertaining to therapeutic advances in TGF-β pathway inhibition, STAT3, Hedgehog signaling, and additional therapeutic venues being actively explored in MDS.

1. INTRODUCTION

The myelodysplastic syndromes (MDSs) are a heterogenous group of myeloid disorders characterized by cytopenias, a varying risk of progression to acute myeloid leukemia (AML), and dysplasia of the various blood and bone marrow elements. One of the inherent difficulties in investigating and treating this disorder is the bewildering array of clinical presentations and, far more challenging, the pronounced heterogeneity at a molecular level. At least 40 mutations are seen in MDS alongside perturbations in splicing and epigenetic regulation, making subclassification of specific patient subsets quite difficult [1,2]. To complicate things further, unlike other neoplastic and hematologic malignancies, whereby an animal or xenograft model can attempt at a faithful recapitulation of the disease process, based on a unique molecular aberration, the study of MDS in model systems is limited and arduous, although recent data challenge this notion [3]. Progress in the clinical field is additionally impeded by a low rate of patient accrual to clinical trials of novel MDS agents [4]. This may be accounted for by the aging demographics of the target population, diagnostic ambiguity, logistic barriers, and clinical overlap/distinction with AML. Moreover, leading authors in the field believe that focusing solely on response rates, as a measure of clinical efficacy of MDS targeting agents, may not capture the complete clinical picture of MDS, which should also include quality of life improvements (e.g., transfusion dependency, hospital admissions), sustainability of response, and overall survival [5].

Owing to the relative paucity of novel effective therapies for MDS, the field has recently focused on optimizing prognostic models [6–9] and mapping the molecular landscape of MDS [10–13]. Yet, in order to improve our results in the clinical arena, we must endeavor to introduce new agents and therapeutic targets for the benefit of our patients. Finally, it is important to note that therapeutic goals in MDS patients differ according to the risk of disease. Therefore, the goal for patients with lower risk disease (defined by the International Prognostic Scoring System) is to achieve transfusion independence, in contrast to that in higher risk patients, where clinicians endeavor to prolong survival and mitigate the risk for disease evolution to AML. In this review, we outline recent emerging therapies and targetable pathways in MDS.

2. TARGETING THE TGF-β PATHWAY IN MDS

Owing to the recent FDA priority review of luspatercept (ACE-536), a novel inhibitor of transforming growth factor (TGF)-β signaling, this has gained considerable attention in the field of MDS. This superfamily of more than 30 soluble growth factors regulates key elements of hematopoiesis, namely hematopoietic stem cell (HSC) proliferation and differentiation [14,15]. A vast body of research published over the past three decades unveiled the complex mechanism of the TGF-β pathway's regulation of hematopoiesis, whereby TGF-β is secreted by local bone marrow niche elements such as megakaryocytes [16] and Schwann cells [17]. TGF-β receptor activation then triggers a signaling cascade which either inhibits or activates mothers against decapentaplegic homologs (SMAD) proteins (e.g., SMAD2/3/6/7) which, in their turn, regulate erythroid differentiation and proliferation [18,19]. Intriguingly, it has been shown that perturbations in TGF-β signaling are commonly

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[*] Email: Jonathan.Canaani@sheba.health.gov.il
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identified in patients with MDS, where expression of key genes such as SMAD7 and SKI are decreased, thus leading to inhibition of hematopoiesis [15]. Furthermore, emerging data suggest that activated TGF-β signaling also affects additional signaling pathways such NF-kB, RAS/MAPK/ERK, and the PI3K/mTOR pathways, which also regulate the activity and function of various SMAD proteins, leading to inhibition of erythropoiesis [20,21]. Thus, considering the established role of aberrant TGF-β signaling in the pathogenesis of MDS, targeting this pathway became an attractive investigative venue for drug development, resulting in the generation of several agents specifically targeting this pathway.

Galunisertib, an oral small molecule inhibitor of the TGF-β receptor type I kinase with consequent decreased phosphorylation of SMAD2/3, was evaluated in a phase II study of 41 MDS patients with low to intermediate risk IPSS-R, and was shown to be well tolerated from a safety standpoint. It led to improvement in transfusion requirements in 26% of patients, and 4 patients on study became transfusion independent. However, the indices of the other blood cell parameters, namely platelet and neutrophil counts, were not improved on therapy [22]. A phase III trial is currently evaluating galunisertib in patients with low-risk MDS.

Sotatercept (ACE-011) is a recombinant human activin receptor IIA fused to the Fc domain of human IgG1 which has been shown in a preclinical model to decrease the duration of chemotherapy-induced anemia [23]. These encouraging results were followed by a phase 2 study in IPSS low/INT-I MDS patients showing a significant 49% rate of hemoglobin level improvement as well as a 27% rate of transfusion independence [24]. Notably, patients with more than 15% ringed sideroblasts were more likely to respond to sotatercept compared to those with less than 15% ringed sideroblasts (59% *versus* 15%). This agent is currently being evaluated in a phase 2 study in patients with MDS/MPN and myelofibrosis (NCT01712308).

However, most of the attention in the field has been focused on luspatercept, a recombinant protein consisting of a modified extracellular domain of human activin receptor IIB linked to the Fc region of human IgG1. The initial data from an MDS murine preclinical model showed that the murine version of luspatercept increased hemoglobin levels by promoting maturation of late-stage erythroid precursors via reduction of SMAD2/3 activity [25]. The subsequent phase 1 study in 40 postmenopausal women showed a notable increase of hemoglobin beyond the 10 g/L threshold in over 80% of the tested volunteers [26]. Further supporting the therapeutic efficacy of luspatercept, the phase 2 trial (PACE-MDS) in MDS patients demonstrated an impressive 63% rate in erythroid response in IPSS low/INT-1 patients, which was more pronounced in the patient cohort with more than 15% ringed sideroblasts, as well as in those with the *SF3B1* mutation [27]. The pivotal phase 3 study (MEDALIST) presented at the 2018 American Society of Hematology (ASH) annual meeting was a placebo-controlled trial randomizing IPSS low/INT-1 MDS patients with more than 15% ringed sideroblasts (or more than 5% sideroblasts and harboring the *SF3B1* mutation) to luspatercept *versus* placebo. The exciting results of the trial showed a significant advantage for luspatercept with regard to transfusion independence (37% *versus* 13%), as well as median duration of response (30 *versus* 13 weeks), with no significant difference in adverse events between arms. In aggregate, these data suggest that the TGF-β pathway is an important therapeutic target

in MDS. It remains to be seen whether luspatercept and additional agents targeting TGF-β will be able to change the natural history and clinical course of MDS patients irrespective of these agents' action on erythropoiesis.

3. NOVEL THERAPEUTIC VENUES IN MDS

The transcription factor signal transducer and activator of transcription 3 (*STAT3*) has been previously shown to be overexpressed in MDS hematopoietic progenitor cells, and is thought to be part of the disease process [28,29]. In an elegant paper published recently by Shastri and colleagues from the Albert Einstein College of Medicine [30], the investigators used AZD9150, a STAT3 antisense oligonucleotide, and showed that STAT3 inhibition led to reduced proliferation and increased apoptosis in leukemic cell lines. Furthermore, use of AZD9150 in primary MDS cells led to enhanced hematopoietic differentiation as well as decreased engraftment of MDS/AML cells in a xenograft model, possibly establishing STAT3 inhibition as a therapeutic target in future clinical trials.

The Hedgehog signaling pathway has been demonstrated to be involved in myeloid malignancies owing to its pivotal role in maintenance and propagation of leukemia stem cells [31,32]. The introduction of glasdegib, an oral small molecule inhibitor of this pathway, into the therapeutic arsenal of AML and high-risk MDS has been facilitated by the publication of the results of the clinical trials showing encouraging data for AML and high-risk MDS patients treated with glasdegib and standard chemotherapy [33,34]. Data from the ongoing phase II trial randomizing older unfit patients to either glasdegib/low dose cytarabine compared to low dose cytarabine monotherapy are also supportive of a survival advantage for the glasdegib arm [35]. In the same vein, data from Lau and colleagues also implicate a specific member of the Hedgehog signaling pathway, GLI1, in the pathogenesis of MDS [36]. Using a murine model of MDS, the investigators show that GLI1 activation is involved in transformation to leukemia, as well as acquisition of self-renewal potential in a committed hematopoietic progenitor population. Thus, inhibition of GLI1 may prove to be an attractive therapeutic target in MDS.

An additional agent explored in recent years has been indisulam, a sulfonamide derivative with antitumor activity due to its suppression of several cell cycle checkpoints molecules such as cyclins A, B1, H, and CDK2, with ensuant reduction in Rb phosphorylation and induction of p53 and p21 [37]. In a recent phase 2 study [38] combining indisulam, idarubicin and cytarabine in patients with relapsed AML and high-risk MDS, investigators from the MD Anderson Cancer Center showed modest clinical outcomes, and suggested that future trials with this agent should possibly be centered on patients with spliceosome mutations, based on preclinical data suggesting possible efficacy in this specific subgroup of patients [39]. Modulation of the *TP53* pathway has also been addressed with the use of APR-246, a prodrug which binds to cysteins in mutated p53, resulting in subsequent induction of apoptosis and cell cycle arrest.

Phase 2 data presented recently by the French MDS study group suggest that the combination of azacitidine and APR-246 in MDS and AML patients with the p53 mutation is highly active, with

response rates of over 60%, and molecular remission in 78% of patients achieving a complete remission (CR) [40]. Considering the hypermethylated state of DNA of patients with MDS which is associated with deacetylated histones, as well as preclinical studies showing therapeutic synergism combining hypomethylating agents (HMAs) with histone deacetylase inhibitors [41], this approach has also been explored in the clinical MDS setting. In a randomized phase II study of higher risk MDS patients, azacitidine monotherapy was compared with combination therapy of pracinostat, a histone deacetylase inhibitor, and azacitidine [42]. Unfortunately, the results of this clinical trial did not suggest a clinical advantage in terms of either overall or progression-free survival. One of the burdensome aspects of treating MDS patients with the currently available hypomethylating agents, namely azacitidine and decitabine, is the need for multiple-day clinic visits for the intravenous or subcutaneous administration of the said drugs. An additional pharmacodynamic aspect of these monthly regimens is the fluctuating hypomethylating state induced by these agents, and the consequent decreased clinical efficacy. Cedazuridine is a novel oral HMA which was recently tested in combination with decitabine in a phase 1 trial of MDS patients [43]. The encouraging data suggest that this combination is safe and well tolerated, prompting further investigations of this novel agent in the MDS patient population.

As mutations in the cellular splicing machinery are some of the commonest genetic aberrations seen in MDS, this area is being actively investigated, with recent publications revealing that modulation of the SF3b splicing complex is capable of targeted elimination of spliceosome-mutant cells [44]. These data are being followed with a first in human trial of H3B-8800, a small molecule which binds to the SF3b complex. Although, thus far, the clinical data have not been supportive of a robust clinical effect in MDS or AML patients, up to 14% of patients experienced improvement in transfusion needs [45].

We conclude this section by noting the recently published results of the SUPPORT trial, which was a phase 3, randomized, double-blind, placebo-controlled study exploring the role of eltrombopag in combination with azacitidine for IPSS INT I or above MDS patients [46]. It was hoped that eltrombopag would mitigate the decrease in platelet count often seen during therapy of MDS patients with azacitidine. However, the trial had to be terminated earlier than expected, because of an interim analysis which indicated that the combination arm worsened platelet recovery and had lower response rates, as well as a trend toward increased progression to AML.

4. EXPLORING NOVEL AML AGENTS IN MDS

In the last three years, the armamentarium of therapies for AML has significantly expanded, with the introduction of several novel agents targeting various aspects of leukemogenesis. Given, the genetic proximity of MDS to AML, it is thus of considerable interest to the field to explore these agents also in the MDS arena. Venetoclax, an oral selective BCL-2 inhibitor, has been shown to have robust anti-leukemia activity, owing to its marked efficacy in inducing leukemia cell apoptosis. Recent data suggest that combining venetoclax with azacitidine, in a therapeutic scheme similar to that for AML patients, has encouraging results also in MDS patients, even in those with prior failure with HMAs [47]. Furthermore, their data suggest that this approach may possibly spare healthy HSCs, thus leading to renewed normal hematopoiesis. An ongoing phase 1 study is exploring this approach in the treatment of naïve higher risk MDS patients (NCT02942290).

Mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 are seen in 3%–10% of MDS patients, and have garnered a considerable clinical focus, given the development of oral agents targeting *IDH1* (ivosidenib) and *IDH2* (enasidenib), and their established efficacy in patients with relapsed/refractory AML. In two abstracts presented at the ASH 2019 Annual Meeting, encouraging results were reported. In the 12 MDS patients treated with ivosidenib, a CR was seen in 41% of the cohort, and 9 patients were able to achieve a transfusion-free state for at least 56 days [48]. The preliminary results of the phase 2 in IDH2-mutated MDS patients revealed an overall response rate of 67% for the entire cohort, with 100% response in patients without prior exposure to HMAs who were treated with the combination of azacitidine and enasidenib. In patients with prior failure to HMA, the response rate was 50% of the enasidenib monotherapy, results which are clearly encouraging for a highly challenging patient subset [49].

CPX-351 is a novel liposomal formulation of cytarabine and daunorubicin aimed at delivering synergistic drug ratios to leukemia cells, and which has been recently approved for secondary AML. In a pilot study presented at the 2019 ASH meeting, 10 evaluable patients with high-risk MDS and relapsed-refractory (R/R) AML were treated with CPX-351 in combination with gemtuzumab ozogamicin, an anti-CD33 monoclonal antibody used in AML. The data show an overall response rate of 50%, possibly suggesting a future role for this drug combination in high-risk MDS [50].

5. CONCLUDING REMARKS

Much progress remains to be seen in the challenging field of MDS disorders. However, it is anticipated that, with the routine implementation of deep sequencing modalities in clinic, as well as enhanced understanding of the complex interaction between the various components of the MDS bone marrow milieu and immune system elements, we will be able to further improve patient outcomes. Table 1 outlines several selected innovative trials targeting various pathogenetic facets of MDS, including TP53, checkpoint inhibition, bromodomain proteins, apoptosis, and splicing.

Table 1 | Selected ongoing clinical trials in MDS.

Agent	Clinicaltrials.gov Registry ID	Phase	Therapeutic Approach/Target	Clinical Setting
APR-246	NCT03745716	III	Restore *wt* TP53 activity	TP53-mutated MDS
Rigosertib	NCT02562443	III	Multi-kinase inhibitor	MDS refractory to HMA
Ipilimumab + decitabine	NCT02890329	I	Checkpoint inhibitor	Relapsed/refractory MDS
Venetoclax	NCT02966782	I	Bcl-2 antagonist	Relapsed/refractory MDS
H3B-8800	NCT02841540	I	Splicing modulator	MDS
PLX51107 + azacitidine	NCT04022785	I	Bromodomain Inhibitor	MDS
Daratumumab	NCT03067571	II	CD38 monoclonal antibody	High-risk MDS
Roxadustat	NCT03263091	III	HIF modulator	Low-risk MDS

wt = wild type; HMA = hypomethylating agents; HIF = hypoxia-inducing factor; MDS = myelodysplastic syndrome.

CONFLICT OF INTEREST

There are no conflicts of interest.

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