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PUBLISHED ABSTRACT

Therapeutic Options in Myelodysplastic Syndromes Following Hypomethylating Agent Failure

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Background

Hypomethylating agents (HMA) azacitidine and decitabine are standard of care for the treatment of myelodysplastic syndromes (MDS). Although HMA have revolutionized the treatment of MDS, only approximately half of patients respond to these agents with variable duration of effect, known as primary and secondary HMA failure, respectively.

Methods

Therapeutic options following HMA failure remain limited; however, growing understanding of the pathogenesis underlying MDS has resulted in the development of multiple targeted therapies showing varying degrees of success in clinical trials.

Results

Drugs that target molecular alterations (such as abnormal histone regulation, IDH mutations, and spliceosome gene mutations), abnormal signaling pathways (such as the multikinase inhibitor rigosertib), cellular apoptosis (such as the Bcl2 inhibitor venetoclax), and immune checkpoint inhibition are under development (**Table 1**). Agents recently approved for use in higher-risk acute myeloid leukemia, such as FLT3-inhibitors and CPX-351, are also being studied in MDS. Several more agents, including two first in class agents, a novel immune regulator targeting CD47, and pevonedistat, a NEDD8-activating enzyme inhibitor, are under investigation.

Conclusions

In the absence of established therapeutic approaches following HMA failure, decisions in therapy should be based on the type of HMA resistance as well as the patient's clinical and molecular characteristics. As targeted therapies continue to be developed, a comprehensive re-evaluation of the patient including the mutational profile at the time of HMA failure may reveal new treatment options. Here, emerging therapeutic approaches to HMA failure in MDS are reviewed.

Table 1: Agents under active investigation in patients with myelodysplastic syndromes (MDS).

Mechanism	Agent	NCT identifier	Phase	Relevant study population	Status
Epigenetic regulators					
Hypomethylating agents	Guadecitabine	#NCT02935361	II	Int-1 or HR-MDS + HMAf	Recruiting
		#NCT02131597	II	HR-MDS	Active, not recruiting
		#NCT02907359	III	MDS + HMAf	
Histone deacetylase inhibitors	Vorinostat, mocetinostat, panobinostat, etc.	No active studies in this population			

(Contd.)

Mechanism	Agent	NCT identifier	Phase	Relevant study population	Status
Mutant IDH1/2 inhibitors	Enasidenib	#NCT03383575	II	mIDH2 MDS +/– HMAf	Recruiting
		#NCT03744390	II		
	Ivosidenib	#NCT02074839	I	mIDH1 r/r MDS	
		#NCT03471260	Ib/II	IDH1-mutant MDS	
		#NCT03503409	II	mIDH1: HR-MDS, treatment-naïve MDS, ESA-resistant LR-MDS	
LSD1 inhibitors	Tranylcypromine	#NCT02273102	I	R/r MDS	Active, not recruiting
		#NCT02717884	II	Int-/HR-MDS + HMAf	Recruiting
	GSK2879552	No active studies			
Signal transduction regulators					
TGF-beta signaling modulators	Galunisertib	No active studies in this population			
	Sotatercept				
	Luspatercept	#NCT02631070	II	Very low, low, or int-risk MDS refractory to ESA	Active, not recruiting
		#NCT03682536	III	Very low, low, or int-risk MDS in ESA-naïve	Recruiting
TLR inhibitors	Tomaralimab (OPN-305)	No active studies in this population			
Multi-kinase inhibitors	Rigosertib	#NCT01926587	I/II	Int-1, Int-2 (Int-2) or HR-MDS	Active, not recruiting
		#NCT01904682	II	LR or Int-1 risk-MDS	
		#NCT01928537	III	MDS+excess blasts + HMAf	
		#NCT01241500	III		
		#NCT02562443	III	Very high-risk MDS + HMAf	Recruiting
FLT-3 inhibitors	Midostaurin	#NCT00819546	I	R/r MDS and AML	Active, not recruiting
	Gilteritinib	No active studies in this population			
	Sorafenib	#NCT02728050	II	HR-MDS	Recruiting
Immunotherapy					
PD-1 inhibitors	Nivolumab	#NCT02530463	II	MDS +/– HMAf	Recruiting
		#NCT02464657	II		
		#NCT03417154	II		
	Durvalumab	#NCT02775903	II	Treatment naïve, HR-MDS	Active, not recruiting
		#NCT02281084	II	MDS + HMAf	
	Pembrolizumab	#NCT02936752	I	MDS +/– HMAf	Recruiting
		#NCT03094637	II	Int-1 or HR-MDS +/– HMAf	
	Atezolizumab	#NCT02935361, see guadecitabine			
CTLA-4 inhibitors	Ipilimumab	#NCT02530463, see nivolumab			
		#NCT02890329	I	MDS +/– HMAf	Recruiting
Anti-CD47 antibody	Hu5F9-G4	#NCT03248479	I	R/r and treatment-naïve MDS	Recruiting
Bispecific T cell engaging antibodies	MCLA-117	No active studies in this population			
	AMG330				
	AMV564	#NCT03516591	I	Int-2 or HR-MDS with HMAf or standard AML CTX	Active, not recruiting

(Contd.)

Mechanism	Agent	NCT identifier	Phase	Relevant study population	Status
Cell death regulators					
Bcl-2 inhibitors	Venetoclax	#NCT02966782	I	HR-MDS + HMAf	Active, not recruiting
		#NCT04017546	I	MDS with ≥10% blasts	Recruiting
		#NCT02942290	I	Treatment-naïve HR-MDS	
		#NCT03113643	I	HR-MDS	
		#NCT04160052	I/II	HR-MDS +/– HMAf	
		#NCT03404193	II	HR-MDS + HMAf	
		#NCT02115295	II	MDS with ≥10% blasts	
NEDD 8 activating enzyme	Pevonedistat	#NCT03772925	I	HR-MDS + HMAf	Recruiting
		#NCT03813147	I	HR-MDS	
		#NCT03459859	I	MDS +/– HMAf	
		#NCT03814005	I	HR-MDS + HMAf	
		#NCT03238248	II	MDS+ HMAf	
		#NCT02610777	II	HR-MDS	Active, not recruiting
		#NCT03268954	III	HR-MDS	Recruiting
Other agents					
RNA splicing modulators	H3B-8800	#NCT02841540	I	HR-MDS + HMAf, LR-MDS refractory to ESA	Active, not recruiting
Cytotoxic agents	CPX-351	#NCT02019069	I	HR-MDS + HMAf	Recruiting
		#NCT03896269	I		
		#NCT03957876	II	MDS + HMAf	
		#NCT03672539	II	HR-MDS + HMAf	

CTX = chemotherapy, ESA = erythropoiesis-stimulating agents, HMAf = hypomethylating agent failure, HR = high risk Int = intermediate, LR = low risk, MDS = myelodysplastic syndromes, mIDH = mutant IDH, R/r = relapsed/refractory, TLR = toll-like receptor.

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