Leukemia insights

DECEMBER 2022

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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In this month's Leukemia Insights newsletter, written by Guillermo Garcia-Manero, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we provide a summary of our approach to patients with myelodysplastic syndrome (MDS) and a list of active clinical trials. Learn more about our Leukemia program.

An update on the MDS program at MD Anderson

Introduction

The section of myelodysplastic syndrome (MDS) at MD Anderson Cancer Center is the largest program of its class in the world. In fiscal year 2022, 370 were evaluated at MD Anderson. Reasons for these visits included confirmation of diagnosis, treatment, or evaluation for allogeneic stem cell transplantation (alloSCT). A majority of patients referred here are eventually enrolled in a clinical trial. Patients are evaluated by a multidisciplinary team that includes leukemia physicians, hematopathologists, stem cell transplant experts, pharmacists, advanced practice providers and research nurses. The MDS program also performs extensive translational and basic research and is supported in part by MD Anderson's Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) Moon Shot® Program.

In the past few years, we have witnessed an explosion in our understanding of MDS. This resulted in the approval in 2020 of two agents: luspatercept and the oral hypomethylating agent (HMA) decitabine/cedazuridine. MD Anderson was a leader of the trials that resulted in their approval. This reinforces the importance of referring patients to our center for clinical trials. Despite this progress, prognosis of our patients still is poor, and we are in need of more advanced treatment options. Below, we provide a summary of our approach to patients with MDS and list active clinical trials.

Current Conceptual Framework for the Therapy of MDS

Patients with MDS are stratified according to the IPSS and IPSS-R scoring systems. Using IPSS and IPSS-R, patients with MDS are divided in two broad subgroups: lower- and higher-risk disease. Several other important data points are needed when making treatment decisions: age; type and

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severity of comorbidities; number and degree of cytopenias; transfusion needs; presence of specific genomic alterations; percentage of bone marrow blasts; cytogenetic profile; potential for alloSCT; and, importantly, prior treatment with an HMA. First is the subset of patients without a morphologic diagnosis of MDS who instead have diagnoses that include idiopathic cytopenia of unknown significance (ICUS), clonal hematopoiesis of indetermined potential (CHIP), and clonal cytopenia of unknown significance (CCUS). The approach to this subset of patients was described in the previous newsletter by Drs. Chien and Hammond. Next, we divide patients with MDS into lower or higher risk, and then further subdivide them based on whether they have been exposed to an HMA. Figure 1 summarizes our current approach to treatment. This may change in the future as we include the new IPSS-M molecular classification. The IPSS-M includes genomic information to variables already included in the IPSS-R, resulting, in general, in an "upstaging" of prognosis (Bernard et al, NEJM Evidence).

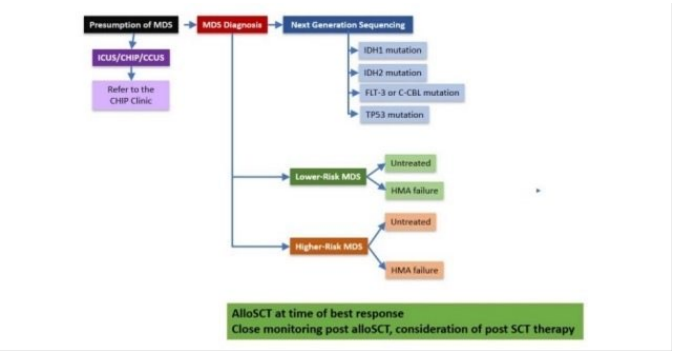

Figure 1: Treatment approaches in MDS at MD Anderson

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Clinical Trials for Lower-Risk MDS

Targeting IL-1 in Patients with Lower Risk MDS: A Phase I-II Trial of Canakinumab for Patients with Lower-Risk MDS. Our group has extensively documented the role of altered innate immune signaling in MDS. One key cytokine is IL-1. Canakinumab is a potent inhibitor of IL-1 that is currently approved for rare inflammatory disorders. This study is first accruing patients already treated with an HMA. This is an important study because this agent not only targets MDS but also can impact concomitant comorbidities known to affect outcomes in MDS. Initial results from this trial were presented at the 2022 ASH Meeting in New Orleans. Results indicated that canakinumab is safe in this patient population and active in specific subsets of patients. The study continues including patients with earlier-stage disease. In addition, MD Anderson is participating on a trial of the combinations of MBG453, NIS793, and canakinumab in this patient population.

Targeting Lower-Risk MDS with Oral Hypomethylating Agents: ASTX727. One of the major developments in 2020 was the approval of ASTX727 (decitabine/cedazuridine), an oral form of decitabine, for patients with MDS. Our group has pioneered the use of attenuated schedules of HMAs in lower-risk MDS. At ASH 2022, we presented data from the final results of a phase 1 trial of low dose oral decitabine/cedazuridine. The selected dose is now being compared with a 3 day schedule in a phase 2 randomized trial.

Targeting ALK2 in Lower-Risk MDS. ALK2 is a kinase that regulates hepcidin, a key molecule in hemoglobin regulation. We are investigating INCB000928, an ALK2 inhibitor, for patients with lower-risk MDS. This study is a phase 1 trial open to patients who have failed other options for anemia such as growth factors, luspatercept or other investigational agents.

Fostamatinib in Lower-Risk MDS. Fostamatinib is a spleen tyrosine kinase inhibitor approved for patients with ITP. Work performed at MD Anderson by Yue Wei, Ph.D., and others has suggested that this pathway could also be important in patients with anemia and thrombocytopenia. Our study is exploring the safety and clinical activity of fostamatinib in this group of patients.

Other agents being studied in lower risk MDS include the IRAK4 inhibitor R289 and the SF3B1 inhibitor RVT-2001 (formerly H3B-8800).

Clinical Trials for Previously Treated Higher-Risk MDS

The standard of care for a majority of patients with higher-risk MDS still is single-agent HMA. A number of clinical trials are challenging this concept.

New Oral HMA: ASTX030 (Oral Azacitidine + Cedazuridine). In addition to the recent development of ASTX727, described above, ASTX030 is a combination of azacitidine and the cytidine deaminase inhibitor cedazuridine. The goal of this study is to develop an oral HMA pharmacokinetically identical to standard parenteral azacitidine. Such an agent will be transformative in MDS as it could represent a true pharmacokinetic analogue to parenteral azacitidine.

Targeting BCL-2 in MDS: The addition of venetoclax, a BCL-2 inhibitor, to an HMA has transformed the care of patients with AML. Several studies are evaluating combinations of venetoclax in MDS. This is an area of significant interest at MD Anderson and some of these data was recently published in the journal Lancet Hematology [1]. Recent data published in Nature Medicine by Simona Colla, Ph.D., and her colleagues identified subsets of patients that could benefit from this combination[2]. This is being prospectively studied in our center and is supported by the MDS/AML Moon Shot. MD Anderson also participated in the Verona trial, the pivotal registration trial of azacitidine with or without venetoclax in front-line, higher-risk MDS. Results from this trial may change the standard of care for patients with higher risk MDS. In addition, MD Anderson is studying total oral combinations of decitabine/cedazuridine with venetoclax and also in a phase 1 trial of azacitidine and venetoclax. These last 2 studies were presented at ASH 2021 and showed ORR from 90% to 100% with OS not reached at the time of presentation.

Targeting CD47 in MDS. Investigators at Stanford identified CD47 as a key molecule controlling phagocytic activity of macrophages. A number of monoclonal antibodies are targeting CD47 in MDS. MD Anderson is a part of the ENHANCE trial, a phase 3 randomized study of azacitidine +/- magrolimab in higher risk MDS. Hopefully, as the Verona trial, the results of these study may change our approach to higher risk MDS. In addition, we are also testing second-generation antiCD47 antibodies such as ALX-148. Data presented at ASH in 2022 indicated a safe profile and activity in patients with poor-risk disease.
Other studies in front-line, higher-risk MDS include combinations with cladribine, fludarabine and venetoclax, as well as combinations with decitabine.

Clinical Trials for Patients with Higher-Risk MDS Previously Treated with an HMA

The prognosis of patients with HMA-failure MDS is poor. No drug is approved for these patients. This critical area of research is a high priority at to MD Anderson and is supported by the MDS/AML Moon Shot.

Targeting BCL-2 in HMA Failure MDS: One common question is the potential addition of venetoclax in HMA failure. We have two studies evaluating this concept. Data published in 2022 in Lancet Hematology demonstrated a high rate of response but rare complete responses and a range of OS of 8.5 to 10.5 months, which could be better than previously reported data in front-line randomized studies[1].

Role of Chemotherapy in HMA Failure HR MDS: Role of Lower Doses of CPX-351. Our group reported that a specific subset of patients with HR MDS HMA failure with diploid cytogenetics can benefit from lower doses of conventional AML-like therapy. CPX-351 is approved for patients with AML. In this phase 1 study, we are investigating attenuated schedules of this active compound in diploid patients with HR MDS already treated with an HMA.

Other studies include several phase 1 trials. One trial of interest is the study of the IRAK4 inhibitor CA-4948 (presented at EHA 2022). Data presented at EHA 2022 indicated that this agent has significant clinical activity. We are now planning to combine this agent with azacitidine and venetoclax.

Incorporating Precision Medicine in MDS

One of the major advances in research in MDS has been the incorporation of next generation sequencing assays in the clinic. This data not only allows better understanding and prognostication of the disease but also better design of targeted approaches for patients with MDS. Genes of interest include *SF3B1, IDH2, IDH1, Flt-3, C-CBL and p53.*

Targeting *SF3B1.* As describe above, we just opened a study with the splicing inhibitor RVT-2001 that targets specifically SF3B1. This is the most common mutation in MDS, particularly in patients with ring sideroblasts, one of the most common presentations of MDS.

Targeting IDH1 and 2. IDH1 and IDH2 are mutated in MDS in 5% to 15% of patients, respectively. Initial data in AML studies that included a small group of patients with MDS suggested significant activity of IDH inhibitors. A multicenter Phase 2 trial of the IDH2 inhibitor with or without azacitidine led by MD Anderson showed significant activity of enasidenib in MDS, both in front line and relapsed disease[3] . We are now studying combinations of ivosidenib and CPX-351 in higher risk, IDH1-mutated disease.

Targeting Flt3 in MDS: Despite the fact that Flt-3 mutations are rare in patients with MDS, they have been shown to occur in 15% to 30% of patients with HMA failure. Those patients tend to have leukocytosis. Data from an add-back study indicated significant activity with the addition of the Flt-3 inhibitor sorafenib to azacitidine in patients with HMA failure. We are now expanding this observation with a study combining azacitidine and quizartinib. Of note, this drug also targets mutations in the *C-CBL* gene. Initial results presented by Dr. Guillermo Montalban-Bravo at ASH 2021 indicated a high level of activity with this combination in relapsed Flt-3 + disease. Other studies include the combination of decitabine, venetoclax and quizartinib.

Targeting P53. Mutations of the p53 gene have been reported in close to 10% of patients with MDS, most of whom have therapy-related disease, complex cytogenetics and, therefore, a poor prognosis. These patients tend to be resistant to conventional chemotherapy and, although sensitive to HMA-based therapy, responses are short and the prognosis still dismal. At MD Anderson, this group of patients constitutes close to 30% of our referrals. We had studied the compound APR-246 all the way to phase 3 trials. We are now exploring an oral version of this compound knowns as APR-548.

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Announcements

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Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

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