Leukemia insights

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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.

Myelodysplastic syndrome (MDS) Clinical Trial 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. Nearly 400 patients are referred annually to this program to confirm diagnosis, and many remain to receive treatment. Approximately 80% 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 the myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) Moon Shot Program at MD Anderson. Over the last few years, we have witnessed an explosion in our understanding, evaluation and treatment of MDS. This has resulted in the approval in 2020 of two new agents for patients with MDS: luspatercept (1) and the oral hypomethylating agent (HMA) ASTX727 (2). MD Anderson was a leader of the trials that resulted in the approval of these two compounds, reinforcing the importance of referring patients to our center for clinical trials. Below, we provide a summary of our approach to patients with MDS and a list of 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. These are important because they are part of the main eligibility criteria for clinical trials past and present. Using IPSS and IPSS-R, patients with MDS are generally divided in two broad subgroups: lower- and higher-risk disease. Several other important data points are needed when making treatment decisions, including age of the patient, type and severity of comorbidities, significance and number of cytopenias, transfusion needs, presence of specific genomic alterations, percentage of bone marrow blasts, cytogenetic profile, potential for allogeneic stem cell transplantation (alloSCT) and, importantly, prior treatment with an HMA. Figure 1 summarizes our current view of different subsets of patients with MDS with different needs for treatment. First is the subset of patients without morphologic diagnosis of MDS who instead have diagnoses that include idiopathic

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cytopenia of unknown significance (ICUS), clonal hematopoiesis of indetermined potential (CHIP), and clonal cytopenia of unknown significance (CCUS). 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 2 summarizes our current approach to treatment.

Clinical Trials for Lower-Risk MDS

Treatment of ICUS/CHIP/CCUS: Today, there is no basis to treat patients with ICUS/CHIP/CCUS. Individuals with ICUS have no genomic or cytogenetic alterations and likely have a very low risk of progressing to MDS or other myeloid malignancy. Patients with CHIP or CCUS have molecular alterations, in particular in the context of cytopenia (CCUS). We have developed a "CHIP Clinic" to follow such patients and to develop guidelines of care. An important finding associated with CHIP/CCUS is not only the increased risk of transformation to MDS/AML/MPN but also the collateral risk of associated comorbidities. Therapies directed towards those comorbidities, i.e. cardiovascular disease, are warranted. We are interested in evaluating patients with of ICUS/CHIP/CCUS in our center.

Treatment of Isolated Anemia in Lower-Risk MDS: The COMMANDS Trial. This is a trial of luspatercept versus erythropoiesis stimulating agent (ESA) for red cell transfusion dependent lower risk MDS. Luspatercept is a TGF-b modulator that was recently approved for patients with refractory anemia with ringed sideroblasts (RARS) who had already been treated with an ESA. This drug is not approved for other types of MDS. COMMANDS serve as the registration trial of luspatercept for patients with lower-risk MDS.

Targeting IL-1 in Patients with Lower Risk MDS: A Phase I-II Trial of Canakinumab for Patients with Lower-Risk. 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 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.

Targeting Lower-Risk MDS with Oral Hypomethylating Agents: ASTX727 and ASTX030. One of the major developments in 2020 has been the approval of ASTX727 (Inqovi), an oral form of decitabine, for patients with MDS. Our group has pioneered the use of attenuated schedules of HMAs in lower-risk MDS. An oral agent specific for these patients will be a major contribution. This study is exploring a lower dose of ASTX727 as compared to that currently approved for these patients. ASTX030 is discussed below.

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 Azacytidine + 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.

Incorporating Immune Checkpoint Inhibitors in Higher-Risk MDS: Targeting CTLA-4 and TIM-3. Data from prior studies at MD Anderson indicates that blocking CTLA-4 is associated with a high response rate in MDS. Our trial examines the combination of ipilimumab and azacitidine. This study allows administration of azacitidine with local physician and is therefore designed to facilitate access to the study. Another study combines azacitidine and the TIM-3 inhibitor MBG453 (another immune checkpoint inhibitor).*Targeting BCL-2 in MDS:* The addition of venetoclax to an HMA has transformed the care of patients with AML. Several studies are studying combinations of venetoclax in MDS. This is an area of significant interest at MD Anderson. We have two studies that are evaluating different doses and schedules of venetoclax in previously untreated patients with higher-risk MDS.

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

The prognosis of patients with HMA-failure MDS is very poor. No drug is approved for these patients. This is an area of high relevance 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 studying this concept. One important detail is the realization that we do not know the proper dose and schedule of venetoclax in these patients. These is being studied in these Phase I and II trials.

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 study, we are

investigating, in a Phase I trial, attenuated schedules of this active compound in diploid patients with HR MDS already treated with an HMA.

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 IDH2, IDH1, Flt-3, and p53.

Targeting IDH2 and IDH1. 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 in MDS. A multicenter Phase 2 trial of the IDH2 inhibitor with or without azacitidine lead by MD Anderson is being studied for patients with MDS and IDH2 mutations. Our group also has two studies targeting IDH1 in MDS.

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. Our study combines azacitidine with the potent Flt-3 inhibitor quizartinib. Of note, this drug has also potential to have activity in patients with mutations in the *C-CBL* gene.

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. APR-246 is an agent that has shown significant activity in p53-mutated MDS. Our study is exploring the combination of azacitidine, APR-246 and venetoclax for patients with p53 AML. This is a follow-up after the completion of the randomized registration trial of azacitidine +/- APR-246 for patients with HR MDS.

Figure Legends

Figure 1. Functional classification of MDS. From a clinical perspective, patients with MDS can be divided into 5 subsets. An initial group (ICUS/CHIP/CCUS) without morphological features of MDS but with unexplained cytopenias or with cytogenetic or molecular alterations seen in MDS. Patients with MDS morphology are divided into lower and higher risk. Subsequently, these patients should be divided into those that have not received prior therapy and those that have already been treated with a hypomethylating agent. A sixth group is that of patients with AML evolving from MDS, many of them previously exposed to an HMA. This is a group of patients with very poor risk.

Figure 2. Proposed treatment algorithm for patients with MDS. Figure is discussed in the body of the manuscript. MDS: myelodysplastic syndrome, INT-1: intermediate-1, VL: very low, L: low, BM: bone marrow, H: high, VH: very high; HMA: hypomethylating agent; 5-AZA: 5-azacytidine

References:

1. Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. N Engl J Med. 2020;382(2):140-51.
2. Garcia-Manero G, Griffiths EA, Steensma DP, Roboz GJ, Wells RA, McCloskey J, et al. Oral cedazuridine/decitabine: a phase 2, pharmacokinetic/pharmacodynamic, randomized, crossover study in MDS and CMML. Blood. 2020.

Announcements

Leukemia Insights Newsletter

Our Leukemia Insights e-newsletter is now available online. Started in 2007 by Hagop Kantarjian, M.D., Leukemia Insights focuses on our various therapy options at MD Anderson Cancer Center. Click here to visit our new website.

Emil J Freireich Hematology Grand Rounds

The MD Anderson Cancer Center Emil J Freireich Hematology Grand Rounds now has a virtual format. This series highlights the incredible research taking place at MD Anderson Cancer Center while showcasing leaders from our research community, in an effort to remain engaged and inspired during the COVID-19 pandemic. Hosted by the Department of Leukemia in collaboration with the Department of Lymphoma/Myeloma, and Department of Stem Cell Transplantation and Cellular Therapy, we aim to strengthen the connections between the scientific and medical community at MD Anderson Cancer Center, our colleagues, patients and friends from around the world. Click here to visit our new website.

Announcements

(Continued)

Texas Virtual MPN Workshop (TMW) 2020

The UT Health San Antonio MD Anderson Cancer Center and MD Anderson Cancer Center invite you to attend the Texas Virtual MPN Workshop (TMW) 2020: First Annual Workshop and Meeting. This two-day online workshop, open to the broader MPN community, physicians, and providers, brings together medical experts in the field of myeloproliferative neoplasms to discuss the many new research and therapy options in development for patients with MPN. Registration is free for all and includes a slate of online sessions featuring key international speakers, and a newly added discussion section on COVID-19 and MPNs. Go to https://mayscc.eventsair.com/texasmpn/#Registration to register for this FREE event.

8th Annual Society of Hematologic Oncology (SOHO) Meeting

SOHO 2020 Virtual Registration is now available for delegates that are unable to attend the SOHO annual meeting in person due to COVID-19 travel restrictions or other reasons. The registration fee for virtual attendance includes LIVE stream multi-track session broadcast in real time; opportunities to submit questions to presenters; ability to engage with other virtual participants via chat and other tools; access to the virtual exhibit hall for collaborations, information and FREE giveaways; access to the poster hall for viewing, discussions and collaborations; an online copy of the final program and abstract proceedings published in the official CLML journal supplement, CME credits for physicians and CNE credits for nurses. In addition, on-demand recordings will be available to all delegates for 4-months following the meeting. Go to https://soho.click/2020 to begin the secure registration process.
Note that SOHO members receive a significant discount on registration fees. Sign up now to receive a SOHO member discount code to apply towards your annual meeting registration fee. Go to https://soho.click/join to claim your FREE membership.

Faculty Contacts

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.

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