

ASH 2010 meeting report—Top 10 clinically-oriented abstracts in myelodysplastic syndromes (MDS)

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The December 2010 American Society of Hematology (ASH) annual meeting in Orlando, Florida included more than 150 abstracts in the myelodysplastic syndromes (MDS) category. Thirty-six MDS-focused abstracts were presented in 6 oral sessions, and 120 additional abstracts were presented in 3 poster sessions. Although the 2010 ASH annual meeting included relatively little new MDS clinical trial data, with only one large randomized trial presented (the Intergroup E1905 study), it was an exciting conference from the standpoint of molecular discoveries in myeloid neoplasms, as various investigative groups presented results offering novel insights into MDS pathobiology, generated via high-throughput genomic sequencing and other innovative laboratory techniques. Here I summarize and discuss 10 MDS-related abstracts of special interest, which contain information that informs clinical practice. All 10 of these abstracts are published in full in the November 19, 2010 issue of *Blood* (volume 116, issue 21) and are identified here by their abstract number and title.

Diagnosis and Prognosis

No. 1

Discrepancy in diagnosis of myelodysplastic syndrome (MDS) between referral and tertiary care centers: experience at MD Anderson cancer center (MDACC) (Abstract # 1870).

Abstract summary

The MD Anderson cancer center (MDACC) leukemia group reviewed data from 915 patients who presented to their institution in Houston, Texas between 2005 and 2009 carrying an outside diagnosis of myelodysplastic syndrome (MDS). Among these 915 patients, there was discordance in diagnosis between the referring practice and the referral center in 150 patients (16%). Sixty of the 150 patients had been diagnosed prior to MDACC referral with forms of MDS without excess marrow blasts [i.e., refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), and refractory cytopenias with multilineage dysplasia (RCMD)]; 46 of these 60 were reassessed at MDACC as having refractory anemia with excess blasts (RAEB), and 6 were rediagnosed as RAEB in transformation (RAEB-t; these patients would be classified as having acute myeloid leukemia (AML) by World Health Organization (WHO) diagnostic criteria [1]). Fifteen patients diagnosed with RAEB on the outside were assessed as having lower-risk MDS at MDACC (i.e., with less than 5% blasts), while 40 patients diagnosed with RAEB on the outside were rediagnosed with RAEB-t. A handful of other patients labeled as MDS underwent diagnostic revision to one of the myeloproliferative neoplasms (MPN), MDS/MPN overlap syndromes, AML, or a benign disorder or indeterminate condition. Causes of diagnostic discrepancy included inadequate initial diagnostic material, differences in sample preparation and staining, over-reliance on flow cytometric assessment of blast proportion, and interpretive differences. While the changes in diagnosis did not have a significant global impact in terms of median survival or clinical outcome, new diagnoses did alter treatment recommendations, clinical trial eligibility, and prognosis for individual patients.

Discussion

MDS remains a challenging diagnosis for clinicians and morphologists [2,3]. The MDACC observations concerning a substantial degree of diagnostic discordance between referring practices and a tertiary care referral center were first reported in 1998 in a much smaller group of patients [4], and are consistent with my own clinical experience, both at Mayo Clinic and at the Dana-Farber Cancer Institute, where at least 15% of referred patients undergo diagnostic revision to another disease or reassignment to another risk category within the same disease cluster (unpublished data).

It is possible that some patients who are reclassified from lower-risk MDS at an initial local evaluation to higher-risk disease at the time of referral to a center like MDACC have experienced rapid disease progression between the two assessments, but re-interpretation of the outside slides used for original diagnosis is also common [3]. The degree of discordance in MDS diagnosis between different tertiary centers is unknown, but the extent of disagreement among expert hematopathologists in workshops sponsored by the MDS Foundation and other groups suggests that lack of consensus would be widespread [5].

These results underscore the complexity of clinicopathologic diagnosis of MDS, the value of expert morphologists, and the limitations of current morphology-based disease classifications. We need better molecular diagnostic tools for diagnosis and sub-classification of chronic myeloid disorders. In the case of MDS, there is a particular need with respect to better assessment of patients with idiopathic cytopenia(s) of undetermined significance (ICUS), as patients with ICUS may have MDS or another clonal neoplasm limiting life expectancy, but may also have a reactive condition that is unlikely to progress [6,7].

No. 2

Point mutations in myelodysplastic syndromes are associated with clinical features and are independent predictors of overall survival (Abstract # 300).

Abstract summary

Bejar et al. in the Ebert laboratory in Boston assessed marrow samples from a cohort of 439 patients (samples were obtained from MDACC and from Azra Raza's tissue bank; corresponding buccal samples were available for 219 patients) for mutations in a series of cancer-associated genes, including a comprehensive assessment of known MDS-associated mutations. The investigators began by screening 191 samples using an OncoMap platform, which allowed assessment for the presence of 953 described oncogenic mutations in 111 cancer-related genes. Genes with identified mutations were then examined in a larger cohort of 439 patient samples. The investigators found somatic mutations in six genes, including three patients with activating mutations of *GNAS*, which was not previously recognized as an MDS-associated gene. The other somatic mutations detected using OncoMap (e.g., *KRAS*, *NRAS*, and *JAK2*) are well-described in MDS [8]. Germline mutations or polymorphisms were detected in *MET*, *EGFR*, and *CDH1* (<1% of cases for each) and were not evaluated further.

Using the full cohort of 439 patients, the investigators pyrosequenced or Sanger sequenced a series of other genes previously associated with hematological malignancies, including (listed together with the six OncoMap genes in the order of the frequency in which mutations were detected) *TET2*, *ASXL1*, *RUNX1*, *TP53*, *EZH2*, *NRAS*, *JAK2*, *ETV6*, *CBL*, *IDH2*, *NPM1*, *IDH1*, *KRAS*, *GNAS*, *PTPN11*, *BRAF*, *PTEN*, and *CDKN2A*. Bejar et al. then correlated mutations in these 18 genes with clinical features and overall survival.

The investigators found that 51% of samples had at least one point mutation. The most frequently mutated gene was *TET2* (in 21% of samples, similar to the frequency reported in the populations evaluated by the Nijmegen and Paris laboratories where this mutation was first described [9,10]), followed by *ASXL1* (14%), *RUNX1* (9%), and *TP53* (8%). *TP53* mutations were usually found in isolation, and were associated with a complex karyotype and with abnormalities of chromosome 17 where *TP53* is physically localized. *TET2* mutations, in contrast, were regularly detected in association with other gene mutations, and were overrepresented in cases with normal cytogenetics. A lower platelet count was associated with mutations in *RUNX1*, *NRAS*, and *TP53*. The association of thrombocytopenia with somatic mutations *RUNX1* is interesting, given the known association of germline *RUNX1* mutations with familial platelet disorder associated with predisposition to AML (FPD-AML, Online Mendelian Inheritance in Man #601399) [11]. Mutations in *CBL*, *RUNX1*, *NRAS*, and *TP53* were

associated with a higher marrow blast proportion. In a multivariable model, there were five genes that were associated with poorer overall survival, independent of international prognostic scoring system (IPSS [12]) risk group, age, and sex: *TP53*, *EZH2*, *ETV6*, *RUNX1*, and *ASXL1*. Despite a higher prevalence in IPSS lower-risk cases, mutations of *EZH2* were associated with a high hazard ratio for death, identifying a group in which clinical risk may be underestimated using the IPSS alone. Overall, 31.2% of patient samples tested carried mutations in one or more of the five prognostic genes. In contrast, none of the other detected gene mutations were associated with better survival in an IPSS-independent fashion.

Discussion

During the last 2 years, various investigative groups in Europe and North America have described a series of new MDS-associated gene mutations [13]. SNP array findings led to the initial discovery of several of these, including *EZH2* and *TET2* mutations, which are associated with loss of heterozygosity at chromosomal loci 7q35 and 4q24, respectively [9,10,14]. There are now more than 20 different genes that have been described as somatically mutated in association with MDS, but most are detected at low frequency (<5% of cases), which underscores the heterogeneity of this group of disorders. *TET2* is the most commonly described mutation thus far in MDS, yet 75–80% of patients do not have a *TET2* mutation, and furthermore, 49% of patients in the Bejar et al. series had no detectable mutations at all in any of the 18 tested genes. Clearly, there will be many additional mutation discoveries in the years to come, which will hopefully be accompanied by a better understanding of how the known mutations cooperate with one another and with the larger-scale changes resulting from chromosomal rearrangements.

If we consider these 20+ MDS-associated genes globally, some patterns begin to emerge. For instance, at least five of the mutated genes detected in this series appear to be involved in epigenetic regulation of gene expression: *TET2*, *EZH2*, *ASXL1*, *IDH1*, and *IDH2*. In addition, two recurrently mutated genes not identified as somatic mutations in this study are also involved in regulation of DNA or histone methylation: mutations in *KDM6A* (*UTX*), encoding a histone H3K27 demethylase, were detected in 6% of 63 chronic myelomonocytic leukemia (CMML) samples by Jankowska and coworkers in Jaroslaw Maciejewski's laboratory at Cleveland Clinic (ASH 2010 Abstract #611), and Walter and coworkers at Washington University in St. Louis described mutations in *DNMT3A* (encoding DNA methyltransferase 3A) for the first time in MDS, in 12 out of 150 patients assayed (8%) (ASH 2010 Abstract #299). In a recent *New England Journal of Medicine* paper published by Ley et al. (from the same institution as Matthew Walter), *DNMT3A* mutations were associated with adverse prognosis in AML, were detected primarily in patients with intermediate-risk cytogenetics, and were not found in patients with core binding factor leukemias [15].

Soon, clinical laboratory testing for these mutations will be widely available and will inform how physicians assess and treat patients with MDS. Beginning in early 2011, for example, Dana-Farber Cancer Institute will perform custom OncoMap testing on all new patients who undergo a biopsy at the institution for any neoplasm, including hematological neoplasms, and other institutions are developing similar initiatives. This 500+ gene assay will initially not be charged to patients or their insurance companies, but is part of a broad-based personalized medicine effort funded by philanthropic donations. In addition to prognostic value, several of these mutations may also alter the effectiveness of treatment with specific drugs, such as the hypomethylating agents in MDS (see No. 6 below), or might prompt rational off-label use of compounds initially developed for other conditions.

No. 3

Validation of the newly proposed MD Anderson prognostic risk model for patients with myelodysplastic syndromes (Abstract # 444).

Abstract summary

Komrokji presented data from 844 patients with MDS evaluated at the H. Lee Moffitt Cancer Center in Tampa, Florida between January 2001 and December 2009; the investigators assessed the validity of the MDACC risk model for MDS published by Kantarjian et al. in 2008 [16]. Komrokji et al. confirmed the prognostic value of the MDACC risk model, including the model's ability to distinguish subsets of patients with higher and lower risk within IPSS risk groups. Using the MDACC risk model, 20% of the 844 Moffitt patients were classified in the low risk group, 30% of patients in the intermediate-1

risk group, 22% patients in the intermediate-2 risk group, and 16% in the high risk group; for 11% of patients, data were incomplete and so the patients could not be classified. The median overall survival from the time of diagnosis was 92 months, 49 months, 26 months, and 15 months for the low, intermediate-1, intermediate-2, and high risk MDACC model groups, respectively. The median survival for the four risk groups was 58 months, 28 months, 15 months, and 8 months from the time of presentation to Moffitt Cancer Center. AML transformation occurred in 5.9% of the low risk group compared to 16.8% of intermediate-1, 36.3% of intermediate-2, and 50.4% of high risk MDACC risk model-classified patients.

Discussion

The numerous limitations of the 1997 IPSS risk model for MDS are well recognized and are reviewed elsewhere [17]. The WHO classification-based prognostic scoring system (WPSS) proposed by Malcovati et al. in 2007 [18] and revised in 2009 [19] and the MDACC risk model appear to offer some advantages over the IPSS. At the 2009 ASH annual meeting, Hugo et al. presented data comparing these three prognostic scoring systems (i.e., the IPSS, WPSS, and the MDACC risk model) in a group of 1,503 patients with MDS evaluated at Mayo Clinic [20]. The Mayo investigators confirmed the validity of all three systems, but found that the MDACC risk model classified the broadest number of patients, including patients with secondary, treatment-related MDS [20]. It is striking how similar the patient median survival times from the time of tertiary center referral are among the Mayo data, the Moffitt Cancer Center data, and the original 2008 paper presenting the MDACC risk model, with the lowest risk group in all three studies having a median survival of between 51 and 58 months and the highest risk group having a survival of between 4 and 8 months. Such comparisons from the time of tertiary referral center evaluation are valid because, unlike the IPSS, the MDACC risk model is dynamic and can be applied at any time in the disease course.

The MDACC risk model offers the unique advantage that it is sensitive to the degree of peripheral blood cytopenias. Several studies presented at the 2010 ASH annual meeting again highlighted the IPSS-independent adverse predictive value of severe thrombocytopenia (ASH 2010 Abstracts #4021 and #2905), an observation that has been published by several groups [21,22].

The IPSS is currently under revision using international multi-center data from more than 10,000 patients, and a draft version will likely be presented at the 11th International Symposium on MDS in Edinburgh, Scotland in May 2011 (<http://www.kenes.com/mds/>). Although details of the draft model have not yet been finalized, it is anticipated that the new IPSS will be more sensitive to degree of cytopenias and will incorporate a broader range of cytogenetic abnormalities, as data continue to emerge on the importance of various recurrent but uncommon karyotypes not included in the original IPSS [23].

No. 4

Comorbidities and overall survival in myelodysplastic syndromes (MDS): development of a prognostic model incorporating IPSS and age with ACE-27 comorbidity index (Abstract #605).

Abstract summary

To better understand how comorbidities influence outcomes in patients with MDS, the MDACC leukemia group reviewed medical records of 600 consecutive patients with MDS who presented to their center between January 2002 and June 2004. The severity of comorbid conditions was assessed in this cohort using the Adult Comorbidity Evaluation-27 (ACE-27) tool, a well-validated 27-item comorbidity index that has been used in patients with cancer for more than 10 years [24]. While 28.8% of the patients had no significant comorbidities, an ACE-27 comorbidity score of "mild" was assigned to 42.3% of patients, "moderate" to 21.2% of patients, and "severe" to 13.7% of patients. The overall median survival in this group was 18.6 months, and median survival stratified according to ACE-27 results was 31.8, 16.8, 15.2, and 9.7 months for no, mild, moderate, and severe comorbidity score, respectively, ($P < 0.0001$). The investigators developed a final prognostic model incorporating comorbidity scores with patient age and IPSS risk group (Table I).

Discussion

Patients with MDS in the United States (US) are diagnosed at a median age of ~71 years [25]. As a result of their advanced age, patients with MDS frequently suffer from other nonhematologic medical conditions, which may alter the patients' symptoms or expected survival, and may also influence

TABLE 1. Proposed IPSS-Based Prognostic Scoring System Incorporating ACE-27 Comorbidity Index

Risk factor	Points(Sum, 0-8)
Age: >65 years	2
IPSS risk group: Intermediate-2	2
IPSS risk group: High	3
ACE-27 score: Mild or moderate	1
ACE-27 score: Severe	3
Risk group	Median survival (months)
Low (0–1 points)	43
Intermediate (2–4 points)	23
High (5–8 points)	9

the success of treatments directed at the MDS [26–28]. Comorbidities are not included in any of the prognostic scoring systems or risk models for MDS described above. Investigators are now paying more attention to the importance of comorbidities, since serious diseases like MDS cannot be considered in isolation from patients' other medical problems. To use an extreme example, a patient with one of the lowest-risk forms of MDS (e.g., RARS with a normal karyotype) who has advanced pancreas cancer or New York Heart Association Class 4 congestive heart failure has a life expectancy of only a few months, but that patient's clinical course will be determined by the comorbid condition rather than by the bone marrow disorder. Therefore, when developing a treatment plan, one must consider not just the bone marrow status but the whole patient. It is not yet clear which of the several tools now available for measuring comorbidities (e.g., ACE-27, Charlson Comorbidity Index, Hematopoietic Stem-Cell Transplantation-Specific Comorbidity Index) performs the best—several research groups have recently published comorbidity assessments in MDS populations using tools other than ACE-27 [26–28]—but it seems apparent that further refinement of comorbidity assessment in MDS will help hematologists estimate patient outcomes more accurately.

No. 5

Highly transfused MDS patients often have cardiac iron overload, as shown by MRI assessment (Abstract #2906).

Abstract summary

The Groupe Francophone des Myélodysplasies (GFM) co-operative group prospectively evaluated 73 patients with MDS who were chronically receiving red blood cell transfusions from four centers using cardiac T2* MRI methods, and also assessed those patients' cardiac function by routine echocardiography. Patients in this study had a median serum ferritin level of 1,750 ng mL⁻¹, and 54 of 73 (74%) of patients were receiving iron chelation therapy. Patients were, in general, heavily transfused, having received a median number of 68 U of red blood cells (range, 5–574 U). Evidence of cardiac iron overload, defined by MRI T2* time less than or equal to 20 ms, was present in 14 of 73 patients (19%). In 13 of 59 (22%) patients who underwent echocardiography, the left ventricular ejection fraction (LVEF) was below normal. However, while there was a correlation between cardiac T2* time and the number of red cell units transfused, there was no correlation between cardiac T2* and serum ferritin level or hepatic liver iron correlation, nor was there a correlation between LVEF and cardiac T2* result.

Discussion

The clinical importance of iron overload in MDS and the risk-benefit balance of iron chelation therapy are incompletely understood and controversial topics at present [29,30]. There have been at least three prior publications assessing cardiac iron overload measured noninvasively using newer T2*/R2* MRI techniques in heavily transfused MDS populations, and these three studies all suggested that cardiac iron overload is infrequent and is less common than hepatic iron overload in heavily transfused patients with MDS [31–33]. The new GFM cardiac MRI study reported at ASH 2010 included a cohort of patients with a high median number of red cell units transfused (68 U), but so did the three previous studies: a median of 63 U in the 11-patient United Kingdom study by Chacko et al., 90 U in the 10-patient Israeli study by Konen et al., and 36 U in the 11-MDS-patient Chinese study by Au et al. [31–33] It is notable that serum ferritin did not predict cardiac iron overload

in any of these studies, which emphasizes the poor test characteristics of serum ferritin measurement. Most of the existing expert consensus guidelines for iron chelation therapy in MDS, such as those of the National Comprehensive Cancer Network [34] or the MDS Foundation [35], suggest that clinicians should initiate chelation treatment on the basis of serum ferritin measurements and number of red cell units transfused, but this recommendation is highly problematic, as serum ferritin is subject to many influences including inflammatory state, and may not truly reflect the degree of organ iron deposition or iron-related clinical risk.

Some patients who do not have excessive tissue iron loading might still be at risk for complications related to reactive nontransferrin-bound iron species, including labile plasma iron or labile cellular iron molecules that are highly redox active and could contribute to genomic instability or risk of infection with siderophoric microorganisms [36]. This hypothesis remains unproven. The ongoing industry-sponsored TELESTO clinical trial, which will enroll more than 600 patients with lower-risk MDS who are receiving red cell transfusions and have a serum ferritin >1,000 ng mL⁻¹, and will treat these patients with either deferasirox or placebo for up to 5 years, should help to better define the risk-benefit balance of iron chelation therapy in the MDS population, including whether this intervention has any effect on morbidity and mortality.

Treatment Including Biomarkers of Response

No. 6

Presence of TET2 mutations predicts a higher response rate to Azacitidine in MDS and AML Post MDS (Abstract # 439).

Abstract summary

The highly productive GFM MDS group assessed 103 patients with MDS, AML, or CMML who had received at least one cycle of azacitidine and who either had a bone marrow evaluation after at least four cycles of treatment, or died or progressed before completion of four cycles (the latter patients were considered treatment failures). Azacitidine responses were scored according to standardized International Working Group (IWG) 2006 MDS treatment response criteria [37]. The median number of azacitidine cycles administered was 7. *TET2* mutations were found in 17 (17%) of the 103 patients. Patients with *TET2*-mutant MDS had less frequent unfavorable cytogenetics than *TET2* wild-type (6% vs. 37%, respectively). Notably, the overall response rate was higher in patients with *TET2* mutations, with 11 of 17 complete responses (CRs) or marrow CRs (mCRs) in this group (65%) versus 26 of 86 CRs/mCRs (30%) among *TET2* wild-type patients (*P* = 0.01). The treatment response duration was similar in the two groups. If one includes stable marrow disease with hematologic improvement as a response, then 14 of 17 patients (82%) with *TET2* mutations responded to azacitidine versus 39 of 86 (45%) *TET2* wild-type patients (*P* = 0.007).

Discussion

At present, despite several earlier proposals that could not be confirmed (such as monosomy 7 karyotype [38]) and extensive efforts at identifying a predictive global methylation profile [39], there is as yet no biomarker that can help clinicians predict MDS patients' response to hypomethylating agent therapy. Although the GFM findings of *TET2* mutation status predicting clinical response to azacitidine are not as dramatic in terms of the magnitude of response difference as is seen with *KRAS* mutation status and cetuximab in colorectal cancer [40] or gefitinib and *EGFR* mutation status in non-small cell lung cancer [41], it is notable that overall azacitidine response rate in this cohort was nearly twice as high among patients with *TET2* mutations compared to those without mutations. This is a mechanistically plausible association because, as detailed in ASH annual meeting Abstract #1 (in the Plenary Scientific Session), the *TET2* protein is involved in converting 5-methylcytosine to 5-hydroxymethylcytosine in DNA [42], a process that has substantial implications for epigenetic regulation in myeloid malignancies. If azacitidine and decitabine indeed work via epigenetic mechanisms, pretreatment epigenetic patterns may influence clinical response to these drugs.

TET2 mutation testing is expected to be available clinically in early 2011. However, the GFM cohort reported here was relatively small, and the result needs to be confirmed by others. There was also an ASH 2010 annual meeting abstract by Kulasekararaj and coworkers from Ghulam Mufti's group in the United Kingdom (Abstract #125), which hypothesized that *EZH2* mutations (the *EZH2* protein also affects epigenetic gene regulation, specifically by catalyzing H3K27 trimethylation) may predict response to

hypomethylating agent therapy. In that series, seven of eight patients (88%) with detectable *EZH2* mutations responded to azacitidine therapy. Further assessment using large cohorts of patients, e.g., from prior multicenter clinical trials of azacitidine or decitabine, will be of considerable interest.

No. 7

Prolonged administration of Azacitidine with or without entinostat increases rate of hematologic normalization for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US leukemia intergroup trial E1905 (Abstract 601).

Abstract summary

The current standard of care for disease-modifying treatment of higher-risk patients with MDS is a hypomethylating agent, with azacitidine now the preferred drug because of data from the AZA-001 clinical trial indicating that azacitidine treatment improves survival compared to supportive care alone [34,43]. However, up to one-half of patients with MDS do not receive any benefit from azacitidine therapy, and the median response duration to hypomethylating agent treatment is less than 2 years, so new approaches are needed to build on azacitidine's encouraging but modest success. *In vitro*, hypomethylating agents and histone deacetylase (HDAC) inhibitors have synergy with respect to gene expression and cellular effects [44]. Therefore, the Eastern Cooperative Oncology Group (ECOG), together with other US leukemia co-operative groups, undertook a randomized clinical trial, ECOG-led Intergroup trial E1905, to assess whether combining azacitidine with entinostat (formerly MS-275, SNDX-275), an orally bioavailable HDAC inhibitor, would be more effective than azacitidine alone.

The E1905 study used a 10-day azacitidine schedule, 50 mg m⁻² per day subcutaneously for 10 out of every 28 days, which had been shown to be effective in MDS in a Phase I trial combining azacitidine and sodium phenylbutyrate conducted by Gore et al. at Johns Hopkins University in Baltimore, Maryland [45]. In the E1905 combination therapy randomization group, 10-day azacitidine treatment was combined with entinostat, 4 mg m⁻² per day orally, administered on Days 3 and 10.

The E1905 study randomized 150 patients, of whom 136 were both eligible and evaluable. This included 88 patients with MDS, 5 with CMML, and 43 with AML with trilineage dysplasia (eligible AML patients were required to have a white blood count WBC <30,000/mm³, measured on two occasions 4 weeks apart). Among patients with MDS, 72% were in higher-risk IPSS categories. The primary endpoint was trilineage hematologic improvement, including either CR, partial response (PR), or hematologic improvement in all three lineages, assessed using IWG 2,000 response criteria [46].

There was no difference in the overall trilineage hematological response rate between arms: 31% in the azacitidine monotherapy arm, versus 24% in the azacitidine plus entinostat combination therapy arm. Non-trilineage hematologic improvement was seen in 12% of patients in the monotherapy arm and 19% in the combination arm, so the total response rate was 43% vs. 44%. As expected, there was more thrombocytopenia and fatigue in the combination therapy arm; thrombocytopenia and fatigue are common adverse effects in HDAC inhibitor trials. The investigators compared the hematologic normalization rate in E1905 to the Cancer and Leukemia Group B (CALGB) 9221 study conducted during the 1990s [47], the trial which led to the Food and Drug Administration (FDA) approval of azacitidine in the US in 2004. The trilineage improvement rate was 15% in CALGB 9221 compared to 31% with azacitidine monotherapy in E1905 and the cytogenetic response rate was also higher (ASH 2010 Abstract #4013), so the E1905 investigators postulated that the 10-day azacitidine therapy might be more effective than the FDA-approved 7-day schedule used in CALGB 9221.

Discussion

There is considerable interest in combining azacitidine or decitabine with other agents in patients with MDS. Although the relatively weak HDAC inhibitor valproic acid did not improve responses to decitabine in a randomized trial of decitabine monotherapy versus combination therapy [48], ongoing trials are assessing combinations of azacitidine with vorinostat [49], a more potent HDAC inhibitor that is currently approved for treatment of patients with cutaneous T-cell lymphoma. In addition, an azacitidine plus lenalidomide combination regimen is also moving forward, based on encouraging Phase I data from the Bone Marrow Failure Consortium [50]. However, it is discouraging that combination therapy with azacitidine and entinostat was not more efficacious than azacitidine monotherapy in the E1905 trial. One

potential explanation is that entinostat may have been the wrong HDAC inhibitor to use, particularly because it is a potent inhibitor of the cell cycle, and azacitidine's clinical activity appears to be cell-cycle dependent. However, it is possible that HDAC inhibitors as a class will not be useful clinically in patients with MDS. HDAC inhibitors seem to have only modest activity as single agents in MDS [44].

The investigators' comparison of response rates in E1905 to historical results from CALGB 9221 is of uncertain validity. Patients enrolled in the E1905 study might have been better selected for potential response to hypomethylating agent therapy than participants in CALGB 9221, given the decade of clinical experience with azacitidine between the two trials. In addition, the median number of azacitidine cycles that patients enrolled in E1905 received (six cycles) is more than was administered in the CALGB study (<4 cycles), and there may be a correlation between number of hypomethylating agent cycles administered and response rate or depth of response [51]. Further exploration of different doses and schedules of hypomethylating agents, alone and in combination with other HDAC inhibitors, is ongoing in patients with MDS.

No. 8

Evaluation of oral Azacitidine using extended treatment schedule: a Phase I study (Abstract # 603).

Abstract summary

Garcia-Manero from MDACC reported results from an ongoing multi-center Phase I exploration of extended oral azacitidine therapy in patients with MDS. Enrolled patients had to be cytopenic, and could not have received prior azanucleoside therapy. Patients received oral azacitidine either once or twice daily on 14 or 21-day schedules, at total daily doses of either 300 or 400 mg per day. Data on 15 patients with MDS were presented at the meeting. Using IWG 2006 criteria, two patients had a CR and six patients experienced hematologic improvement. When assessing the pharmacokinetics of the 300 mg orally once daily every 21 days, the cumulative exposure was ~58% of the drug exposure that would be expected with the subcutaneous schedule. The extension phase will be a Phase II study of 21-day dosing. The oral azacitidine was quite well tolerated overall, with febrile neutropenia being the most common adverse effect in the daily dosing schedules; febrile neutropenia appeared more common in the 21-day cohort compared to the 14-day cohort.

Discussion

As stated above, azacitidine is currently the standard of care for higher risk patients with myelodysplastic syndrome, but parenteral administration is inconvenient for some patients, especially patients who must travel from a distance to a clinical facility to receive azacitidine multiple consecutive days each month. Oral azacitidine might offer some advantages for those patients, and oral azacitidine will also allow exploration of longer-term, low-dose schedules that more closely mimic predicted optimal dosing based on *in vitro* results, but which are not currently feasible in the US with an injectable agent such as azacitidine due to Medicare regulations preventing self-administration of parenteral therapy. Although the oral azacitidine data presented by Garcia-Manero et al. are preliminary, this new formulation is worthy of further exploration. In early studies of oral azacitidine, there was wide variability in the degree of drug absorption and pharmacokinetics, but different formulations seem to have addressed part of that problem [52].

No. 9

Effectiveness of various dosage regimens of Azacitidine in patients with myelodysplastic syndromes: safety and efficacy final data from the Spanish Azacitidine compassionate use registry (Abstract # 1853).

Abstract summary

Investigators from the Spanish Azacitidine Compassionate Use Registry reported final results from 181 patients with MDS who had been treated with azacitidine prior to the drug's regulatory approval in Spain (May 2009). At the discretion of the treating physician, patients were treated using either a 5-consecutive-day per month schedule, a 7-total-day per month schedule omitting weekends ("5 plus 2"), or a 7-consecutive-day per month schedule. The median number of azacitidine cycles administered [6] was similar for patients treated using all three schedules, and demographic and disease characteristics of the patients were also similar. Using IWG 2006 response criteria, better overall response rates were seen with either of the two 7-day per month regimens than with the 5-day regimen: a 38% overall response

rate (ORR) for the 5-day cohort (32% of the 181 patients were treated on this schedule); 71% ORR for the 5 plus 2 group (a schedule used in 28% of the patients); and 52% ORR for the 7-consecutive days schedule that was used in 37% of cases ($P = 0.0005$ for comparison of 5-day versus 5 plus 2). The CR rate was also higher using either of the 7-day-per-month regimens: 22% in the 5 plus 2 weekend-sparing regimen, compared to 16% in the 7-consecutive day regimen and 12% in the 5-day regimen. Adverse event rates did not differ between the three schedules.

Discussion

Although the FDA-approved azacitidine schedule is 7 consecutive days repeated every 28 days, and this is the regimen that was used in the AZA-001 survival study, many infusion therapy centers in the US are not open on weekends, and therefore a number of clinicians have adopted "weekend-sparing" azacitidine schedules [53]. Some clinicians currently administer azacitidine for only 5 days out of every 28 days, omitting Days 6 and 7. However, the data from the Spanish registry, as well as data from a US Oncology network in Georgia presented at the American Society of Clinical Oncology annual meeting earlier in 2010 [54], suggest that response rates may be higher in patients who get 7 days of azacitidine per month, whether or not weekend administration occurs.

At this point, although the 10-day E1905 Azacitidine regimen described in No. 7 above remains experimental, administration of azacitidine for 7 days per month—either consecutively or "5 plus 2"—should be considered standard practice, and clinicians should make every effort to give patients 7 days of azacitidine therapy rather than 5 days. Administering the drug for only 5 days per month may be short-changing some patients. In 2009, Lyons et al. published results of a US Oncology multicenter study that compared three different weekend-sparing azacitidine regimens, including 5-day and 5-plus-2 regimens, and the investigators did not observe any significant differences between these schedules [55]. However, patients enrolled in the US Oncology study were rather poorly characterized (many did not have IPSS or cytogenetic or marrow biopsy results), and the approved standard 7-consecutive-day approved regimen was not used as a comparator arm in that study, so it is difficult to interpret those results.

No. 10

Phase II multicenter trial of rabbit anti-thymocyte serotherapy in myelodysplastic syndrome: rate of hematological improvement associated with pre-treatment disease duration (Abstract # 602).

Abstract summary

P.K. Epling-Burnette from the H. Lee Moffitt Cancer Center presented results on behalf of the Bone Marrow Failure Consortium describing 21 evaluable patients with MDS who were recruited over 6 years and treated with rabbit anti-thymocyte globulin (rATG) on a Phase II multi-center clinical trial. The rATG dose administered was 2.5 mg kg^{-1} per day intravenously for 4 consecutive days. Eligible patients had cytopenias, $<10\%$ marrow blasts, and adequate organ function; patients with CMML were excluded. Notably, 39 patients were enrolled in the trial, but 18 enrolled patients were not evaluable, mostly due to failure to meet inclusion and exclusion criteria (seven patients), major protocol violations (e.g., five patients also received nonstudy therapy), or death prior to treatment initiation.

Nine of the 21 evaluable patients (43%) experienced a hematologic improvement after rATG therapy, using IWG 2000 response criteria. The median time to treatment response was 75 days, with a range of 3 days to 3.7 months, and the median duration of response was 7.2 months. Only four of the evaluable patients bore the HLA-DR15 allele, and three of those four experienced hematologic improvement; in previous trials, HLA-DR15 has predicted a higher likelihood response to immunosuppressive therapy [56]. There were no clinical features among enrolled patients that predicted response to treatment, other than a trend for shorter time from diagnosis to treatment among responders (i.e., median 8 months from MDS diagnosis to protocol treatment in those who responded to rATG, versus 42 months in non-responders), and even that parameter did not achieve statistical significance. Of note, normal karyotype or trisomy 8, low age-adjusted marrow cellularity, and low transfusion burden—parameters that have predicted immunosuppressive therapy response in other trials—did not predict a treatment response in this study. The investigators concluded that rATG is active in MDS. The most common adverse events were infusion-related reactions, which usually occurred with the first dose of rATG. There were three deaths related to infection.

Discussion

A subset of patients diagnosed with MDS will respond to immunosuppressive therapy, probably because auto-reactive T cell clones contribute to hematopoietic suppression in some patients. The chief difficulty for clinicians has been in reliably identifying those patients with a high likelihood of response to immunosuppressive treatment. In previously published studies, various investigative groups have reported that a hypoplastic/hypocellular marrow, presence of a paroxysmal nocturnal hemoglobinuria (PNH) clone, trisomy 8 cytogenetics, younger age, HLA-DR15 allele, relatively low transfusion burden, lower IPSS score, short time from diagnosis to therapy, or normal karyotype have predicted response to immunosuppressive therapy [56–59]. In the Bone Marrow Failure Consortium study, however, none of the above parameters clearly predicted treatment response, although small patient numbers may have been a contributing factor to the lack of statistical significance for all comparisons. Therefore, it remains challenging to predict which group of patients will respond and to interpret studies of immunosuppressive therapy in MDS. The response rate to ATG-based therapy in unselected patients with MDS appears to be quite low [60].

The optimal immunosuppressive regimen for use in patients with MDS remains unclear. Several immunosuppressive agents are now available, including equine ATG, rATG, calcineurin inhibitors (cyclosporine or tacrolimus), and alemtuzumab; these agents are sometimes used in combination with one other as well as with other drugs such as etanercept [61], including adjunctive use of corticosteroids. It is also unclear the extent to which mechanisms of the well-documented clinical responses to "immunomodulatory" agents (iMiDs) in MDS, such as thalidomide and lenalidomide, might overlap with mechanisms of response to immunosuppressive therapies, since iMiDs can also alter T-cell subsets. Data presented by Sloand et al. at the American Society of Hematology annual meeting in 2009 suggested that in carefully selected patients with MDS, the response rate to alemtuzumab is quite high [62]. Patients were selected for the alemtuzumab trial using a predictive model for immunosuppressive therapy in MDS that incorporates age, red cell transfusion burden, and HLA-DR15 status [56].

These rATG Phase II study results need to be interpreted in the context of a randomized trial in patients with severe acquired aplastic anemia presented as a late-breaking abstract at the ASH meeting (LBA-4). In that study from the National Institutes of Health's Intramural Hematology Branch, 120 patients were randomized to receive either equine ATG or rATG. Compared to the rATG-treated patients, patients receiving equine ATG were less likely to die (3 deaths versus 14 deaths in the rATG arm) and had a higher rate of hematological response at 3 months and 6 months post-therapy (69% vs. 35% for the latter comparison); these results were highly statistically significant. At least one study—from Germany—has compared equine ATG to rATG in MDS [63]. Although the response rates and adverse events with the two ATG preparations appeared equivalent in that study, only 35 patients were enrolled.

T-cell depleting therapies such as rATG need to be evaluated further with molecular correlates to how patients who respond to immunosuppressive therapies differ from other patients with MDS. Of note, a recently completed European open-label randomized Phase III trial of ATG plus cyclosporine versus supportive care enrolled 88 patients with MDS, and the investigators reported that while hematological responses were observed in a subset of patients [13 of 45 (29%) patients with immunosuppressive therapy achieved a response, compared to 4 of 43 (9%) with supportive care], there was no difference in overall survival or disease progression [64].

Conclusions

Despite the relative paucity of reports of novel therapies for patients with MDS at the 2010 ASH annual meeting, it was difficult to choose just 10 clinically informative abstracts for inclusion in this series. The pace of molecular discovery in MDS is accelerating, as demonstrated by the description of numerous new MDS-associated gene mutations since 2008 [including *TET2*, *EZH2*, *ASXL1*, *DNMT3A*, *IDH1*, *IDH2*, *KDM6A* (*UTX*) and *CBL*], which is highly encouraging. However, the rate of introduction of safe and effective new treatments remains agonizingly slow, in part due to the unnecessarily complex and burdensome regulatory and bureaucratic tangle that characterizes the contemporary clinical trial world [65,66]. We may hope that future ASH annual meetings will feature more presentations about clinically active, rationally designed targeted therapies.

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