5 Minute JournalClub

Key ASH Presentations
Issue 8, 2011

Azacitidine for Secondary MDS and as a Bridging Option for Patients with MDS/CMML Before Allogeneic Transplant

For more visit ResearchToPractice.com/5MJCASH2011

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVES

- Apply new research findings with azacitidine to the evidence-based treatment of secondary MDS.
- Recall the effects of pretransplant azacitidine on hematopoietic cell transplantation outcomes in MDS and CMML.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

B Douglas Smith, MD
Associate Professor of Oncology
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, Maryland

Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation; Paid Research: Eisai Inc, Infinity Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Synta Pharmaceuticals Corp.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium — The Takeda Oncology Company, Mundipharma International Limited, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

Last review date: March 2011
Expiration date: March 2012

5 MinuteJournalClub

Key ASH Presentations
Issue 8, 2011

Click here for key papers on AML, MDS and APL

In recent years, the use of hypomethylating agents — specifically decitabine and even more commonly azacitidine (AZA) — has for the first time allowed oncologists to help patients with myelodysplastic syndromes live longer and enjoy a better quality of life. However, as with many systemic agents in oncologic practice, these advances have brought with them controversy. Dr William Blum reviewed this topic in a spectacular ASH discussion, and in his accompanying education book write-up, he colorfully describes this recent chapter of the MDS story with a number of well-known quotes by, of all people, Hall of Fame Yankee baseball player Yogi Berra.

What made this review so worthwhile is that beyond finding a way to make the information entertaining, Dr Blum also made it eminently practical. He speculated that the survival advantage seen with AZA and not with decitabine may have more to do with the amount of drug exposure (median number of cycles delivered was over twice as many in the key trial of AZA) than inherent differences in the two drugs. For patients with high-risk disease, for whom the goal is extending survival, he suggested the same not-always-practical AZA schedule as the pivotal trial (days 1 to 7 every four weeks), but for patients with lower-risk disease being treated for transfusion dependence, he considers the days 1 to 5 every four weeks approach reasonable. He believes that a minimum of four to six cycles should be administered if the patient is tolerating treatment, as responses in some individuals can occur very slowly. Again mimicking the trial approach, treatment until progression is optimal.

When it comes to the less-often utilized decitabine, Dr Blum quoted Yogi: "It's like déjà vu all over again." He prefers the days 1 to 5 schedule à la the ADOPT trial and noted that at least three to four cycles should be administered before "giving up."

While this lively presentation was definitely one of my ASH highlights, the conference is, of course, as much a forum to unveil information as it is to review what we already know. For this reason we profile several new data sets on MDS, AML and one of the world's more fascinating diseases, APL.

1. Three key papers in MDS

Guillermo Garcia-Manero presented a **fascinating study** evaluating ***oral*** AZA — a strategy that perhaps opens up a whole new way to derive more benefit from this agent by delivering lower levels of drug but for more prolonged periods of time. In this study, treatment was administered for up to 21 days of a 28-day cycle, and although only a Phase I effort, data on overall response (67 percent) and tolerability were impressive. Hopefully this pioneering effort will soon be followed by Phase II and III data.

In another interesting **presentation**, Cleveland Clinic MDS maven Mikkael Sekeres presented data from a US-based MDS registry study (AVIDA) demonstrating similar efficacy and tolerability findings for AZA in secondary MDS to those reported for primary disease. Finally, a **report** of 19 patients receiving AZA as a bridge to potentially curative allogeneic stem cell transplant demonstrated favorable safety and efficacy outcomes, supporting this active approach while a donor is sought.

2. Lenalidomide in del(5q) AML

This IMiD® has an established and important role in del(5q) low-risk MDS, and therefore evaluation in del(5q) AML was logical. Unfortunately, results from a **SWOG study** of lenalidomide alone in older patients with AML not eligible for transplant were disappointing in terms of response (five of 37 patients). In another **study**, in which lenalidomide was combined with intensive induction chemotherapy, response rates were reasonable (60 percent) but disease-free survival was short, and investigators want to see further research with this agent in AML before considering it outside of a clinical trial.

3. The shifting winds of APL

A **European study** evaluating arsenic trioxide (ATO) as consolidation after induction with chemotherapy/all-trans retinoic acid (ATRA) did not have enough events at this point to define long-term outcome. However, the MD Anderson group believes this question may now be outdated in view of their just-presented **ASH paper** demonstrating a 98 percent complete response rate with a nonchemo regimen (ATRA/ATO) with higher-risk patents (WBC > 10 x 10^9/L) also receiving gemtuzumab. Dr Garcia-Manero (he seems to be everywhere in these diseases) believes that one dose of idarubicin can be administered instead of the now-unavailable gemtuzumab, but most other investigators seem to want more data before making this major conceptual leap essentially abandoning chemo as induction.

In many ways the papers presented here support the notion that "the future ain't what it used to be" and suggest that things will get better as long as dedicated investigators

like Drs Blum, Garcia-Manero and Sekeres and their colleagues continue to push the field forward and live another Yogi motto, "It ain't over 'til it's over."

Speaking of over, this concludes our ASH edition of this series. Stay tuned for an upcoming four-part GI cancer activity developed from our recent case-based educational symposium at the GI Cancers Symposium in San Francisco.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in each activity.

This program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

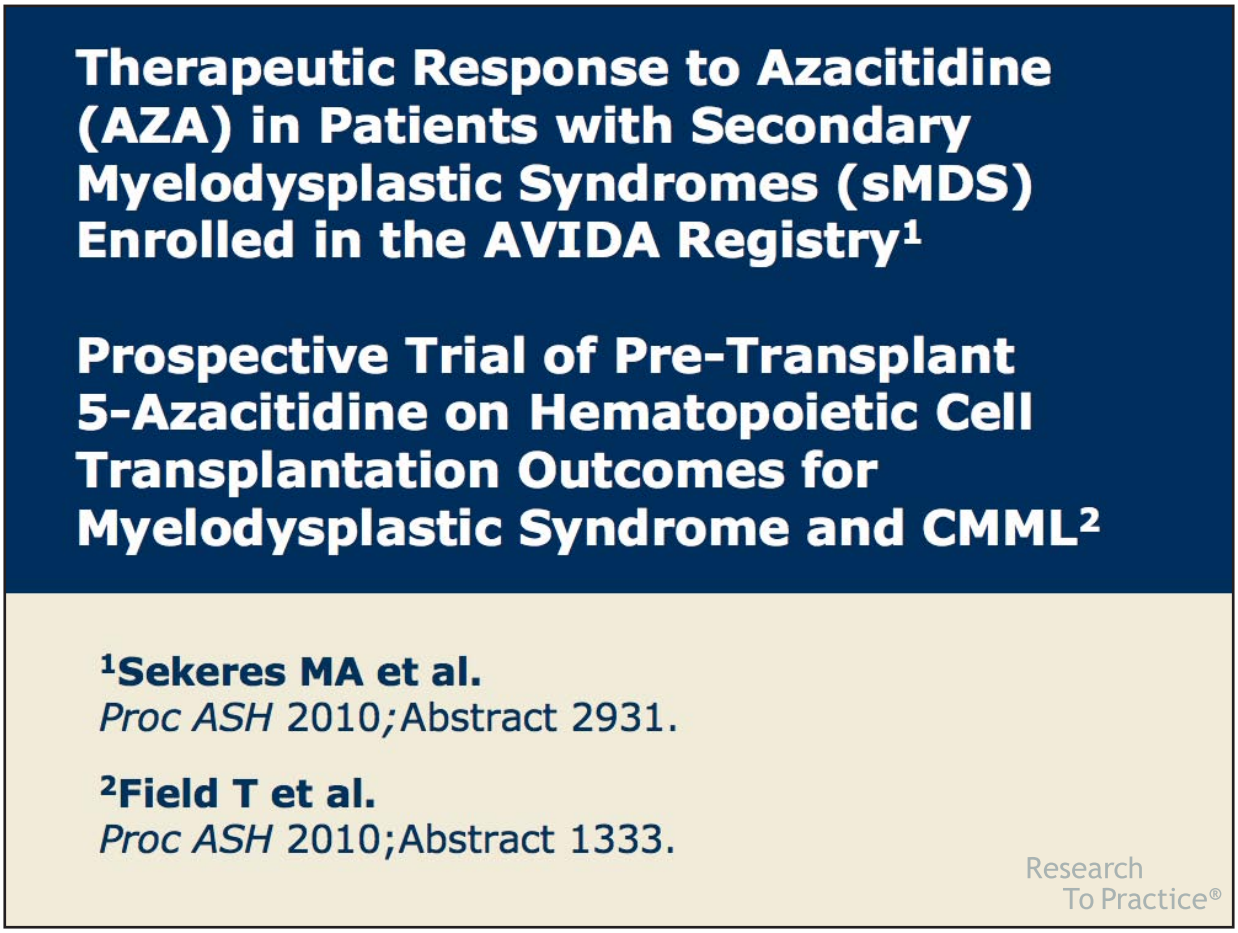
Azacitidine for Secondary MDS and as a Bridging Option for Patients with MDS/CMML Before Allogeneic Transplant

Presentations discussed in this issue

Sekeres MA et al. **Therapeutic response to azacitidine (AZA) in patients with secondary myelodysplastic syndromes (sMDS) enrolled in the AVIDA registry.** *Proc ASH* 2010;**Abstract 2931**.

Field T et al. **Prospective trial of pre-transplant 5-azacitidine on hematopoietic cell transplantation outcomes for myelodysplastic syndrome and CMML.** *Proc ASH* 2010;**Abstract 1333**.

Slides from presentations at ASH 2010 and transcribed comments from a recent interview with B Douglas Smith, MD (1/4/11)



Therapeutic Response to Azacitidine (AZA) in Patients with Secondary Myelodysplastic Syndromes (sMDS) Enrolled in the AVIDA Registry

Sekeres MA et al.

Proc ASH 2010;Abstract 2931.

Background

- Approximately 10% of patients with myelodysplastic syndromes (MDS) have MDS secondary to chemotherapy, radiation therapy or environmental exposure (*J Natl Cancer Inst* 2008;100:1542).
- Patients with secondary MDS (sMDS) have a poor prognosis and are often refractory to treatment (*J Clin Oncol* 2007;25:4285).
- A randomized, international, multicenter, open-label trial for patients with higher-risk MDS reported that azacitidine significantly improved overall survival compared to conventional care regimens (*Lancet Oncol* 2009;10:223).
- Patients with sMDS have been excluded from clinical trials and the effects of azacitidine in sMDS are unknown (*J Clin Oncol* 2002;20:2429).

Research
To Practice®

AVIDA Registry

- Data from patients with MDS treated with azacitidine in a community setting were collected at registry entry (baseline) and then quarterly using electronic data capture.
- Treating physicians determined azacitidine dose, dosing schedule and treatment duration.
- Baseline characteristics of patients with secondary MDS and primary MDS were evaluated.
- Rates of hematologic improvements and transfusion independence were assessed.

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

Baseline Characteristics

	Secondary MDS (n = 37)	Primary MDS (n = 380)
Time from Diagnosis (Median)	1 month	3 months
Median Age	71 years	75 years
Higher-Risk IPSS	55%	30%
Poor Cytogenetics	59%	17%
Chromosome 7 Abnormalities	47%	11%
2-3 Cytopenias	76%	62%
Infections Requiring IV Antibiotics	41%	16%

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

Response Assessment

IWG 2000 Response	Secondary MDS (n = 37*)	Primary MDS (n = 380*)
Hematologic Improvement (HI) or Better	21/35 (60%)	226/369 (61%)
Major HI-Erythroid[1]	14/32 (44%)	157/343 (46%)
Major HI-Platelet[1]	12/29 (41%)	94/206 (46%)
Major HI-Neutrophil[1]	8/28 (29%)	48/195 (25%)
Transfusion Independence		
RBC Transfusion Independence[2]	12/21 (57%)	121/197 (61%)
Platelet Transfusion Independence[2]	4/8 (50%)	32/50 (64%)

* Patients on study for <56 days were not evaluable for hematological improvement.

[1] Individual cell line denominators include only patients evaluable for improvement

[2] Denominators include only patients who were transfusion dependent at baseline (ie, received at least 1 transfusion in the 56 days prior to the start of AZA dosing)

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

Author Conclusions

- Patients with secondary MDS treated with azacitidine had rates of hematologic improvement or better and RBC/platelet transfusion independence comparable to those of patients with primary MDS despite worse pretreatment disease characteristics.
- Azacitidine treatment patterns were similar in secondary MDS and primary MDS (data not shown).
- Azacitidine was well tolerated by patients with secondary MDS and primary MDS (data not shown).
- A diagnosis of secondary MDS should not preclude treatment with the disease-modifying drug azacitidine.

Sekeres MA et al. *Proc ASH* 2010;Abstract 2931.

Prospective Trial of Pre-Transplant 5-Azacitidine on Hematopoietic Cell Transplantation Outcomes for Myelodysplastic Syndrome and CMML

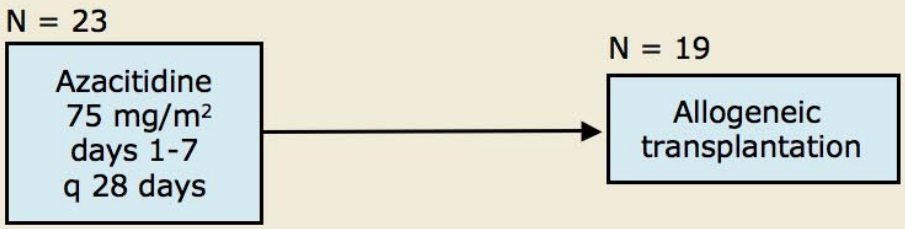
Field T et al.

Proc ASH 2010;Abstract 1333.

Research To Practice®

Prospective Study Schema*

Eligibility: MDS/CMML being evaluated for allogeneic transplantation



Four did not proceed to transplant:

1. Failure to obtain insurance approval due to patient age
2. Failure of the pre-transplant organ evaluation although a donor was identified
3. CNS hemorrhage in setting of chronic anticoagulation five days prior to transplant admission
4. One patient (62 years) declined transplant as only an HLA-A mismatched donor was available

* Prior retrospective analysis reported no adverse effects of pre-transplant 5-azacitidine on subsequent allogeneic hematopoietic cell transplantation outcomes (*Bone Marrow Transplant* 2010;45:255)

Field T et al. *Proc ASH* 2010;Abstract 1333.

Research To Practice®

Efficacy Outcomes (from Abstract)

Response to Azacitidine Prior to Transplant (n = 19)	
Partial Response	42%
Stable Disease	47%
Disease Progression	11%

Post-Transplant Outcome (n = 19)	
Relapsed or No Remission	3/19 (16%)
Nonrelapse Deaths	3/19 (16%)
One-Year Survival	69%
One-Year Disease-Free Survival	63%

Field T et al. *Proc ASH* 2010;Abstract 1333.

Author Conclusions

- Pre-transplant 5-azacitidine is well tolerated (data not shown).
- Pre-transplant 5-azacitidine provides control of disease as a bridge to allogeneic transplant and did not impose additional toxicity after allogeneic transplant.
  - Promising 1-year progression-free survival
- Controlled trials are needed to determine whether post-transplant relapse and survival are improved by pre-transplant 5-azacitidine.

Field T et al. *Proc ASH* 2010;Abstract 1333.

Research To Practice®

Investigator Commentary: Azacitidine for Secondary MDS and as a Bridge to Allogeneic Transplant

The presentation by Sekeres shows that therapy with azacitidine results in similar responses in therapy-related or secondary MDS when compared to primary MDS. This is quite interesting as the results are different from those with traditional chemotherapy, which does not work well in secondary MDS/AML. I believe that these results should affect practice. In the past, we were discouraged when a patient was diagnosed with therapy-related MDS. These data suggest that you should not be approaching these patients differently than those with primary MDS.

The prospective evaluation by Field regarding pretransplant azacitidine for MDS shows that the strategy of bridge therapy with azacitidine before definitive potentially curative therapy with allogeneic transplantation is feasible and safe. Another take-home message is the lack of effect on transplant-related toxicity. This strategy can buy time for patients while the national registries are being searched to find an appropriate donor for the transplant.

Interview with B Douglas Smith, MD, January 4, 2011