5 Minute JournalClub

Key ASH Presentations
Issue 8, 2011

Phase I Study of Extended Treatment Schedules of Oral Azacitidine for Patients with MDS, CMML or AML

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 OBJECTIVE

- Recall the dose-limiting toxicity and preliminary clinical response results with 14- and 21-day extended treatment schedules of daily oral azacitidine.

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 presentation, 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:

Guillermo Garcia-Manero, MD
Associate Professor of Medicine
Chief, Section of Myelodysplastic Syndromes
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

No real or apparent conflicts of interest to disclose.

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.

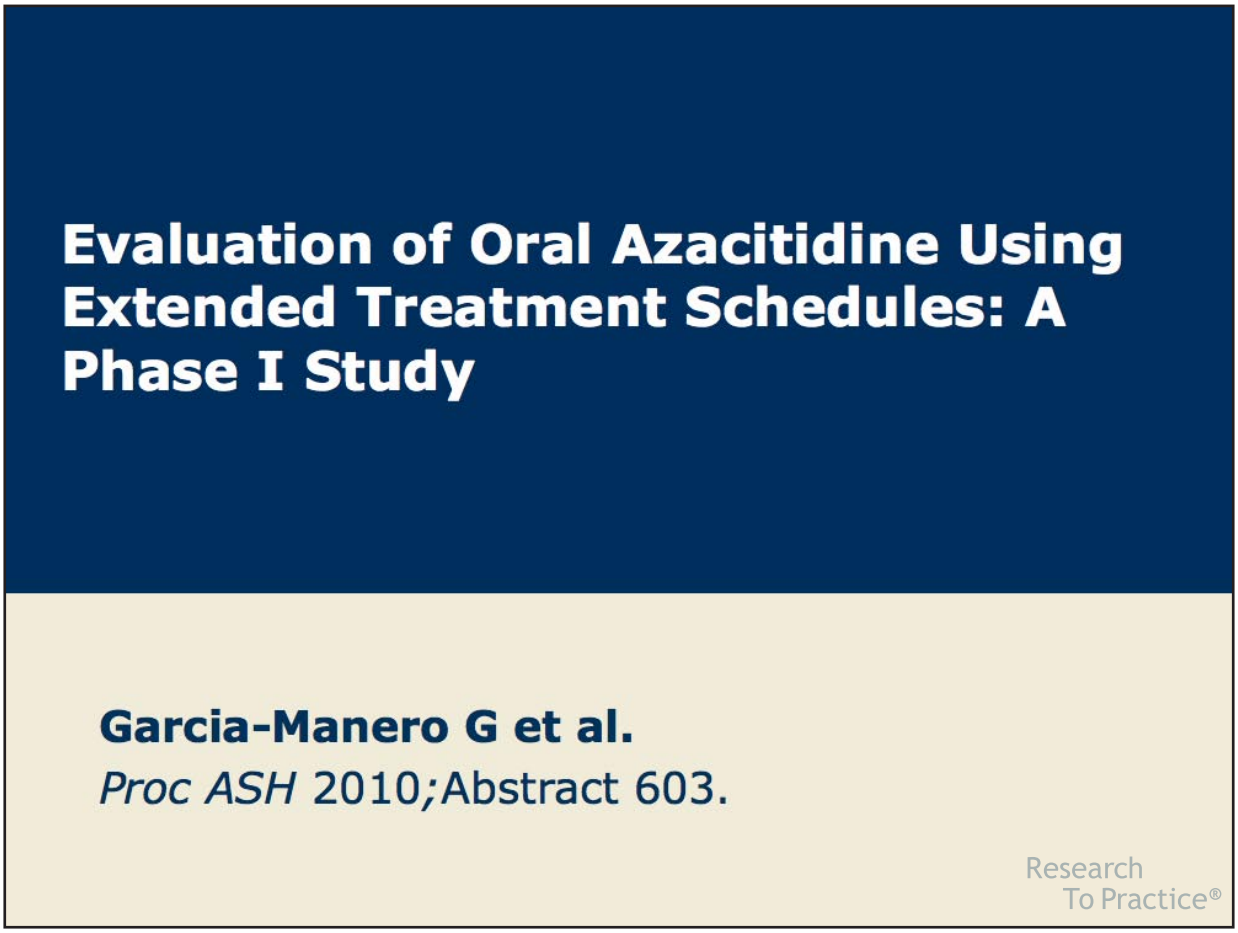
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Phase I Study of Extended Treatment Schedules of Oral Azacitidine for Patients with MDS, CMML or AML

Presentation discussed in this issue

Garcia-Manero G et al. **Evaluation of oral azacitidine using extended treatment schedules: A Phase I study.** *Proc ASH* 2010;**Abstract 603**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Guillermo Garcia-Manero, MD (1/12/11)



Background

- Parenteral azacitidine (AZA) has a short half-life in the plasma, and its incorporation into cellular DNA is restricted to the S-phase of the cell cycle.
- An oral formulation of AZA would allow for chronic daily exposure that may enhance the clinical activity of AZA in a form that is conveniently administered.
- An initial Phase I study of oral AZA administered on days 1-7 of a 28-day treatment schedule in patients with MDS and AML demonstrated that the agent was bioavailable, safe and clinically active (*Proc ASH* 2009;Abstract 117).
- **Current study objective**:
  - Assess the response and safety of extended 14- and 21-day oral AZA treatment schedules in patients with MDS, CMML or AML.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Research To Practice®

Phase I Study of Extended Treatment Schedules of Oral AZA

Eligibility

MDS, CMML or AML (not candidates for other therapies)

Prior azanucleoside therapy not allowed

Hemoglobin ≤9.0 g/dL AND/OR platelet count ≤50x10^9/L AND/OR RBC transfusion dependent

Sequentially dosed

14-day daily (QD)
Starting dose 300 mg
21-day daily (QD)
Starting dose 300 mg
14-day twice daily (BID)
Starting dose 200 mg
21-day twice daily (BID)
Starting dose 200 mg

28-day cycles

→ Treat to progression

Patients were enrolled in cohorts of 6 and evaluated for dose-limiting toxicities (DLTs) at the end of cycle 1.
Patients were monitored continuously for adverse events, and disease response was assessed at the end of every second cycle.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Research To Practice®

Baseline Characteristics

	N = 25
Median age, years (range)	68 (44-87)
Male/female	14/11
Number of patients with MDS	13
Number of patients with AML	7 (de novo) 3 (transformed)
Number of patients with CMML	2
Prior treatment	10

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

DLT Summary

- With 14-day QD oral AZA schedule, two DLTs occurred in 1 of 6 DLT-evaluable patients.
  - Grade 3 nausea and vomiting
- No DLTs observed in the 21-day QD (n = 6) or in the 14-day BID (n = 6) schedules.
- Three DLTs occurred in 1 of 6 evaluable patients in the 21-day BID schedule group.
  - Grade 3 weakness, fatigue and total body pain
- The maximum tolerated dose has not been reached on any of the schedules.
- No patient has received greater than 300 mg/dose.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Preliminary Response of Oral AZA in MDS/CMML

Parameter	MDS/CMML Responders/Evaluable Patients			
	14-day QD	21-day QD	14-day BID	21-day BID
Overall response (CR, marrow CR, any hematologic improvement [HI])*	4/6	3/3	3/3	0/3
HI-Erythroid	1/2	0	1/2	0/2
HI-Platelet	1/5	3/3	0/3	0/2
HI-Neutrophil	0/1	1/1	0/2	0/1
Transfusion independence	3/5	2/2	2/3	0

* IMWG 2006 criteria

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Research To Practice®

Relevant Grade 3/4 Adverse Events

Adverse Event, n (%)	14-day QD (n = 7)	21-day QD (n = 6)	14-day BID (n = 6)	21-day BID (n = 6)
Febrile neutropenia	2 (29)	4 (67)*	2 (33)	1 (17)
Diarrhea	0	1 (17)	0	1 (17)
Nausea	1 (14)	1 (17)	1 (17)	1 (17)
Vomiting	1 (14)	0	0	0
Fatigue	0	0	0	1 (17)

* Observed in three patients with baseline absolute neutrophil count < 0.5 x 10^9/L and/or AML diagnosis

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Research To Practice®

Author Conclusions

- Prolonged administration of oral AZA is feasible and generally well tolerated.
- Compared to standard subcutaneous administration, oral AZA 300 mg over 21 days provides a cumulative exposure of approximately 58% per cycle (data not shown).
- Oral AZA induces global hypomethylation (data not shown).
- Oral AZA is clinically active in patients with MDS/CMML (67% response rate, 10/15 patients).
- Studies of oral AZA for the treatment of lower-risk disease are planned.

Garcia-Manero G et al. *Proc ASH* 2010;Abstract 603.

Investigator Commentary: Extended treatment schedules with oral azacitidine

Patients often complain about having to visit the clinic seven days a month to receive their shots, and they eventually experience associated skin reactions. Last year, we showed oral azacitidine as being significantly active in patients with MDS, with a CR of almost 60 percent, even at very low PK, and having a good safety profile in patients with AML and MDS.

We hypothesized that if we could safely administer the agent for seven days, we could expand the schedule to two or three times per day for 14 or 21 days. We demonstrated quite a bit of activity with some of these schedules, which we found also to be safe, but most importantly, we found that the oral, low-dose approach was extremely effective in both lower- and higher-risk MDS.

I am excited about this approach because this could be a major breakthrough in the use of hypomethylating agents, whether in combination with chemotherapy, in maintenance therapy or as treatment for low, intermediate-1 MDS. We are now planning a Phase II analysis of oral azacitidine in low or intermediate-1, non del 5q MDS.

Interview with Guillermo Garcia-Manero, MD, January 12, 2011