5 Minute JournalClub

Key ASH Presentations
Issue 8, 2011

Lenalidomide and Intensive Chemotherapy for Patients with Higher-Risk MDS or AML with Del(5q)

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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

- Describe the activity and tolerability of the combination of lenalidomide and intensive chemotherapy in patients with higher-risk MDS or AML with del(5q).

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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

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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.

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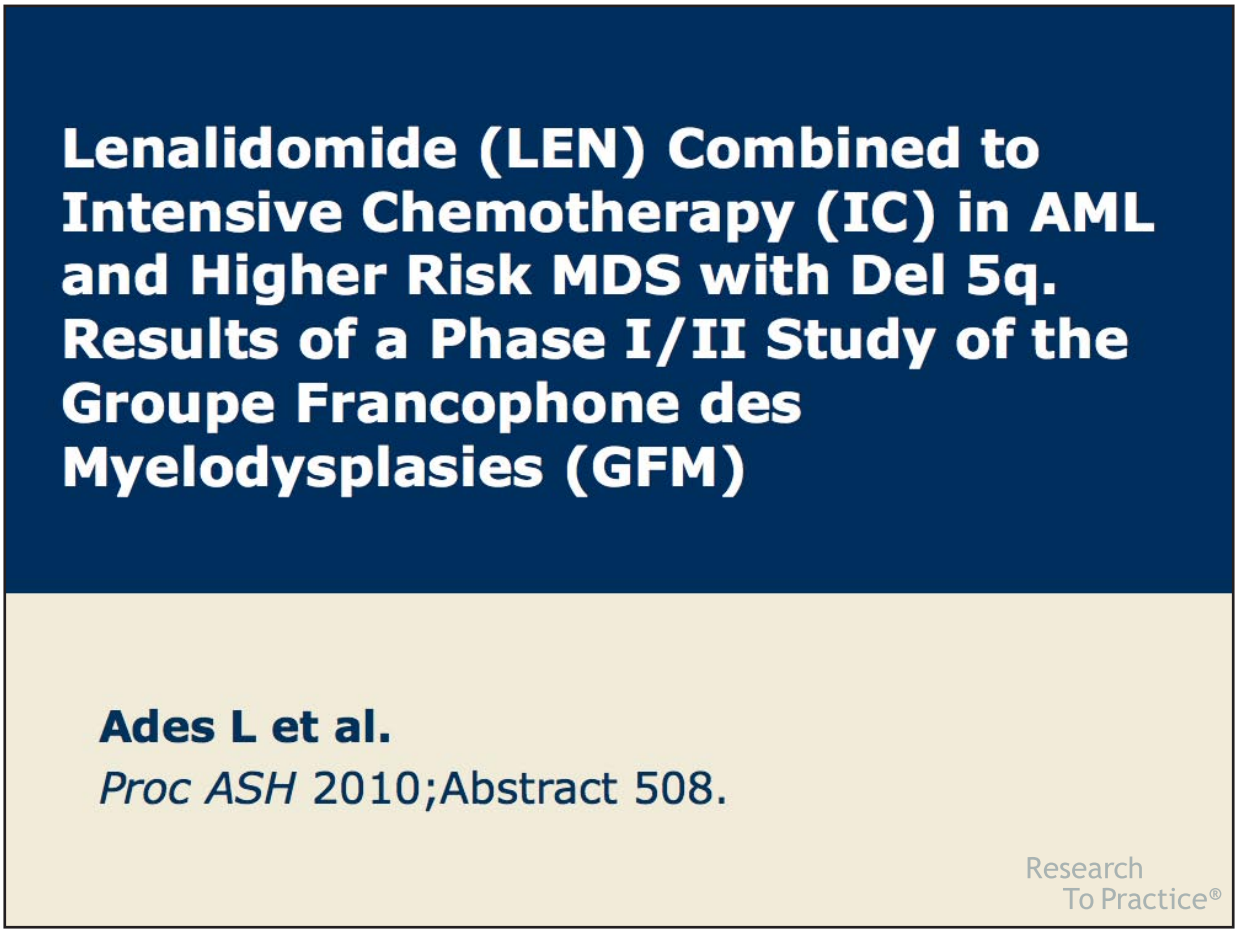
Lenalidomide and Intensive Chemotherapy for Patients with Higher-Risk MDS or AML with Del(5q)

Presentation discussed in this issue

Ades L et al. **Lenalidomide (LEN) combined to intensive chemotherapy (IC) in AML and higher risk MDS with del 5q. Results of a phase I/II study of the Groupe Francophone des Myelodysplasies (GFM).** *Proc ASH* 2010;**Abstract 508**.

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



Background

- Prognosis of myelodysplastic syndrome (MDS) with del(5q) with increased bone marrow blast % and/or additional cytogenetic abnormalities and of acute myeloid leukemia (AML) with del(5q) (isolated or complex) is poor.
- del(5q) is present in 40-50% of higher-risk MDS and AML with complex karyotype.
- These patients respond poorly to intensive chemotherapy with only 20-30% complete remission (CR) rates, of short duration (*Hematologica* 2000;85:246).
- Lenalidomide administration leads to frequent cytogenetic CR in lower-risk MDS with del(5q).
- In a recent Phase II study of lenalidomide in higher-risk MDS or AML with del(5q), 27% of patients achieved hematologic responses, some with cytogenetic responses but with significant myelosuppression (*Blood* 2009;113:3947).

Ades L et al. *Proc ASH* 2010;Abstract 508.

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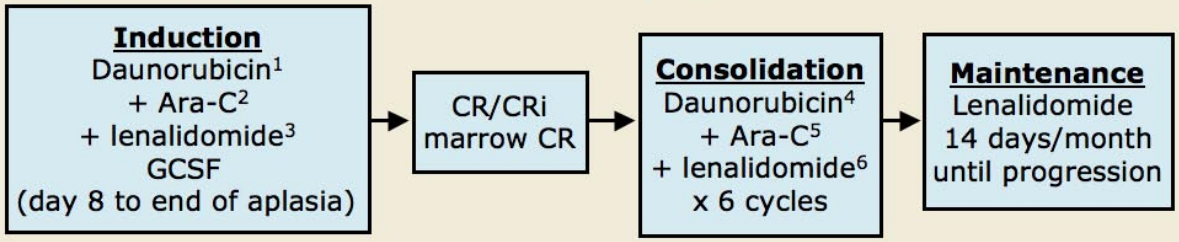
Phase II Study Schema

Eligibility: High-risk MDS or AML with del(5q)



[1] Daunorubicin 45 mg/m^2/day, days 1-3 (Cohort 1, n = 31) and 60 mg/m^2, days 1-3 (Cohort 2, n = 17). After dose in 1st cohort (n = 31) proved safe, escalation of dose in 2nd cohort (n = 17) was made during induction course.
[2] Ara-C 200 mg/m^2/day, days 1-7
[3] Lenalidomide 10 mg/day, days 1-21
[4] Daunorubicin 45 mg/m^2, day 1 (Cohort 1). Dose was escalated to 60 mg/m^2/day in 2nd cohort during consolidation once dose in 1st cohort proved safe.
[5] Ara-C 120 mg/m^2/day x 5 days
[6] Lenalidomide 10 mg/day, days 1-15

Ades L et al. *Proc ASH* 2010;Abstract 508.

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Efficacy Outcomes (from Abstract)

Response Assessment	
Complete Remission (Both Cohorts [n = 48]) Cohort 1 (n = 31) Cohort 2 (n = 17)	50% 55% 47%
Overall Response Rate	60%
1-Year Disease-Free Survival	26.5%

	Isolated del(5q) (n = 5)	del(5q) + one additional abnormality (n = 5)	del(5q) with complex karyotype (n = 38)
CR	80%	80%	45%

Ades L et al. *Proc ASH* 2010;Abstract 508.

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Select Safety Events (from Abstract)

	Incidence (N = 48)
Early Death	10.4%
Median Duration of Hospitalization in Induction	30.5 days
Median Number of RBC Transfusions (During Induction)	9
Median Number of Platelet Transfusions (During Induction)	7

Ades L et al. *Proc ASH* 2010;Abstract 508.

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Author Conclusions

- Intensive chemotherapy and lenalidomide can be combined in higher-risk MDS and AML with del(5q) without unexpected additive myelosuppression.
- In this cohort of patients with very poor cytogenetics, the CR rate was 50% and was higher than generally reported with chemotherapy alone in similar patients.
- Disease-free survival remained short, suggesting that induction or consolidation therapy should be improved.
- Based on the better efficacy of daunorubicin 90 mg/m^2/day (*N Engl J Med* 2009;361:1235 and 1249) in AML and the adequate tolerance of daunorubicin in the 60 mg/m^2 cohort, the dose of daunorubicin will be increased to 90 mg/m^2/day in the next patient cohort.

Ades L et al. *Proc ASH* 2010;Abstract 508.

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Investigator Commentary: Combination of lenalidomide and chemotherapy for patients with higher-risk MDS or AML with del(5q)

Typically lenalidomide is used for low-risk MDS with del(5q) and is effective in that setting. This is a feasibility study in which the authors have combined lenalidomide and intensive chemotherapy for patients with higher-risk MDS or AML with del(5q). The response rates with the combination are reported to be 50 percent, which is higher than what is expected with chemotherapy alone. However, there was no control arm in this study, so such an inference is not conclusive.

Additionally, the disease-free survival was short, so there need to be alternative strategies to build on this approach. One of the strategies the authors are suggesting is to increase the dose of daunorubicin. Overall, I believe this may be a bit of a stretch for such combinations, and my thoughts are that this combination is an interesting avenue but may not be applicable for many patients.

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

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