



Key ASH Presentations

Issue 8, 2011

Novel Strategies Incorporating Arsenic Trioxide into the Initial Treatment of Acute Promyelocytic Leukemia (APL)

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

- Appraise the early safety and efficacy of arsenic trioxide and chemotherapy as consolidation in APL.
- Evaluate ATRA with arsenic trioxide as an option for induction in standard-risk APL.

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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 patients (WBC > 10 × 10⁹/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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Novel Strategies Incorporating Arsenic Trioxide into the Initial Treatment of Acute Promyelocytic Leukemia (APL)

Presentations discussed in this issue

Ades L et al. **Arsenic trioxide (ATO) in the consolidation treatment of newly diagnosed APL – First interim analysis of a randomized trial (APL 2006) by the French Belgian Swiss APL Group.** *Proc ASH 2010*; **Abstract 505.**

Ravandi F et al. **Phase II study of all-trans retinoic acid (ATRA), arsenic trioxide (ATO), with or without gemtuzumab ozogamicin (GO) for the frontline therapy of patients with acute promyelocytic leukemia (APL).** *Proc ASH 2010*; **Abstract 1080.**

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

Arsenic Trioxide (ATO) in the Consolidation Treatment of Newly Diagnosed APL – First Interim Analysis of a Randomized Trial (APL 2006) by the French Belgian Swiss APL Group¹

Phase II Study of All-Trans Retinoic Acid (ATRA), Arsenic Trioxide (ATO), with or without Gemtuzumab Ozogamicin (GO) for the Frontline Therapy of Patients with Acute Promyelocytic Leukemia (APL)²

¹Ades L et al.

Proc ASH 2010; Abstract 505.

²Ravandi F et al.

Proc ASH 2010; Abstract 1080.

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Arsenic Trioxide (ATO) in the Consolidation Treatment of Newly Diagnosed APL — First Interim Analysis of a Randomized Trial (APL 2006) by the French Belgian Swiss APL Group

Ades L et al.

Proc ASH 2010;Abstract 505.

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Background

- ATRA in combination with anthracycline-based chemotherapy is the reference treatment for newly diagnosed acute promyelocytic leukemia (APL).
 - This treatment is myelosuppressive and may be associated with long-term cardiac toxicity.
- Use of arsenic trioxide (ATO) may allow for:
 - Reduction of the amount of chemotherapy (and in particular avoid use of Ara-C).
 - Further reduction in relapse risk, especially when used in consolidation treatment (*Proc ASCO 2007;Abstract 2*).

Ades L et al. *Proc ASH 2010;Abstract 505.*

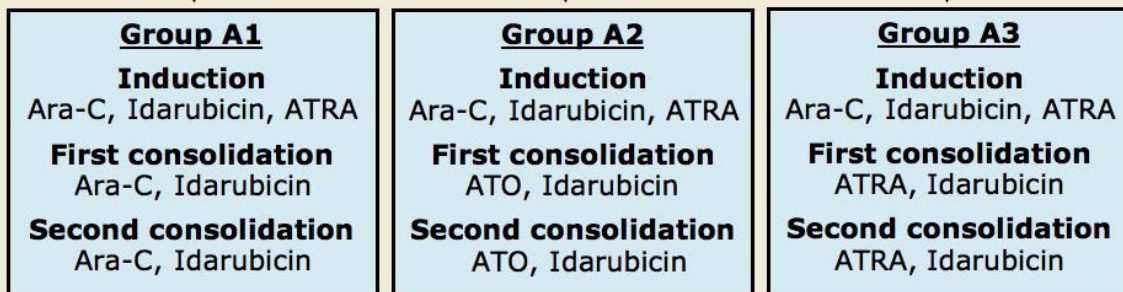
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APL 2006 Study Schema

Eligibility: Group A (standard-risk APL)

Newly diagnosed APL; ≤ 70 years
WBC < 10 G/L

R



All patients received maintenance with ATRA, 6-MP and methotrexate.

Ades L et al. *Proc ASH* 2010;Abstract 505.

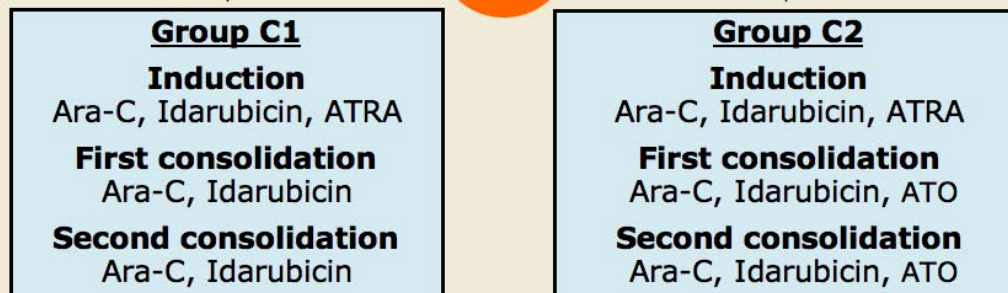
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APL 2006 Study Schema

Eligibility: Group C (high-risk APL)

Newly diagnosed APL; ≤ 70 years
WBC ≥ 10 G/L

R



Treatment in C1 is same as in A1. There is no Group B.

All patients received maintenance with ATRA, 6-MP and methotrexate.
Patients in Group C1 and C2 also received intrathecal chemotherapy.

Ades L et al. *Proc ASH* 2010;Abstract 505.

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Efficacy and Safety Outcomes (from Abstract)

| | Group A1 (n = 45) | Group A2 (n = 45) | Group A3 (n = 51) | Group C1 (n = 24) | Group C2 (n = 21) |
|---|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Complete response | 99.3% | | | 100% | |
| Cumulative incidence of relapse at 18 months | 0% | 0% | 2% | 2% | 2% |
| Median duration of thrombocytopenia (after consolidation cycles) (days) | 44 | 35 | 25 | 43.5 | 48 |
| Median duration of neutropenia (after consolidation cycles) (days) | 43.5 | 40 | 20 | 45.5 | 51.5 |
| Median duration of hospitalization (days) | 51 | 59 | 26 | 53.5 | 65 |

Ades L et al. *Proc ASH* 2010;Abstract 505.

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Author Conclusions

- Results of this first interim analysis show that very high CR rates (>95%) can be observed in multicenter trials in APL by combining ATRA and anthracycline-based chemotherapy, while the relapse rate with consolidation and maintenance was very low in all treatments arms, including in patients with WBC > 10 G/L.
- ATO, when combined with chemotherapy during consolidation cycles, increases myelosuppression.
- An amendment further reducing chemotherapy in patients receiving ATO as part of consolidation is thus being implemented in the trial.

Ades L et al. *Proc ASH* 2010;Abstract 505.

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Phase II Study of All-Trans Retinoic Acid (ATRA), Arsenic Trioxide (ATO), with or without Gemtuzumab Ozogamicin (GO) for the Frontline Therapy of Patients with Acute Promyelocytic Leukemia (APL)

Ravandi F et al.

Proc ASH 2010;Abstract 1080.

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Study Schema

Eligibility: Newly diagnosed APL

Cohort 1 (n = 47)

- ATRA 45 mg/m² PO daily
- ATO 0.15 mg/kg/daily beginning on day 10 of ATRA induction
- High-risk patients (WBC > 10 x 10⁹/L) received gemtuzumab 9 mg/m² on the first day of induction.

Cohort 2 (n = 57)

- ATRA 45 mg/m² PO daily
- ATO 0.15 mg/kg/daily beginning on day 1 of ATRA induction
- High-risk patients also received gemtuzumab 9 mg/m² on day 1.
- Gemtuzumab also administered (all patients) if at any time during induction the WBC rose to >30 x 10⁹/L (and more recently if >10 x 10⁹/L).

Ravandi F et al. *Proc ASH 2010;Abstract 1080.*

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Efficacy Outcomes

| | Both cohorts combined (n = 104) |
|-------------------------------------|------------------------------------|
| Complete remission (CR) | 98% |
| Five-year overall survival (OS) | 88% |
| Five-year event-free survival (EFS) | 86% |

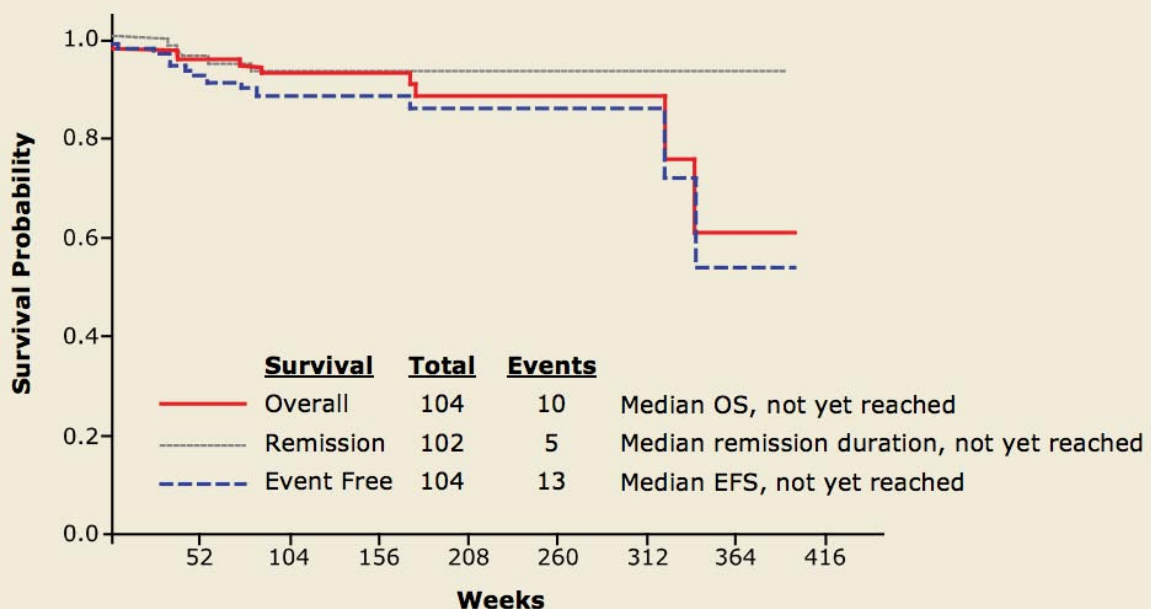
Median follow-up of 115 weeks

Only 5 patients achieving a CR (5%) experienced disease relapse.

Ravandi F et al. *Proc ASH 2010*;Abstract 1080.

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Overall Outcomes



With permission from Ravandi F et al. *Proc ASH 2010*;Abstract 1080.

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Author Conclusions

- The combination of ATRA and arsenic trioxide (with or without gemtuzumab) as initial therapy for APL is highly effective and safe.
 - Overall, 98% of patients achieved CR with only 2 induction deaths
 - Only 5 patients achieving CR (5%) have experienced disease relapse
 - Estimated 5-year survival 88%, EFS 86%
- This combination can potentially substitute for chemotherapy-containing regimens for patients at both high and low risk.

Ravandi F et al. *Proc ASH 2010*;Abstract 1080.

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Investigator comment on arsenic trioxide as part of initial therapy for APL

The study by ADES is trying to figure out the best combination therapy for consolidation in APL, especially the best way of incorporating arsenic trioxide in consolidation, in combination with chemotherapy. Currently, we don't have the follow-up data from this study to know any effects on longer-term outcomes. An observation has been the duration of hospitalization and myelosuppression, which appear to increase when arsenic trioxide is combined with chemotherapy in consolidation cycles.

In the study presented by Ravandi, the issue is that gemtuzumab has been pulled off the market, so any combination with gemtuzumab is not doable anymore. Gemtuzumab was a pretty good drug, and we would have liked it to be available for APL. The presented data on combination ATRA and arsenic trioxide add to the literature that this is a highly effective and safe combination in the initial treatment of APL.

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

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