4.32: Oral Azacitidine for AML and Nelarabine for T-ALL with Dr. Bernard Marini

Season	4
Type	Plenary Session

We Discuss:

Plenary Session 4.32 Show Notes

Overview

Conversation with Dr. Bernard Marini

- **Introduction [0:45]**
  - Dr. Bernard Marini is a Pharmacist and Clinical Associate Professor at the University of Michigan Medical Center
    - He specializes in hematologic malignancies (e.g., Acute Leukemias, Aggressive Lymphomas, etc.)
- **Service [4:00]**

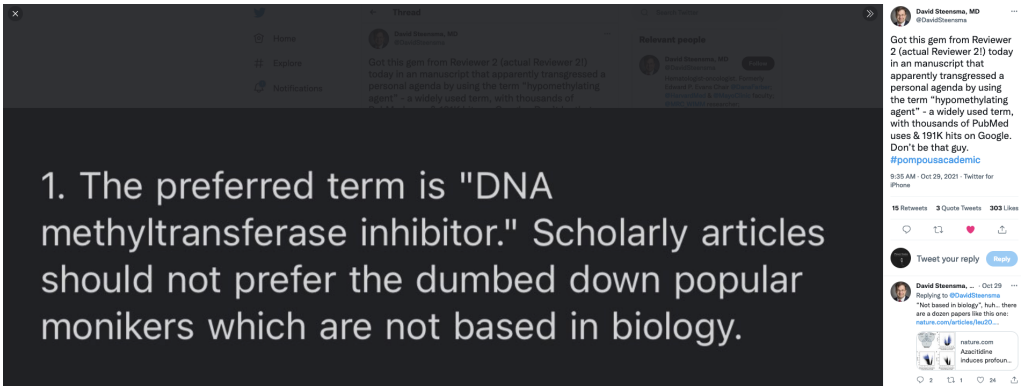
> "I feel like when you come on service – maybe a chunk of the year – you only see the same thing a couple different times" - Bernard Marini

    - Obviously people have clinic experiences where they see patients of a typical presentation
        - But when rotating between the different services, clinical pharmacists start to see differences in practice
            - It's what allows clinical pharmacists to do many research investigations, which although not always sponsored, add to the literature

- **AML [5:00]**
    - Oral azacitadine

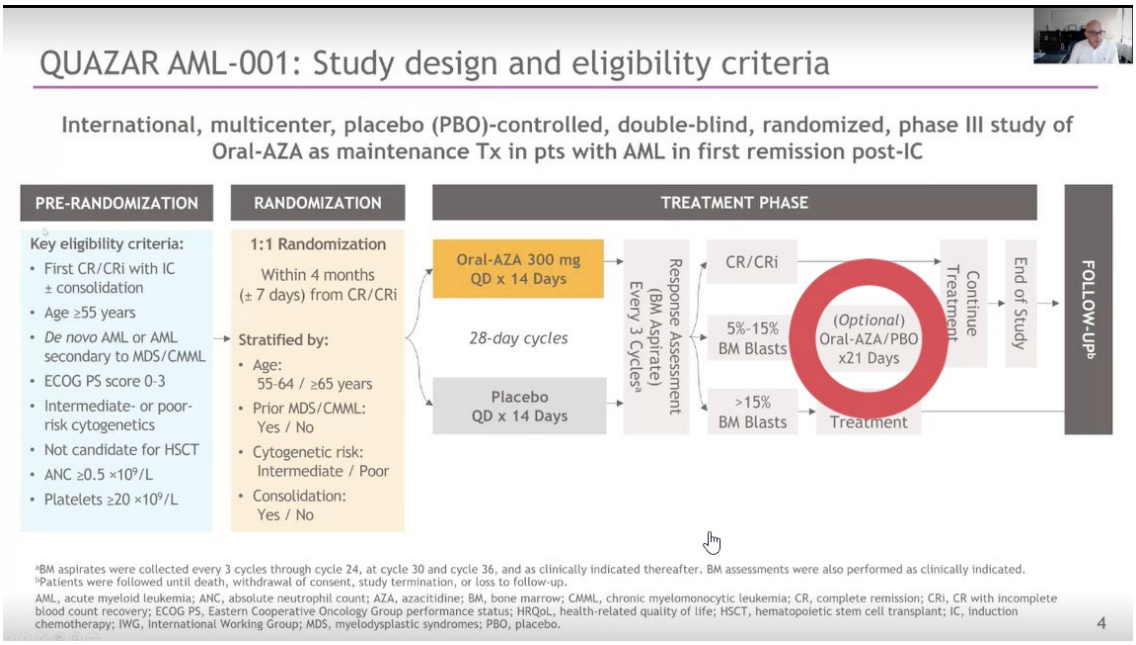
> 📘 *"Exerts antineoplastic effect by inhibiting DNA methyltransferase, thereby causing hypomethylation of DNA, and by direct cytotoxic effect on abnormal hematopoietic cells in the bone marrow." - Amboss*

        - TLDR; it messes with the epigenetics of the cell
            - Funny tweet



Source

- Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission
  - Wei et al., NEJM, 2020
    - One major issue exists in the randomized study of oral AZA
      - And the main issue is, what happens when you have progression?
- Trial design



Source

- Issues:
  1. Consolidation therapy
     a. The issue is that they did not use consolidation treatment as standard of care in this trial
        i. Consolidation improves these outcomes in AML patients
           1. We have data from the late 1980s that showed that if you gave individuals induction and then nothing, or if you gave them induction and then maintenance with old school chemotherapy, or one cycle of consolidation, you significantly enhanced survival

> "And the analogy to POLO, of course, is this is like taking somebody who's responding to platinum and stopping treatment. This is taking somebody who should be getting consolidation and stopping treatment" - Vinay Prasad

2. These patients were supposed to be ineligible for transplant
    a. The majority of these patients were at intermediate risk*
        i. So, theoretically, these individuals should have received transplants but, for unknown reasons, did not.

> *NOTE: *Intermediate risk is a more subtle topic. However, if you have a healthy patient under the age of 65 with no comorbidities who is on the upper end of the intermediate risk scale and has a decent donor, you take them to transplant.*

3. Double dosing
    a. Every three cycles, the researchers did another bone marrow biopsy to see where the disease was
        i. If they saw 5 to 15% blasts, which is AML relapse, they just increased the dose of whatever they were on (either oral AZA or placebo) from 14 days to 21 days
            1. Giving relapsed AML patients placebo → big issue
4. Other issues
    a. Of the people who got subsequent therapy, about 30 to 40%, were intensive chemotherapy strategies in the placebo arm, and about 47% were low intensity therapy
        i. Oral Azacitidine Maintenance for Acute Myeloid Leukemia
            1. Letter to the editor; NEJM; Marini et al.

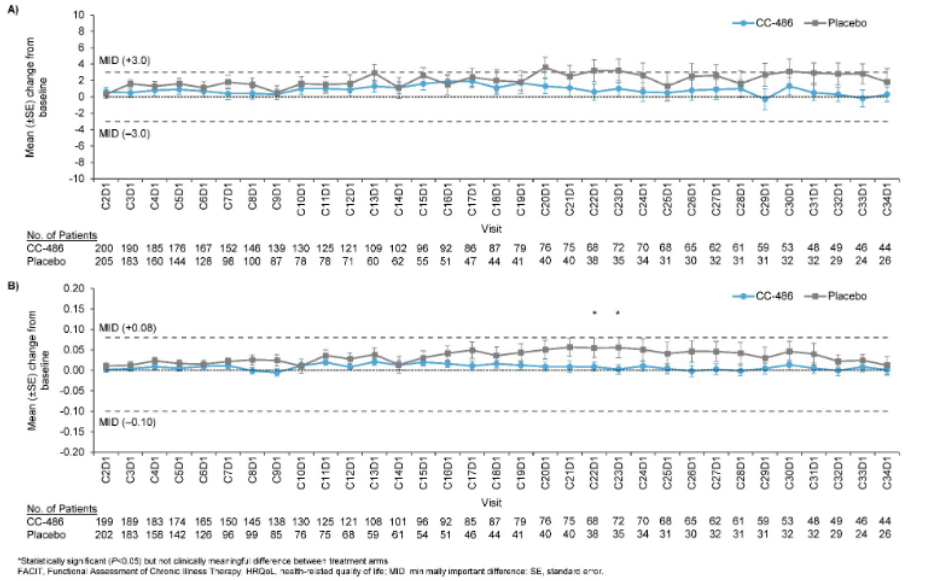
a. Cytarabine at low doses is obviously inferior to alternatives, which has been shown in randomized trials

b. In reference to hydroxyurea → no one even knows

5. Quality of life

a. If you look at the toxicity profile, you'll see that the oral AZA arm has considerably greater toxicity than the placebo arm

Figure S3. Mean changes from baseline in (A) FACIT-Fatigue and (B) EQ-5D-3L health utility scores across treatment (HRQoL-evaluable population). Data are reported up to cycle 34, the last cycle with ≥25 patients in both treatment groups. Statistical testing consisted of 2-sample, 2-sided t-tests comparing CC-486 *vs.* placebo.



*Statistically significant (*P*<0.05) but not clinically meaningful difference between treatment arms
FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; MID, minimally important difference; SE, standard error.

Source

- An example of the difficulty of interpretation

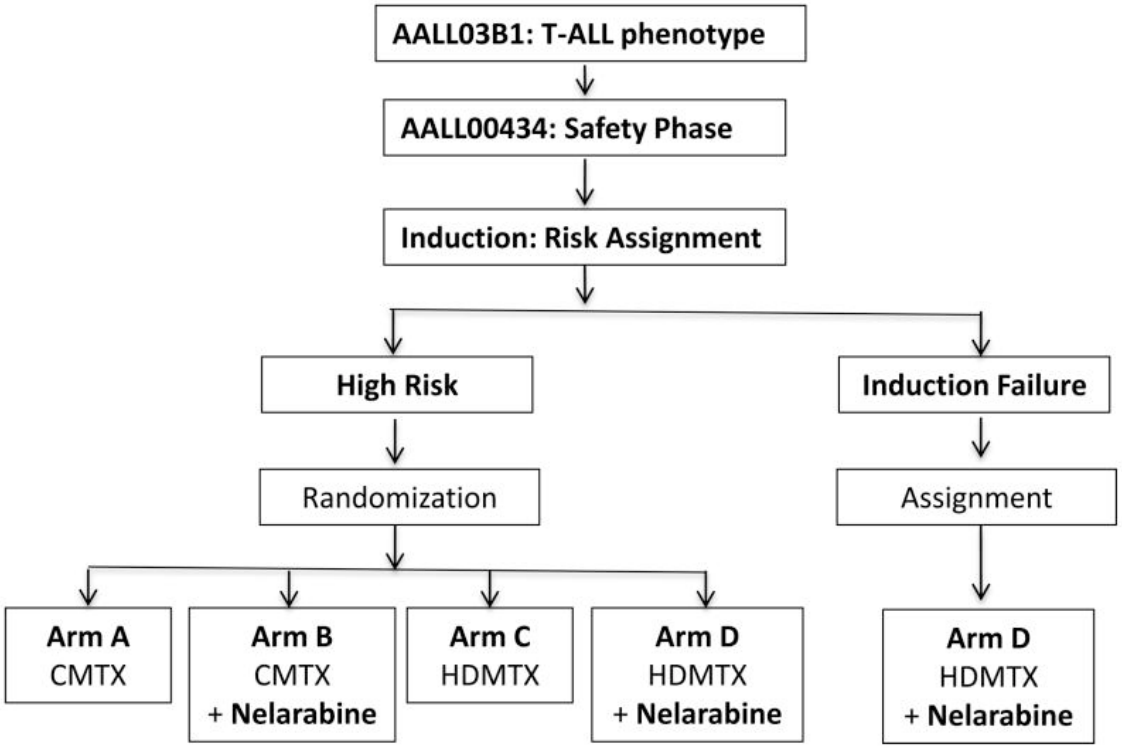
> *"Mixed-effects models with repeated measures, which controlled for baseline health-related quality-of-life scores and other preselected covariates, showed no clinically meaningful differences in least-squares mean changes from baseline between the treatment groups at any visit, a finding that supported the noninferiority of CC-486 relative to placebo for health-related quality of life." Wei et al.*

- **Nelarabine [37:00]**
  - COG AALL0434: A randomized trial testing nelarabine in newly diagnosed t-cell malignancy
    - Dunsmore et al., JCO
  - Mechanism of action

    > *- Prodrug of the deoxyguanosine analog ara-G, which is subsequently converted to the active 5'-triphosphate, ara-GTP*

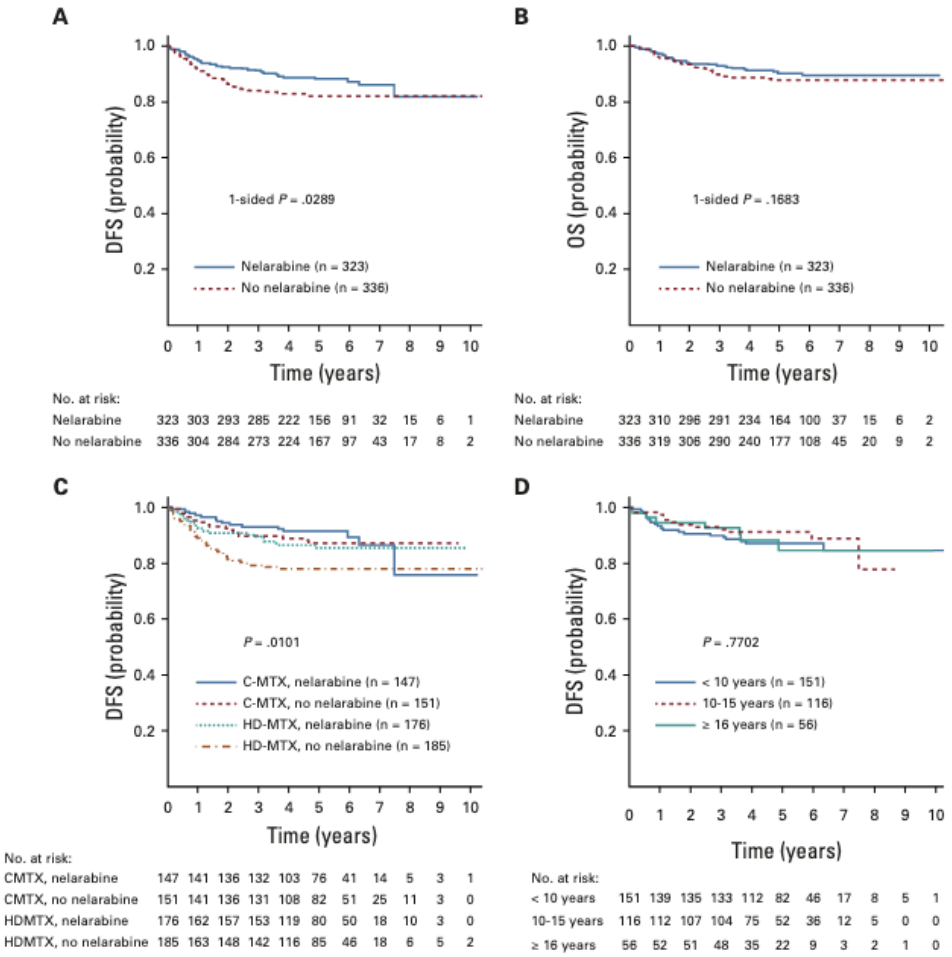
    > *- Ara-GTP accumulates in leukemic blasts and incorporates into DNA, inducing fragmentation and apoptosis.*

  - Trial design



Source

- Issues
  1. Subverted randomization
     a. They took all patients that had CNS disease, and they put them on the high dose methotrexate arm (i.e., pseudorandomization)
  2. One arm gets more pegaspargase than the other arm
  3. Primary endpoint
     a. Their primary endpoint here was disease free survival
        i. There was a statistically significant difference in DFS but not OS



Source

4. Grade 3/4 neurotoxicity

> "You're adding a drug that might move the needle a teeny tiny bit for DFS, but not when you compare it to just compete the methotrexate only against that one arm that performed poorly, and there's no survival benefit. And you're putting them at risk for having toxicity – and that's what I have a problem with." - Bernie Marini

5. Lowering the standard

        a. We're just lowering the bar because we wanted the results to be positive
            i. What we need to do is take the people you think will benefit the most and run a new randomized control trial

- **Other people mentioned:**
    - David Steensma, MD
- **Other literature mentioned:**
    - The Things They Carried
        - Book by Tim O'Brien
    - ECHELON1
    - POLARIX Phase 3 Trial

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