Toxicity in Pediatric Patients Treated with ATRA and Arsenic Trioxide Induction: A Report from the Children's Oncology Group Study AAML1331

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COG AAML1331 Study Design

- Phase III, non-randomized cooperative group trial
  - Historical control: AIDA0493 pediatric patients; (AAML0631- amendment in process)
- Eligibility
  - Age 1 to < 22 years
  - De novo APL confirmed by PML-RARA PCR
  - No prior therapy
  - Exclusions for prolonged QTc and renal dysfunction
- Risk Group based on diagnostic WBC count
  - Standard risk (SR) for WBC < 10,000
  - High risk (HR) for WBC $\geq$ 10,000.

AAML1331 Treatment

Induction:

Standard Risk Patients (WBC <10,000 at diagnosis)

Day: 1……28

ATRA (further daily doses if not CR on Day 28 bone marrow)

ATO (further daily doses if not CR on Day 28 bone marrow)

(Hydroxyurea and dexamethasone will be used to control leukocytosis if WBC rises to >10,000 during induction)

High Risk Patients (WBC ≥10,000 at diagnosis)

Day: 1……14……28

ATRA (further daily doses if not CR on Day 28 bone marrow)

ATO (further daily doses if not CR on Day 28 bone marrow)

Dex

Ida XXXX

(Ida= Idarubicin given on Days 1, 3, 5, 7)

Consolidation:

Standard Risk and High Risk Patients

Week 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28

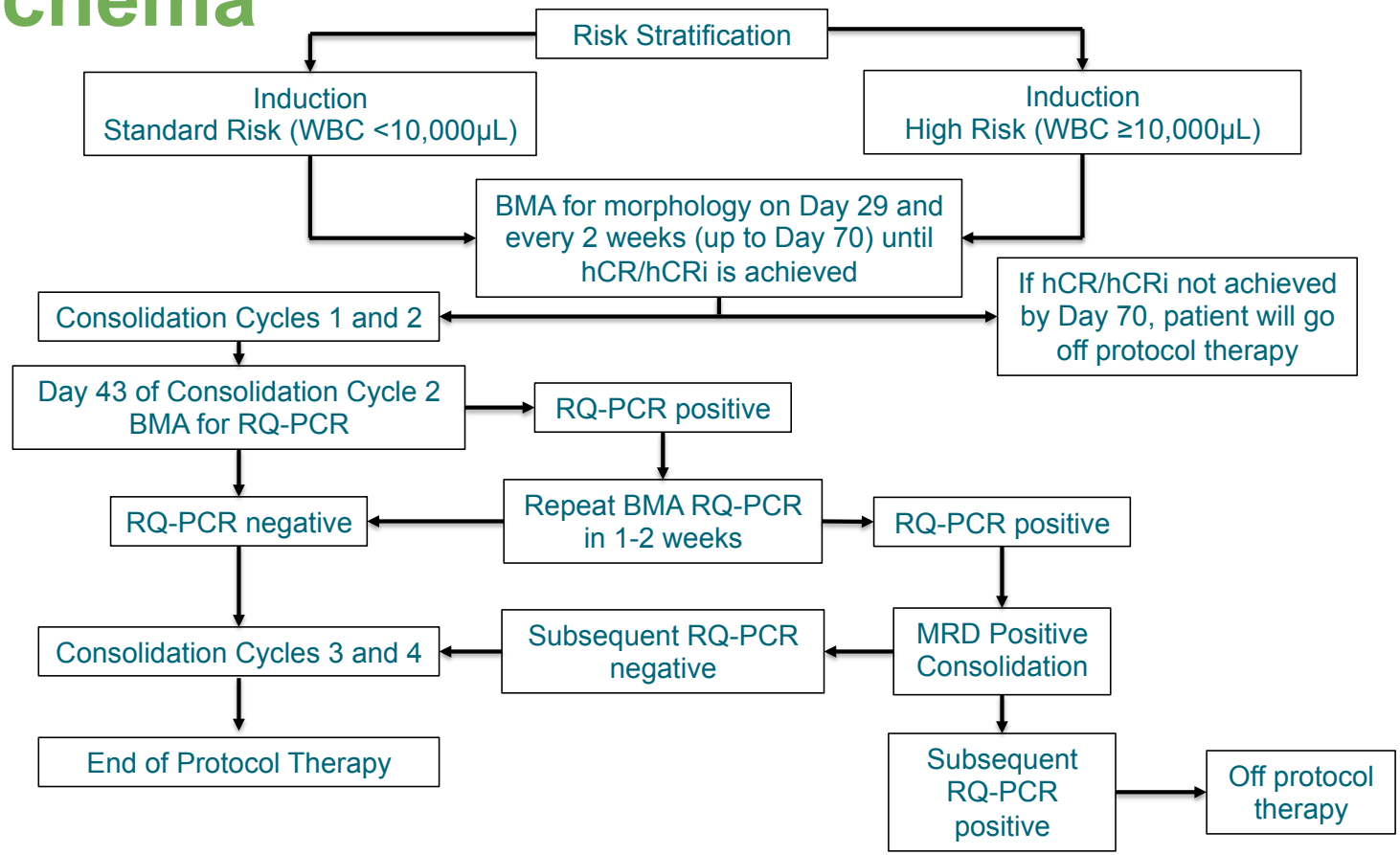
ATRA

ATO

RQ-PCR testing: ↑ ↑* ↑

(*Only if Week 14 RQ-PCR positive, repeat testing in 1-2 weeks)

Study Schema



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Coagulopathy Management

Educational email sent upon enrollment!

- **During at least the first 7 days of therapy (or longer if needed until coagulopathy resolves),** aggressive blood product support should be employed as follows:
  - Maintain platelet count above 50,000/μL. For patients with CNS hemorrhage maintain the platelet count above 100,000/μL until bleeding stable, coagulopathy improved and a minimum of 7 days from diagnosis of the bleed.
- Obtain stat CT scan of the head for any patient with neurologic symptoms consistent with possible intracranial bleed. If CNS bleed present, consider neurosurgery consultation for help in management.
- Transfuse cryoprecipitate to maintain fibrinogen above 150 mg/dL
- Transfuse fresh frozen plasma to maintain PT within normal range and PTT within normal range.
- Routine use of heparin or anti-fibrinolytics is not recommended.

Leukocytosis and DS Management

- High risk patients receive dexamethasone as prophylaxis against DS, and Idarubicin results in leukoreduction
- Patients with standard risk APL may have increasing WBC due to the differentiating effects of ATO and ATRA
- SR APL Patients who develop WBC >10,000
  - Start on dexamethasone at prophylaxis dosing (2.5mg/m2/dose BID Days 1-14) to prevent DS
  - Start on hydroxyurea for leukoreduction
- Patients with differentiation syndrome (DS)
  - Hold ATRA/ATO
  - Dexamethasone at treatment dosing (5.8mg/m2/dose, max 10mg, IV BID) for minimum of 3 days or until resolution of DS

Leukocytosis

- First 18 months following study activation, 4 SR APL patients developed leukocytosis WBC >50,000
  - Highest was WBC 95,700
- Hydroxyurea for Leukocytosis:
  - APL0406
    - 500mg QID for WBC 10,000-50,000
    - 1000mg QID for WBC >50,000
  - AAML1331
    - 15 mg/kg/dose (max 500mg) QID for WBC 10,000-50,000
    - 30 mg/kg/dose (max 1000mg) QID for WBC >50,000

Leukocytosis

- January 2016 activated amendment including change to hydroxyurea dosing
  - 30 mg/kg/dose (max 1000mg) QID for WBC >10,000
- Only one SR APL patient with WBC >50,000 post amendment with new hydroxyurea dosing

Interim Analysis of Induction Toxicity

- Trial opened to accrual 6/29/2015
- Interim Analysis frozen on 3/31/2017
- 63 Evaluable patients
  - 47 SR APL
  - 16 HR APL

Leukocytosis

- Among 43 SR APL patients
  - 14% (N=6) developed WBC >10,000 during induction therapy
- Differentiation syndrome developed in:
  - 33% (2/6) of SR APL patients with leukocytosis
  - 22% (8/37) of SR APL patients without leukocytosis

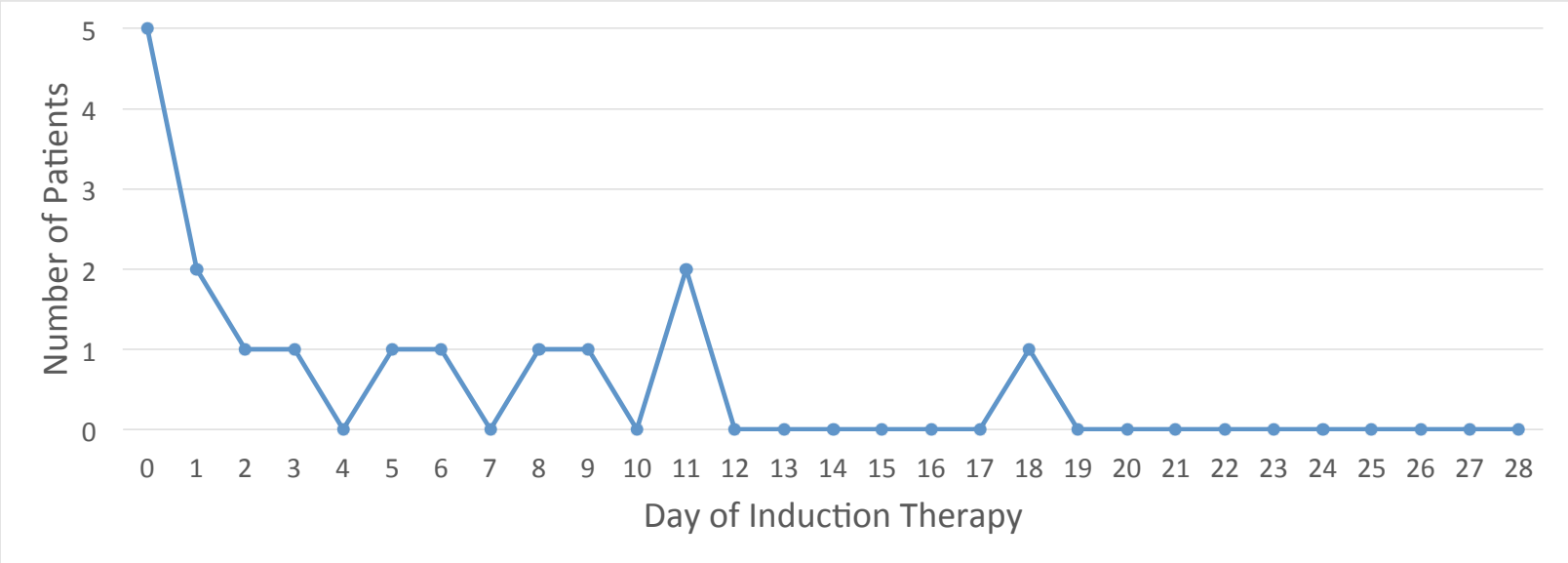
(4 SR APL patients missing data on leukocytosis)

Differentiation Syndrome

- Overall rate of 25% (16/63) and similar SR and HR (P=1.0)
- Monitored 12 signs/symptoms of DS
  - Present in >50% of patients:
    - Respiratory distress (N=10)
    - Fever (N=10)
    - Weight Gain (N=9)
  - Life threatening events more rare:
    - Pleural effusion (N=4)
    - Pericardial effusion (N=2)
    - Acute renal failure (N=2)
    - No cases of heart failure

Incidence of Differentiation Syndrome by Day of Induction

- Occurred at median of 2.5 days (range 0-18)



Protocol recommends inpatient hospitalization for first 2 weeks of induction

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Dose Modification

- DS was most common reason for holding ATO/ATRA
- Pseudotumor cerebri (N=4)
- AST/ALT elevation (N=6)
- C diff colitis (N=1)
- Acute kidney injury (N=1)
- Majority of patients had doses held ≤3 days

Early Death

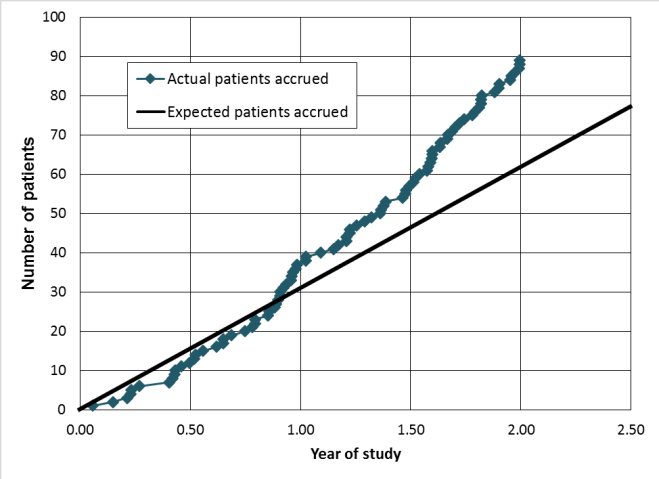
- 1 patient death during induction
  - SR APL patient developed leukocytosis >50,000, acute renal failure requiring dialysis, and coagulopathy
  - At day 22 of induction, when WBC <10,000 and coagulopathy resolved, developed enterococcal sepsis with severe hypotension and respiratory failure. Hypoxic brain injury and died a week later.

Conclusions

- ATO/ATRA for SR APL and ATO/ATRA/Ida induction is well tolerated in pediatric APL patients but disease complications of differentiation syndrome and leukocytosis require careful management
  - DS risk is highest during first 2 weeks of induction, consider hospitalization throughout this period
  - Higher dose Hydroxyurea helps prevent more severe leukocytosis
- Aggressive management of coagulopathy can help prevent fatal bleeding or clotting events

Current Sites and Enrollments

- Local IRB approved Sites: 151
- Goal Accrual: 150 patients
- Current Enrollments: 100
  - Accrual 3.7/month (expected was 2.6/month)



Anticipate completion of accrual in Fall 2018.

Hope we can present the 3 year survival outcomes at the 8th International Symposium on APL

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Study Committee

- Chair: Matthew Kutny
- Vice Chair: John Gregory
- Andy Kolb (AML Chair)
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- Soheil Meshinchi (Biology)
- Jeannette Cassar (Prot Coordinator)
- Wendy Lee (Res Coordinator)
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- Samir Kahwash (Pathology)
- Atif Khan (Radiology)
- Kristina Hardy (Behavioral)
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- Betsy Hirsch (Cytogenetics)
- Susana Raimondi (Cytogenetics)
- James Feusner (H/O)
- Madhvi Rajpurkar (H/O)
- Lillian Sung (H/O)
- Cecilia Fu (H/O)
- Della Howell (H/O)
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- Weili Sun (H/O)
- Kristen ODwyer (SWOG)