Dasatinib in High Risk ALL

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- 16 yo boy, WBC 120 at presentation
- Confirmed precursor B cell ALL by flow
- CNS negative
- Enrolled on AALL1131 (HR ALL)

- Day 8 MRD 3%
- End of induction BMA showed induction failure with 66% blasts
Pediatric ALL genetics

**Case**

**Background**

**Indications**
- Ph+ ALL
- Ph-like ALL

**Side Effects**

**Conclusion**
BCR-ABL

Almost all CML

3% of ALL in kids
Targeting BCR-ABL

- **Indications**
  - Ph+ ALL
  - Ph-like ALL

- **Side Effects**
  - Imatinib competitively binds to site and inhibits protein

- **Conclusion**
  - Substrate activated by phosphorylation
  - Tumor cell cannot proliferate
Targeting Ph+ ALL in Peds

- AALL0031: addition of imatinib to intensive chemo
  - No increased toxicity
  - 5 year EFS for kids treated with chemo and imatinib was 70 +/- 12%
The Newer Generation....

First generation TKI $\rightarrow$ Imatinib
- Poor CNS penetration
- Resistance noted in CML patients

Second generation TKI $\rightarrow$ Dasatinib
- Improved CNS penetration
- 300x more potent inhibitor of BCR-ABL, also inhibits other TKs
- Earlier/more efficient reduction of leukemia cells
What is the role for Dasatinib in Pediatric Ph+ ALL?
# COG AALL0622 - Phase II/III Trial

| Patients | Accrual occurred between July 2008-February 2012  
|          | Patients eligible if age 2-30 yrs (no DS patients)  
|          | Enrolled 63 Ph+ ALL patients |
| Aims     | Evaluate safety/efficacy of combining **dasatinib** with same chemotherapy backbone used in AALL0031  
|          | Determine contribution of dasatinib on MRD |
| Methods  | Dasatinib (60mg/m2/dose) added on Induction day 15 when Ph status known  
|          | Cohort 1 – discontinuous dasatinib  
|          | Cohort 2 – continuous dasatinib |
| Outcome  | Dasatinib with intensive chemotherapy was well tolerated.  
|          | Further follow-up and additional trials are necessary to define the relative role of dasatinib and imatinib in promoting long-term survival in pediatric Ph+ ALL. |

Birdsall et al. ASCO Abstract 2015
# AALL1122 – Phase II Multicenter Study

| Partnerships          | • COG and EsPhALL group  
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| **Patients**         | • Accrual occurred between Feb 2012 – May 2014  
|                      | • Patients eligible if > 1 yr and < 18 yrs (no DS pts)  
|                      | • May not have had prior treatment with BCR-ABL inhibitor |
| **Aims**             | • Evaluate safety/efficacy of continuous **dasatinib** on a less intensive EsPhALL chemotherapy backbone  
|                      | • Determine prognostic value of MRD on EFS |
| **Methods**          | • Dasatinib added on Induction day 15  
|                      | • 60 mg/m²/dose for 2 yrs |
Ph+ ALL

• **Frontline therapy with Imatinib**
  – AALL1631 will compare Imatinib + COG/BFM backbone to EsPhALL

• **Dasatinib safe and comparable, but reserved for cases when Imatinib is not tolerated or ineffective**
What is the role for Dasatinib in Pediatric Ph+-LIKE ALL?
What is “Ph-like” ALL?

- > 10-15% childhood ALL, > 30% in young adults
- Gene expression profile similar to Ph+ ALL
- Mostly CRLF2-JAK mutations
Ph-like ALL $\rightarrow$ very poor outcomes

5 y EFS 59% vs 85%
Ph-like ALL increases with age

Case
Background
Indications
Ph+ ALL
Ph-like ALL
Side Effects
Conclusion

POGO
PEDIATRIC ONCOLOGY GROUP OF ONTARIO
Identifying Children with Ph-like ALL in Real Time

HR B-ALL
AALL1131

Not Ph-like
Risk-adapted chemotherapy

Ph-like
CRLF2+
CRLF2-
multiplex RT-PCR kinase fusion
ABL class kinase fusion
JAK2 fusion
IL7R alteration

CRLF2-R + JAK1/JAK2 mutation analysis
FISH & PCR

Other testing recommended
FoundationOne
ArcherDx (RNA seq)

EPOR rearrangement
Other fusions?

Ph+
imatinib/dasatinib + chemo

Post-induction
AALL1521
ruxolitinib

Post-induction
AALL1131
dasatinib

NCI TARGET & COG ALL Committee
University of New Mexico
Nationwide Children’s Hospital
University of Alabama, Birmingham
Noah

• LDA showed a Ph-like signature with ABL class fusion

• Started therapy with continuous dasatinib following induction

• End of consolidation MRD <0.01%

• Ongoing monitoring for side effects
Dasatinib: pharmacology

- Oral drug, no special rules for food

- Only tablets
  - Can’t crush (dissolve intact tablet in 1 oz of apple/orange juice or lemonade)

- Hepatic metabolism
  - CYP 3A4 (avoid grapefruit/juice)
  - Reduced effect with antacids (pH dep solubility) at least 2 hours apart
Dasatinib: Special Precautions

- **Prolongation of QT interval**
  - Increased risk with
    - hypoK, hypoMg
    - drugs that alter CYP3A4 activity
    - High dose anthracyclines
  - ECG screening prior to starting

- Rare cases of pulmonary hypertension
  - Consider if dyspnea, fatigue NYD
Dasatinib:
Common Side Effects (>30%)

• Myelosuppression, fever, rash, diarrhea, bleeding, pain

• Fluid retention (50%, 10% severe)
  – Generalized edema
  – Pulmonary edema
  – pleural/pericardial effusion
  – ascites
Dasatinib

- Second generation Tyrosine Kinase Inhibitor

- Used in patients with Ph+ or Ph+ like leukemias

*Be familiar with the side effect profile and have a high clinical suspicion if/when symptoms arise*


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