Lymphoblastic leukemia with a kinase-activating alteration

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Patient – 59 female who presented with persistent B-lymphoblastic leukemia

• First diagnosis - 5 months prior, WBC 92.6 x 10⁹/L, Initial CSF analysis was positive for blasts

• Therapy included hyper-CVAD through cycle 2A, blinatumumab, and two cycles of ICE, plus five intrathecal treatments

• In the five months since diagnosis she maintained 40-60% blasts in the bone marrow over five subsequent biopsies

• She came to our institution and was initiated onto a clinical trial (SWOG 1312) with plans underway for allogeneic hematopoietic stem cell transplant
Peripheral blood
WBC 1.82 x 10^9/L; Hgb 9.7 g/dL; Plt 69 x 10^9/L, 8% blasts
Bone marrow aspirate 71% blasts
Flow cytometry – bone marrow aspirate
46,XX,t(5;17)(q33;p11.2~13)[7]/45,iddem,-7[6]/46,XX[12]
PDGFRB 5q32 Breakapart Probe

Cytocell, Cambridge, UK
46,XX,t(5;17)(q33;p11.2~13)[7]/45,idem,-7[6]/46,XX[12]

• Chr 17 breakpoint – either p11.2 or p13

• t(5;17) with 17p13 was described in:
  • One case of T-lymphoblastic leukemia with myeloid neoplasm and PDGFRB rearranged to RABEP1 (Ondrejka et al, Haematologica 2014)
  • One case of CMML with PDGFRB-RABEP1 (Magnusson et al, Blood 2001)

• t(5;17) with 17p11.2 was described in:
  • One case of JMML involving PDGFRB-SPECC (Panarello, Atlas Genet Cytogenet Oncol Haematol 2004)

• Monosomy 7 - present 4-6 % of B-ALL, most often as a secondary anomaly of the t(9;22); the association t(9;22), -7 is present in 16 % of the Ph+ ALL
Send-out multiplex RT-PCR fusion for Ph-like ALL—**Negative** for fusion transcript products

Fusion genes detected in the assay:

- 12 ABL1 fusions
- 11 JAK2 fusions
- 15 kinase fusions including: EBF1-PDGFRB, ZEB2-PDGFRB, TNIP-PDGFRB, ATF7IP-PDGFRB, ZMYND8-PDGFRB, ETV6-PDGFRB, AGGF1-PDGFRB
Proposed diagnosis:
Ph-like B-lymphoblastic leukemia with PDGFRB translocation

Panel diagnosis:
B-lymphoblastic leukemia, BCR-ABL1-like

Arber DA et al, WHO revision, Blood 2016
Differential diagnosis

• Myeloid and lymphoid neoplasm with eosinophilia and PDGFRB rearrangement
  - No evidence of myeloid neoplasm or eosinophilia at diagnosis or in five subsequent marrows.
  - No myeloid neoplasm or eosinophilia upon presentation at our hospital or in a bone marrow biopsy after first cycle of SWOG-1312
Patient follow-up

• Bone marrow biopsy after first cycle on SWOG-1312 was morphologically negative, but there was minimal residual disease detected by flow cytometry (0.062%) and persistence of t(5;17)(q33;p11.2) in 6 metaphase cells.

• She continued therapy for another cycle and proceeded to allogeneic bone marrow transplant at another institution

• A bone marrow biopsy one month after transplant was normocellular with trilineage hematopoiesis and no evidence of B-lymphoblastic leukemia; karyotype //46,XY[20]
B-lymphoblastic leukemia, \textit{BCR-ABL1}-like

- Range of genetic alterations that activate cytokine receptor genes and kinase signaling pathways
  - Rearrangements of \textit{CRLF2} +/- JAK mutation
  - \textit{ABL-class gene rearrangements}
  - \textit{JAK-STAT alterations}
  - JAK2 and \textit{EPOR} rearrangements
  - Other rare kinase alterations (ie \textit{NTRK3})
B-lymphoblastic leukemia, in adults

Adult (40-59 yrs; n=304)

- **BCR-ABL1**: 24%
- **Ph-like**: 20.4%
- **MLL**: 17.1%
- **ETV6-RUNX1**: 3.9%
- **TCF3-PBX1**: 3.9%
- **ERG**: 2.3%
- **B-other**: 31.9%

Roberts KG et al, J Clin Oncol 2016
Ph-like lymphoblastic leukemia

Adult (40-59 yrs; n=62)

Roberts KG et al, J Clin Oncol 2016
PDGFRB 5’ fusion partners

- **EBF1**
- **SSBP2**
- **TNIP1**
- **ZEB2**
- **ETV6, ZMYND8**
  - Reshmi SC, et al, Blood 2017
- **SATB1**
- **AGGF1**
- **DOCK2**
  - Heilmann AM et al, Leukemia 2017

Various ways to test for Ph-like ALL

- Enticing option – targeted capture of RNA (targeted locus amplification) – using the TK gene as a known starting point, followed by NGS. Advantage that novel partner genes will be identified.
- Alternative – focus screening approach on high-risk or induction failure
- Low density array card (TLDA) to screen for the Ph-like gene expression profile – then – Additional genetic testing to identify the kinase lesion

- Goal is to therapeutically target the underlying kinase lesion rather than identify the Ph-like GEP:
  - RT-PCR – for known fusions
  - FISH
  - Phosphoflow signaling
  - NanoString assay
Testing algorithm for Ph-like ALL in COG trials

Tran TH and Loh ML, ASH education book 2016
Therapeutic implications

Rearrangements of *CRLF2* +/- JAK mutation
- **Ruxolitinib**

JAK2 and *EPOR* rearrangements
- **Ruxolitinib**

ABL-class gene rearrangements
- **Dasatinib**

JAK-STAT alterations
- **Ruxolitinib**
- **JAK1/JAK3 inhibitor**

Other rare kinase alterations (i.e. *NTRK3*)
- **Crizotinib, MEK or FAK inhibitor**

**COG (AALL131)** - patients with NCI high-risk Ph-like ALL and ABL-class fusions are eligible to have dasatinib added to backbone chemotherapy
Problems in moving forward with Ph-like ALL

• Lots of genetic heterogeneity – difficult to systematically study

• Genetic aberrations are hard to detect by standard diagnostic methods such as karyotyping, FISH or PCR because they are diverse, ever-increasing, and sometimes cryptic.

• Challenging for most laboratories to implement assays that test for these genomic aberrations
Summary / Conclusions

• Patient with Ph-like B-lymphoblastic leukemia with many high risk features – she received allogeneic SCT elsewhere
• Testing for Ph-like alterations in B-lymphoblastic leukemia remains a challenge
• Standardization of screening strategies and cut-offs will help trials evaluating best therapies for these patients
Panel diagnosis: B-lymphoblastic leukemia, BCR-ABL1-like