A Case of Double-hit Mantle Cell Lymphoma with *MYC* Gene Rearrangement

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Faculty Discussant
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Mantle Cell Lymphoma (MCL)

- Cytogenetic Hallmark: translocation t(11;14)(q13;q32) leading to aberrant expression of Cyclin D1 (CCND1)
- Leukemic component in 20%~30% of patients

*Blood, 2013:121(8):1394*
*Semin Cancer Biol 2011, 21(5):322*
Pathogenesis of MCL

• Does the t(11;14)(q13;q32) leading to overexpression of cyclin D1 alone cause the occurrence of MCL?
• What are the patho-genetic roles of other complicated cytogenetic changes in MCL?

• Rationales
  ► The t(11;14)(q13;q32) presents at low levels in the peripheral blood of healthy individuals
  ► The indolent MCL cases have very simple karyotypes with the t(11;14) as the sole alteration
Double-hit Lymphoma?

EMBO J, 1994, 13(9): 2124-2130
EMBO J, 1994, 13(15): 3487-3495

- Cyclin D1 transgenic mice have normal cell cycle in their lymphocytes, though young animals contain fewer mature B- and T-cells.
- No lymphoma occurrence in over 12-month observation.
- Double transgenic mice of Cyclin D1 with either N-myc or L-myc cause pre-B or B cell lymphomagenesis.
- The cooperation of Cyclin D1 with the myc gene activates RAS/RAF and other oncogenes through the E2F-1.
- Cases harboring both Cyclin D1 and MYC translocations occasionally seen (first case reported in 1996).
Double-hit Lymphoma

- Lymphomas with recurrent chromosomal breakpoints activating multiple oncogenes, one of which being MYC, are often referred to as “Dual Hit” or “Double Hit” (DH) lymphomas.
- DH lymphoma is mostly used for mature-B-cell lymphomas with a chromosomal breakpoint affecting the MYC locus.
- Imprecise term: Neither restricted to B-cell lymphomas nor does it exclude 2 translocations activating oncogenes other than MYC.
  The term DH lymphoma has been used for all cases with multiple recurrent breakpoints (triple/quadruple) as well.
- DH mantle cell lymphoma: $\text{CCND1}^+/\text{MYC}^+$

*Blood 2011,117(8):2319-2331*
Case Report

• A 74 M initially presented with fatigue and lymphocytosis, and was diagnosed as Rai’s stage III CLL 7/15/2013.
• Pretx peripheral blood: marked leukocytosis of 300k, composed predominantly of circulating blastoid B cells with neuclear enlargement and hyperchromasia, and nucleolar prominence as well.
• Mild anemia with normal platelets.
• CT C/A/P:
  Diffuse lymphadenopathy in mediastinum, retroperitoneum and inguinal area.
  Significantly splenomegaly 26.5 cm.
• No relevant PMH or FH.
Bone Marrow Studies

BM:

► Hypercellular and predominant of lymphoma cells, which are similar to cells circulating in peripheral blood.
► Remaining marrow cells represented myeloid and erythroid precursors with a full spectrum of maturation. Megakaryocytes had normal morphology.
► Karyotype: 44,X,-Y,add(3)(q25),-8,-10,del(11)(q13), del(11)(q21q23),del(13)(q12q14),der(14),t(10;14)(q11.2;p11.2), t(11;14)(q13;q32),-17,add(18)(q21),+2mar/46,XY

• FCM: 84% are lymphoma cells expressing CD19, CD20, CD38, HLA-DR, and lambda light chain with no CD5, CD10 or CD11c.

• Further work up:
  ► Positive translocation t(11;14) in both peripheral and marrow lymphoma cells.
  ► Cyclin D1 IHC of marrow positive.
Treatment History

- Bendamustine 8/2013: leukocytosis relapsed right after stopped the tx, with rapid decline of his PS
- HyperCVAD 9/2013: WBC 300k→33k with improvement of his PS
- Relapsed in 10/2013, enrolled to clinical trial with Ibrutinib 10/28

**Graph details:**
- **Started Ibrutinib:** Dex 125 mg X 1, then PDN 100 mg daily
- **Stopped Ibrutinib:** Transfer/Dex 40 mg daily
- **Expired with WBC 890**
Monotonous small lymphocytes resembling centrocytes/mantle cells with scant cytoplasm, cleaved, slightly irregular or round nuclei; condensed chromatin.

The neoplastic cells were large with round to irregular nuclei, blastoid chromatin, prominent nucleoli, and moderate amounts of basophilic cytoplasm.
FISH for CCND1/IgH

CCND1/IGH DUAL FUSION PROBE

11q13(CCND1) = Spectrum Orange
14q32(IGH) = Spectrum Green
MYC DUAL COLOR BREAKAPART PROBE

8q24(5' MYC) = Spectrum Orange
8q24(3'MYC) = Spectrum Green
8q24(MYC) = Spectrum Orange/Green Mix

breakapart positive
MYC in Burkitt’s Lymphoma

MYC Translocations

J Clin Oncol 2000, 21:3707-3721
DH Mantle Cell Lymphoma

34 DH lymphoma cases had a $CCND1^+/MYC^+$ combination in Mitelman database: 5% of all MCL.

26 cases reported:
- 15: MYC translocation; 11: additional 8q24 or MYC amplification
- All are stage IV disease with extensive bone marrow involvement
- High WBC and lymphocytosis: median $137.8 \times 10^9/L$
- Leukemic and blastoid, pleomorphic or even Burkitt’s lymphoma-like morphology
- Circulating large lymphoma cells with high LDH
- High Ki-67 (>50%-75%)
- All have complicated cytogenetic changes
- Aggressive clinical course with short PFS after chemo
- Average survival being only 8 mo

Rapid proliferation, leukemic involvement and short survival
Treatment of DH Mantle Cell Lymphoma

4 cases report in Haematologica 2000:
• CR with chlorambucil but relapsed with resistant to tx
• 2 cases obtained CR with VACOP-BP/XRT but relapsed and resistant to tx
• CR with Cis/VP-16 (initial dx small cell carcinoma) but had CNS recurrence

Another 4 cases reported in Int J Clin Exp Pathol 2013:
• R-CHOP/Bendamustine plus Rituxan: CR in 17 mo
• EPOCH/HyperCVAD, CR with survival of 4 mo
• CHOP, HyperCVAD then autologous HSCT, with persistent disease and survived for 13 mo
• Hospice with average survival of 3 mo

No case has been reported with treatment of Ibrutinib.
**MYC^+ DLBCL Treated with R-CHOP**

- MYC^+ DLBCL with R-CHOP had inferior progression-free survival and overall survival.

- MYC^+ DLBCL had a higher risk of central nervous system relapse, independent of other risk factors.

- FISH for MYC rearrangements should be performed in all patients with DLBCL.

- Treatment regimens similar to those used in Burkitt lymphoma may be more appropriate in this patient population.

- Apply in MYC^+ MCL?

*Blood 2009, 114(17):3533*
Ibrutinib in Relapsed or Refractory MCL

FDA approved Ibrutinib for MCL treatment in Nov. 2013 based on Phase II study in NEJM 2013, 369:507-516.

- Response rate: 68% (CRR of 21% and PR of 47%).
- Estimated median response duration: 17.5 mo; estimated median PFS: 13.9 mo; estimated rate of OS was 58% at 18 months.

A choice for DH MCL with MYC+ involvement?

Complications from leukocytosis?

Time frame for tx?

6.5 X 10^9/L before treatment Vs 140 X 10^9/L in HD MCL
Aurora A and B Kinase Inhibitors

Aurora A inhibition: engagement of the mitotic checkpoint, and cause mitotic arrest, promoting apoptosis

Aurora B inhibition: loss of checkpoint with rapid exit from mitosis (mitotic driver), causing genomic instability

Alisertib (MLN8237) & Barasertib (AZD1152)
AURORA Kinase Inhibitors, a Novel Treatment Option?

- Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell NHL.
- The overall RR was 27%, including 3/21 DLBCL, 3/13 MCL, 1/1 Burkitt's lymphoma, 2/5 transformed follicular lymphoma, and 4/8 non cutaneous T-cell lymphoma.

*J Clin Oncol 2014,32:44*

*Medical Oncology 2014,31:931*
CONCLUSIONS

• $CCND1^+/MYC^+$ DH MCL may be more frequent than anticipated and should receive more attention.
• Conventional cytogenetic study can miss the $MYC^+$ translocation.
• FISH should be considered if patient presents with blastoid MCL.
• The BTK inhibitor Ibrutinib might not be an option for DH MCL with $MYC$ involvement with high WBC.
• The aurora kinase inhibitor could be a promising choice in a subset of DH MCL patients with $MYC$ translocation but needs to be further testified.
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