Molecular Genetic Aberrations in Chronic Lymphocytic Leukemia With Richter Transformation

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Abstract/Background

Chronic lymphocytic leukemia (CLL) is a chronic incurable B-cell disease that affects primarily older adults. It is the most common leukemia in the Western world and viewed as a heterogenous disease with a highly variable clinical course.

Approximately 2-10% of CLL patients will develop aggressive histological transformation to diffuse large B-cell lymphoma (DLBCL), commonly recognized as Richter transformation (RT), with a transformation rate of 3% to 25% in patients treated with novel agents.[1, 5] The 2008 World Health Organization defined RT as the transformation of CLL into a more aggressive lymphoma.[3] Richter transformation occurs due to dysregulation of signaling pathways of CLL cells.[1,2,5] Of 2975 pts with advanced CLL, 103 pts developed RT (3%). Median OS after RT diagnosis ~ 9 months [6]

Purpose

The aim of this poster is to increase awareness of predictive factors and associated molecular aberrations in RT. The poster will provide the diagnostic criteria needed to promote early recognition and intervention by advanced practice providers and clinicians towards improving patient outcomes.

Incidence of Genomic Aberrations in CLL

- TP53 disruption (60-80%
- NOTCH1 mutation (30%)
- CDKN2A/B (30%)
- MYC aberration (30%)[5]
- Trisomy 12
- Unmutated IGHV (> 95%)
- BCL2 (30%)

Risk Factors for RT

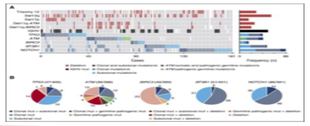
- Advanced Rai stage disease (III-IV) or Binet stage C)
- Unmutated immunoglobulin heavy chain variable IGHV gene
- Del (17p), TP53, Trisomy 12, NOTCH1, c-MYC
- Previously treated CLL
- Germline genetics
- Certain aspects of CLL phase biology[7]

*The 2018 iWCLL guidelines suggest testing of biomarkers on initial evaluation for RT

Molecular Features Associated with Richter Transformation in CLL

- Mutations in NOTCH1 – characterized by Trisomy 12 activating NOTCH1 mutations
- NOTCH1 mutations wild-type less common to develop transformation.
- SF3B1 (associated with non-Richter transformation in CLL) [2]
- CDKN2A/B loss with or without *MYC* abnormalities. CDKN2A gene encodes p161NK4A ⟶ dysregulation of **TP53**[1,4,6]
- Unmutated IGHV status
- c-*MYC* aberrations caused by t(8;14) or other structural alteration[5]
- BCL2 rearrangements by FISH [5]

Fig 1. Gene Mutations (Nadeu et al., 2016)



Diagnostic Approaches

Fig. 3. .Diagnostic Criteria for RT [2,5,6]

Suspect Richter Transformation?

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Obtain Thorough H&P: bulky nodes (> 3 cm), fever, weight loss, ↑fatigue, night sweats, splenomegaly, bruising, petechiae, shortness of breath

↓

Assess Pertinent Lab Test Results: CBC, CMP, NGS panel from peripheral blood or BM, IGHV mutation status, Cytogenetics, and BM biopsy

↓

Obtain PET/CT (18-FDG) to assess for FDG-avid nodes with SUV > 5

↓

If FDG avid node with SUV ≥ 10 cm→ IR excisional node biopsy → confirm DLBCL → Treatment indicated

Implications for APPs in Diagnosis of RT

Advanced practice providers (APPs) are often the initial point of contact on patient presentation in the clinic setting and should be cognizant of the following:

- High risk features in CLL that may lead to RT
- Performing a detailed H&P
- Clinical features on presentation, i.e., bulky nodes, fever
- Past treatment history for CLL
- Be vigilant in assessing predictive clinicopathological factors for RT

Conclusions

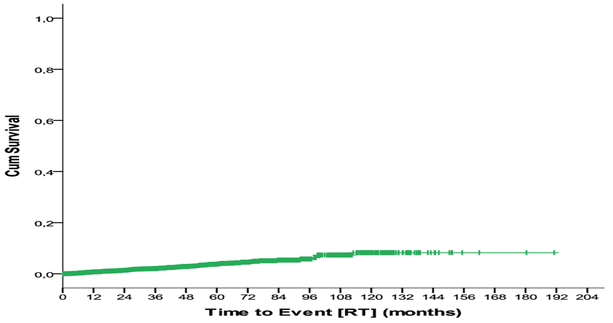
Richter transformation occurs (2-10%) in advanced stage, previously treated B CLL with a transformation rate of 3% to 25% post treatment . CLL patients who present with clinical signs of RT should evaluated immediately with a PET/CT and possible biopsy if indicated. The intent of this poster presentation is to promote early recognition and diagnosis of RT, improve patient outcomes and decrease mortality in this population.

Clinical Features of RT

Table 1. *Presenting Features*

Rapidly enlarging bulky lymph nodes
Increasing fatigue
Unexplained fever
Unexplained weight loss
Shortness of breath
Splenomegaly
Elevated LDH
Anemia
Thrombocytopenia

Fig. 2. Time to RT from Initial CLL Treatment [6]



RT-free	Pts, N	Events, N	Median months	3-year Survival, %	6-year Survival, %	9-year Survival, %	12-year Survival, %
All patients	2971	99 (3.3)	NR	97.9	95.4	92.6	91.7

References

1. Rosati, E., Baldoni, S., De Falco, F., Del Papa, B., Dorillo, E., Rompietti, C., et al. (2018). NOTCH1 aberrations in chronic lymphocytic leukemia. *Frontiers in Oncology, 8*, 229 https://doi.org/10.3389/fonc.2018.00229
2. Khan, M., Siddiqi, R., & Thompson, P. A. (2018). Approach to Richter transformation of chronic lymphocytic leukemia in the era of novel therapies. *Annals of Hematology, 97*, 1-15.
3. Arruga, F., Bracciama, V., Vitale, N., Vaisitti, T., Gizzi, K., Yeomans, A., Coscia, M. et al., (2020). Bidirectional linkage between the B – cell receptor and NOTCH1 in chronic lymphocytic leukemia and in Richter's syndrome: therapeutic implications. *Leukemia, 34*(2), 462-77. https://doi.org/10.1038/s41375-019-0571-0.
4. Ding, W. (2018). Richter transformation in the era of novel agents. *Hematology American Society of Hematology Educational Program, 1*, 256-263. https://doi.org/10. 1182/asheducation-2018.1.256
5. Wang, Y. & Ding, W. (2020). Richter transformation of chronic lymphocytic leukemia in the era of novel agents. *Clinical Advances in Hematology & Oncology, 18*(6), 348-357.
6. Al-Sawafi et al. (2020). Richter transformation in chronic lymphocytic leukemia- a pooled analysis of German CLL study group from frontline treatment trials. *Leukemia*, 35(1), 169-176
7. Kohlhass, V., Blakemore, S. J., Al-Maarri, … et al. (2021). Active Akt signaling triggers CLL toward Richter transformation via overaciivation of NOTCH1. *Blood*, 137(5), 646-660. doi.org://10.1182/blood.2020005734.