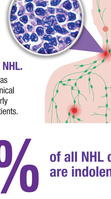
Expanding Treatment Options in Relapsed/Refractory Follicular Lymphoma: *Exploring the Role of Epigenetics*

DISEASE BACKGROUND

Indolent lymphomas tend to grow more slowly and have fewer signs and symptoms when first diagnosed. Indolent subtypes represent about 40% of all non-Hodgkin lymphoma (NHL) cases.



Follicular lymphoma (FL) is the most common subtype of indolent NHL.

FL makes up about 22% of all NHL cases. FL has generally favorable outcomes but a variable clinical course. Recent studies have elucidated that early disease progression in FL occurs in 20% of patients.

40% of all NHL cases are indolent subtypes

22% of all NHL cases are FL

20% of all FL cases are relapsed/refractory (R/R)

Relapse of FL within 24 months of chemoimmunotherapy is now established as a robust marker of poor survival, leading to increased risk of death.

Common Symptoms of FL

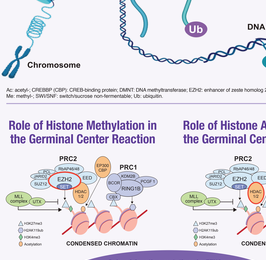
- Swelling of lymph nodes (neck, underarms, abdomen, groin)
- Fatigue

Less Common Symptoms

- Fever
- Night sweats
- Weight loss

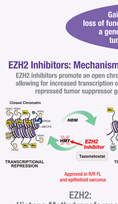
Often, patients with FL have **no obvious symptoms** of the disease and the diagnosis is found incidentally during a routine annual checkup or following imaging studies for unrelated reasons.

EPIGENETICS IN THE PATHOLOGY AND TREATMENT OF FL

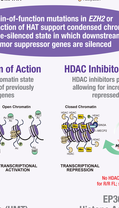


Ac: acetyl-; CREBBP (CBP): CREB-binding protein; DNMT: DNA methyltransferase; EZH2: enhancer of zeste homolog 2; HDAC: histone deacetylase; Me: methyl-; SWI/SNF: switch/sucrose non-fermentable; Ub: ubiquitin.

Role of Histone Methylation in the Germinal Center Reaction



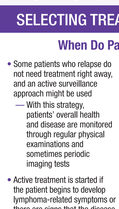
Role of Histone Acetylation in the Germinal Center Reaction



Gain-of-function mutations in *EZH2* or loss of function of HAT support condensed chromatin, a gene-silenced state in which downstream tumor suppressor genes are silenced

EZH2 Inhibitors: Mechanism of Action

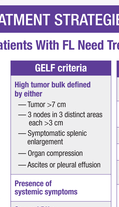
EZH2 inhibitors promote an open chromatin state allowing for increased transcription of previously repressed tumor suppressor genes



Approved in R/R FL and epithelioid sarcoma

HDAC Inhibitors: Mechanism of Action

HDAC inhibitors promote an open chromatin state allowing for increased transcription of previously repressed tumor suppressor genes



No HDAC inhibitors currently approved for R/R FL; several undergoing investigation

EZH2: Histone Methyltransferase (HMT)

- Activating mutations
- 30% of GC-DLBCL
- ***27% of FL***
- Histone demethylases (HDMs) lead to demethylation of histone, creating an open chromatin state
- EZH2 methylates histone via HMT, creating a condensed chromatin state
- Cancers harboring mutations in the SWI/SNF complex demonstrate unchecked activation of EZH2

EP300 and CREBBP: Histone Acetyltransferase (HAT)

- Loss of function
- 39% of GC-DLBCL
- ***41% of FL***
- HATs lead to acetylation of histone, creating an open chromatin state
- Opposing HAT activity, HDACs deacetylate histones, creating a condensed chromatin state
- No mutations associated with HDACs; however, in some cases they have been found to be overexpressed

GC-DLBCL: germinal center-large B-cell lymphoma.

SELECTING TREATMENT STRATEGIES FOR R/R FL

When Do Patients With FL Need Treatment?

- Some patients who relapse do not need treatment right away, and an active surveillance approach might be used
  - With this strategy, patients' overall health and disease are monitored through regular physical examinations and sometimes periodic imaging tests
- Active treatment is started if the patient begins to develop lymphoma-related symptoms or there are signs that the disease is progressing based on testing during follow-up visits

GELF criteria

High tumor bulk defined by either
- Tumor >7 cm
- 3 nodes in 3 distinct areas each >3 cm
- Symptomatic splenic enlargement
- Organ compression
- Ascites or pleural effusion

Presence of systemic symptoms

Serum LDH or β2-microglobulin above normal values

BNLI criteria

Rapid disease progression in the preceding 3 months

Life-threatening organ involvement

Renal or liver infiltration

Bone lesions

Systemic symptoms or pruritus

Hb <10 g/dL or WBC <3.0 × 10⁹/L or platelet count <100 × 10⁹/L; related to marrow involvement

Considerations in the Choice of Therapy for a Patient With FL Who Has Relapsed

- Indications for therapy
- Bulk of disease
- Comorbidities
- Toxicity concerns
- Interest in and availability of clinical trials
- Risk of transformation
- Grade (typically FL grade 1, 2, and 3A treated similarly)
- Previous therapy/lines of therapy experience
- *EZH2* mutation (and epigenetic testing) status

- FL is generally very responsive to radiation and chemotherapy and many patients go into a remission that lasts for years after their initial treatment; however, the disease often returns
- For patients who relapse or become refractory, second-line therapies are often successful in providing another remission

Treatments for R/R FL

- Rituximab retreatment
- Newer anti-CD20s (generally in combination)
- Radioimmunotherapy
- Lenalidomide + rituximab
- PI3K inhibitors (eg, copanlisib, duvelisib, idelalisib)
- EZH2 inhibitors (eg, tazemetostat)
- Auto-/Allo-SCT
- HDAC inhibitors (*investigational*; eg, abexinostat)

Tazemetostat, approved for patients with R/R disease who:

1) have a known *EZH2* mutation and received ≥ 2 lines of systemic therapy; or

2) irrespective of mutational status who have no other satisfactory options

BNLI: British National Lymphoma Investigation; Hb: hemoglobin; GELF: Groupe d'Etude des Lymphomes Folliculaires; LDH: lactate dehydrogenase; WBC: white blood cell.

KEY TAKE-AWAY MESSAGES

- FL makes up about 22% of all NHL cases; early disease progression in FL occurs in ≈ 20% of patients
- IB-cell lymphomas originating from the germinal center (FL, DLBCL) may be the most sensitive to epigenetic therapies
- **EZH2 inhibitors** have enhanced efficacy in *EZH2*-mutated lymphomas and perhaps copy number gain-of-function conditions such as FL
  - Inhibition of EZH2 may restore normal LZ-DZ recycling, interactions with T cells, and immune surveillance
- Tazemetostat is the first EZH2 inhibitor approved for patients with R/R disease who have a known *EZH2* mutation and have received ≥ 2 lines of systemic therapy or for patients with R/R disease irrespective of mutational status who have no other satisfactory options

IB: immunoblastic; LZ-DZ: light zone-dark zone.

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