

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Evolving Strategies for the Management of Transformed Lymphoma



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### H&O What is transformed lymphoma?

**SS** Transformed lymphoma refers to a more aggressive or fast-growing lymphoma that arises from an indolent histology. The most common example of transformed lymphoma is a follicular lymphoma that evolves into diffuse large B-cell lymphoma (DLBCL), or, less commonly, a high-grade B-cell lymphoma with double-hit biology after the indolent disease acquires a *MYC* rearrangement. In rare cases, follicular lymphoma can transform into high-grade histologies, such as Burkitt lymphoma. Marginal zone lymphoma and lymphoplasmacytic lymphoma can also transform into DLBCL. In the case of chronic lymphocytic leukemia or small lymphocytic lymphoma, transformed disease is known as Richter's transformation. For unclear reasons, these slow-growing lymphomas can acquire mutations or other genomic hits that lead to a very aggressive phenotype that requires urgent, if not emergent, treatment.

The overall incidence of transformation in indolent lymphomas is low. In the rituximab (Rituxan, Genentech/Biogen) era, the risk of transformation is approximately 2% to 3% per year.

### H&O Are there any risk factors?

**SS** It is not always possible to predict whether a certain patient will develop transformed lymphoma. However, the likelihood of transformation depends on several risk factors. In follicular lymphoma, early progression—

namely, progression of disease within 24 months—has emerged as an important core prognostic factor. This observation is based on data from the British Columbia Cancer Agency and a Danish registry showing that most patients with follicular lymphoma who experience disease progression within 24 months have transformed disease at the time of re-biopsy. In the British Columbia experience, 75% of early progressors had transformed disease.

Another risk factor was identified through a subanalysis of the PRIMA study, a large clinical trial that enrolled patients with high tumor-burden follicular lymphoma. Patients with a high baseline Follicular Lymphoma International Prognostic Index (FLIPI) score of 3 to 5 had a higher risk of transformation. Their median time to transformation was relatively short, at 9.6 months, which again reflects early progression. A large registry analysis from 2013 coordinated by the University of Iowa and the Mayo Clinic identified several risk factors for transformation: poor performance status, high levels of lactate dehydrogenase, B symptoms, follicular lymphoma of grade 3A or a high FLIPI, loss of beta-2-microglobulin, increased T cells, and mutations in genes such as *TP53*, *PIMI*, or beta-2-microglobulin.

### H&O What are the distinguishing characteristics between transformed lymphoma and progressive disease?

**SS** Progressive disease is typically defined as an increase in the size or number of lymph nodes or lymphomatous

areas of involvement. Patients with progressive disease typically require treatment, and the goal of treatment is to shrink the lymph nodes (ie, achieve remission). It is important to remember that in patients with progression of an indolent disease, such as follicular lymphoma or marginal zone lymphoma, the goal of treatment for progression is disease control, and not cure, since these are incurable diseases. In transformed lymphoma, a biopsy will show a more aggressive histology, typically DLBCL or high-grade B-cell lymphoma, as discussed above. The more aggressive histology warrants more aggressive treatment; ironically, it is possible to “cure” the more aggressive type of lymphoma, whereas the indolent lymphoma will essentially always recur.

### **H&O** Are there any recent insights into the pathogenesis of transformed lymphoma?

**SS** This is a very exciting area. The first Transformed Lymphomas Scientific Workshop was held in early August 2021. This meeting was convened by the Lymphoma Research Foundation, which is the largest advocacy group for lymphoma in the world and an important funding group for lymphoma-related research. The foundation distributes millions of dollars in grant support, offers educational training programs for clinicians who are interested in careers in lymphoma, and, as an advocacy group, provides patient education. In the past, the foundation has convened panels of experts to hold workshops on specific areas of unmet need, and transformed lymphoma is now one of them. At the workshop, there was an entire session dedicated to the biology of transformation.

Using follicular lymphoma as an example, the t(14;18) rearrangement is pathognomonic. Most patients with follicular lymphoma have a t(14;18) rearrangement. This rearrangement is necessary, although not sufficient, for the disease to develop in most cases. Over time, the patient develops increased epigenetic deregulation, which appears to be an early hallmark of lymphoma progression. Eventually, there are adverse mutations, such as the *TP53* mutation, beta-2-microglobulin mutations, and *PIM1* mutations. There are also changes in the microenvironment. It is not known whether the transformation results from an orderly process or whether there are multiple factors at work simultaneously. The pathogenesis of transformed lymphoma is not known, and work is needed in this area.

### **H&O** What are the traditional treatment approaches for transformed lymphoma?

**SS** The treatment of transformed lymphoma in large part depends on the prior therapies used for the indolent

component. Some patients do not receive treatment for indolent lymphoma; rather, they undergo observation. If these patients develop transformed lymphoma, they will receive treatments such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R), depending on the histology.

Among patients who receive treatment for their initial disease and then relapse quickly, therapy for transformed lymphoma can include a stem cell transplant, enrollment in a clinical trial, or a newer option, such as chimeric antigen receptor (CAR) T-cell therapy. The treatment for transformed lymphoma might be their second, third, or fourth line of treatment overall. The selection of treatment will vary based on the earlier treatments the patient has received. Data regarding treatment sequencing are limited.

The treatment goal in transformed lymphoma is to put the aggressive component into remission indefinitely.

### **H&O** What is the treatment goal for transformed lymphoma?

**SS** The treatment goal in transformed lymphoma is to put the aggressive component into remission indefinitely. Treatment aims to cure the aggressive component. It is not possible to cure the indolent component, so the goal is to delay its return. When the indolent component does return, the hope is that it can be managed with traditional treatments.

### **H&O** Are there any novel treatment strategies for transformed lymphoma?

**SS** Currently, treatment of transformed lymphoma is typically adopted from the approach to DLBCL. All of the treatments under development in DLBCL are also being evaluated in patients with transformed lymphomas. Such treatments include bispecific antibodies and CAR T-cell therapies. In the last 2 years, 4 new regimens were

approved for relapsed/refractory DLBCL: polatuzumab vedotin-piiq (Polivy, Genentech), bendamustine (Bendam, Teva), and rituximab; tafasitamab-cxix (Monjuvi, MorphoSys/Incyte) and lenalidomide (Revlimid, Celgene/Bristol Myers Squibb); loncastuximab tesirine-lpyl (Zynlonta, ADC Therapeutics); and selinexor (Xpovio, Karyopharm Therapeutics). It is possible to also use these treatments in patients with transformed lymphoma.

### H&O Are there any other promising areas of research?

**SS** There are many gaps in the knowledge and much work to be done. My hope is that as treatment options for DLBCL improve, there will be more treatments for transformed lymphoma. Unmet needs include the ability to predict which patients will transform and how to prevent the transformation. Some researchers have suggested that rituximab decreases the risk of transformation. There may be other ways.

### H&O Do you have any other recommendations regarding the treatment of patients with transformed lymphoma?

**SS** It is important for patients to obtain a second opinion and to consider receiving treatment in a tertiary care center. There are many ongoing clinical trials, and there is significant room for improvement in this field. Patients can also visit the Lymphoma Research Foundation website or consult other advocacy groups to obtain more information and guidance.

### Disclosure

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### Suggested Readings

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