

ADVANCES IN LLM

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

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New Developments in Richter Syndrome



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H&O Could you give a brief background on Richter syndrome?

NJ Richter syndrome refers to the transformation of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma to an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL), a type of non-Hodgkin lymphoma. There are also rare cases in which a transformation to Hodgkin lymphoma has been described. Richter syndrome occurs in approximately 5% of patients with CLL, and the average time from diagnosis of CLL to transformation is approximately 2 to 5 years. Originally described in 1928 by Dr Maurice Richter, Richter syndrome is typically characterized by worsening adenopathy, the development or worsening of B symptoms, and rising levels of lactate dehydrogenase (LDH). Prognosis is typically poor, with a median survival of only 8 to 12 months.

H&O Could you describe the current first-line treatment for Richter syndrome?

NJ For Richter syndrome, the traditional treatment strategy has been intensive chemoimmunotherapy. In a study published in *Clinical Lymphoma, Myeloma & Leukemia* in 2013 from our center, data on the use of the chemoimmunotherapy regimen OFAR was reported, in which patients receive oxaliplatin, fludarabine, cytarabine, and rituximab (Rituxan, Genentech/Biogen Idec). A total of 35 patients were treated with this regimen and achieved a response rate of 43%, but the median survival with this regimen—and several other chemotherapy regimens—is less than 1 year.

Stem cell transplant remains the standard and only potentially curative option for patients with Richter

syndrome. All patients with Richter syndrome should have a consultation to consider undergoing stem cell transplant. Unfortunately, only 10% of all patients with Richter syndrome are eligible, because most patients do not have an adequate induction response to qualify for transplant. In addition, many patients are older and have comorbidities that precludes transplant as a viable option.

H&O Could you describe any new treatments currently in clinical trials for Richter syndrome?

NJ There have been several attempts to find new targeted therapies for these patients. A drug called KPT-330 is currently being studied for patients with lymphoma, and there is also a separate phase 2 trial designed for patients with Richter syndrome (NCT02138786). KPT-330 is an oral selective inhibitor of nuclear export (SINE) that specifically blocks exportin 1 (XPO1). There are several other potential new therapies that are in the pipeline; unfortunately, there are not many new treatment strategies for Richter syndrome in clinical trials at this time. There have been no randomized clinical trials for this condition; most studies have been single-arm phase 1/2 trials. In the future, we hope to see more targeted therapies in clinical trials for Richter syndrome, which will hopefully lead to improved clinical outcomes.

H&O Are there any new developments in the diagnosis of Richter syndrome?

NJ Yes, I think this is a very important topic. We typically are concerned about Richter syndrome in patients with CLL who have rapidly growing adenopathy, rising LDH levels,

hypercalcemia, and B symptoms (eg, fever and weight loss). To confirm the diagnosis of Richter syndrome, the first step is getting a positron emission tomography (PET) scan to examine the uptake of radioactive glucose in the areas of disease. In these cases, the site that has the maximum standardized uptake value (SUV), especially more than 5 SUV, is the one to biopsy. Every attempt should be made to biopsy the site with the maximum SUV. The type of diagnostic procedure is important. We published a study in the journal *Blood* in 2014 showing that tissue biopsy is more informative than a fine-needle aspirate in reaching a conclusive diagnosis. A biopsy is also helpful in distinguishing between Richter syndrome and other complications that can occur in patients with CLL, such as infections or progressive CLL.

H&O Are there any new studies on genetic changes that occur in Richter syndrome?

NJ In 2013, studies published in *Blood* and the *Journal of Experimental Medicine* reported on the genetic changes that occur in patients with Richter syndrome. The first study compared the genetic profiles of patients with CLL, the CLL phase prior to the development of Richter syndrome, Richter syndrome, and de novo DLBCL. The study found *TP53* inactivation, by either a mutation or a deletion, in the majority of patients at the time of transformation. The researchers also found activation of *C-MYC* and inactivation of *CDKN2A*, indicating possible cell cycle deregulation. These mutations occurred in approximately half of all Richter syndrome patients, and are likely the major mechanism of transformation. In one-third of the cases, they found trisomy 12 and *NOTCH1* mutations, which commonly occur together. These mutations were mutually exclusive to cases with *TP53* and *CDKN2A* mutations. Interestingly, both studies also noted that the genetic profile after Richter syndrome was distinct from de novo DLBCL.

H&O Are there any new predictive markers for the risk of developing Richter syndrome?

NJ Several features have been described in patients with CLL that lead to a higher rate of Richter syndrome; these can be broadly classified into clinical factors and biological factors. Clinical factors include a lymph node size of more than 3 cm, a large number of prior therapies, and advanced Rai stage (III-IV). Some studies have suggested that previous therapies increase the risk of transformation, including the use of alemtuzumab and the combination of purine analogues and alkylating agents. Biological factors include deletion (17p), deletion (11q), unmutated *IGHV* gene, short telomere length (<5000 bp), stereotyped B-cell receptors, and expression of CD38, CD49d, or ZAP-70.

A study in the *British Journal of Haematology* in 2012 investigated the risk associated with *NOTCH1* mutations in patients with CLL. They found that patients with a *NOTCH1* mutation have a 20% to 30% risk of Richter syndrome, compared with a 5% risk in patients without the *NOTCH1* mutation.

H&O Are there any new markers for prognosis after the patient has developed Richter syndrome?

NJ Several years ago, the MD Anderson group developed a Richter score, published in the *Journal of Clinical Oncology* in 2006. The score is based on Eastern Cooperative Oncology Group performance status (ECOG PS) (>1), elevated serum LDH (>1.5 × normal), low platelet count (<100 × 10⁹/L), larger tumor size (>5 cm), and the number of prior therapies (>1). One point was given for each risk factor, and the scores were divided into 4 different subgroups. The median survival ranged from 1 month to 1.1 years based on this Richter score.

In 2011, a study in *Blood* described a new grouping model for survival in Richter syndrome. They found that one of the most important predictors of survival in patients with Richter syndrome is the presence of *TP53* mutation or deletion (17p), which is associated with a worse outcome. They were able to characterize patients into 3 groups with different survival curves based on 3 factors: *TP53* disruption by a mutation or deletion, ECOG PS greater than 1, and remission status after treatment for Richter syndrome. The high-risk group included patients with a poor ECOG PS (>1) irrespective of *TP53* status and response to induction treatment. This high-risk group had a median survival of only 7.8 months. The intermediate-risk group of patients had a good ECOG PS (≤1), but had *TP53* disruption or did not achieve complete response after induction treatment. This intermediate-risk group had a median survival of 24.6 months. The low-risk group included patients with a good ECOG PS (≤1), no *TP53* disruption, and a complete response after induction treatment. This low-risk group had a 5-year survival rate of 70%.

One of the most important prognostic factors—not included in either scoring system—is whether the DLBCL after transformation is clonally related to the patient's original CLL. In 80% of patients, the DLBCL is clonally related to the original CLL, which is a marker of poor prognosis (median survival, approximately 1 year). In the other 20% of patients, the DLBCL is clonally unrelated to the original CLL—possibly representing a new neoplasm—and the prognosis is similar to de novo DLBCL (median survival, approximately 5 years). A useful future model for prognosis in Richter syndrome should include clonally related or unrelated status along with clinical and genetic risk factors.

H&O Are there any other drugs that might be promising for Richter syndrome in the future?

NJ Several drugs are currently being studied in patients with DLBCL that may also be useful for treating patients with Richter syndrome. One promising target is Bcl-2, which regulates cell death and is involved in a variety of cancers. ABT-199 is a selective Bcl-2 inhibitor that is in clinical trials for patients with CLL and DLBCL, and has early reported activity in some patients with Richter syndrome. Multiple signaling pathways are altered in Richter syndrome, and therefore could be therapeutically targeted. One such target is nuclear factor κ B (NF κ B), because patients with Richter syndrome commonly have activation of this pathway. Additionally, given the recent studies involving the high frequency of *NOTCH1* mutations in Richter syndrome, inhibition of this pathway could be used as a novel therapeutic approach.

As mentioned previously, KPT-330 is already in a phase 2 clinical trial for patients with Richter syndrome. This drug has shown activity in the phase 1 trial for patients with DLBCL, which included patients with Richter syndrome. Therapies that have been studied for patients with acute lymphoblastic leukemia also may be beneficial in patients with Richter syndrome. For example, blinatumomab (Blinicyto, Amgen) and inotuzumab target antigens CD19 and CD22, respectively, which are expressed on the surface of the Richter cells. I hope that

we will begin to test more new therapeutics in clinical trials in the near future, and that these will lead to improved outcomes in patients with Richter syndrome.

Suggested Reading

- Chigrinova E, Rinaldi A, Kwee I, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. *Blood*. 2013;122(15):2673-2682.
- Fabbri G, Khiabani H, Holmes AB, et al. Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome. *J Exp Med*. 2013;210(11):2273-2288.
- Falchi L, Keating MJ, Marom EM, et al. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. *Blood*. 2014;123(18):2783-2790.
- Parikh SA, Kay NE, Shanafelt TD. How we treat Richter syndrome. *Blood*. 2014;123(11):1647-1657.
- Rossi D, Gaidano G. Richter syndrome. *Adv Exp Med Biol*. 2013;792:173-191.
- Rossi D, Rasi S, Spina V, et al. Different impact of NOTCH1 and SF3B1 mutations on the risk of chronic lymphocytic leukemia transformation to Richter syndrome. *Br J Haematol*. 2012;158(3):426-429.
- Rossi D, Spina V, Deambrogi C, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood*. 2011;117(12):3391-3401.
- Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol*. 2006;24(15):2343-2351.
- Tsimberidou AM, Wierda WG, Wen S, et al; Chronic Lymphocytic Leukemia Research Consortium. Phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab therapy in aggressive relapsed/refractory chronic lymphocytic leukemia or Richter syndrome. *Clin Lymphoma Myeloma Leuk*. 2013;13(5):568-574.