Richter's Transformation in Chronic Lymphocytic Leukemia

Richter's transformation, or Richter's syndrome, is an uncommon clinicopathological condition observed in about 5% to 10% of patients with chronic lymphocytic leukemia (CLL). This review summarizes advances in our understanding of the pathobiology and in the management of Richter's transformation in patients with CLL.

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation and proliferation of monoclonal B cells with a characteristic immunophenotype (CD5-, CD19-, and CD23-positive; and FMC-7–, sIgG-, and CD20-diminished). CLL is the most common leukemia in adults in the Western world.[1] It is estimated that 16,060 persons (9490 men, 6570 women) will be diagnosed with CLL and 4580 patients will die of CLL in 2012 in the United States.[2] The median age at diagnosis of CLL is about 72 years, and CLL is predominantly a disease affecting older individuals.

Richter's transformation (or Richter's syndrome) is a clinicopathological term used to describe the rapid development of a histologically proven aggressive lymphoma in a patient with CLL.[3] The most common lymphoma seen in patients with Richter's transformation is diffuse large B-cell lymphoma.[4] Other rarer types of Richter's transformation that have been described are Hodgkin's variant of Richter's transformation,[5,6] composite lymphoma,[7] and very rarely, interdigitating dendritic cell sarcoma.[8] The development of lymphoma in CLL was originally reported by Maurice N. Richter in 1928,[9] and the term “Richter's syndrome” was coined in 1964 by Lortholary et al to describe the development of malignant reticulopathy in 14 patients with CLL.[3] Studies have shown that the diffuse large B-cell lymphoma that develops in Richter's transformation can be clonally related to the original CLL (true Richter's transformation; 78% of cases) or can be clonally unrelated diffuse large B-cell lymphoma (20% of cases).[10,11] It is unclear whether the clonally unrelated diffuse large B-cell lymphoma is a sequential lymphoma or a clonally unrelated transformation in patients with CLL. The term “composite lymphoma” is used whenever there is initial discovery of CLL and another lymphoma at the same time in the same tissue; composite lymphoma is different from Richter's transformation. Richter's transformation should also be differentiated from prolymphocytic transformation[12] and accelerated CLL (expanded proliferation centers without histologically proven large-cell lymphoma).[13]

Every year about 500 patients are diagnosed with Richter's transformation in the United States. The incidence rates of Richter's transformation range from 2% to 10% in most major studies.[4] The largest study of Richter's transformation was reported by investigators at the MD Anderson Cancer Center in 2006.[14] Of 3986 patients with CLL, 148 patients (3.7%) had a histologically proven Richter's transformation and 204 patients (5.1%) had possible Richter's transformation. Survival after Richter's transformation was reported to range from a few weeks to up to 15 years. Two other studies, one from Italy,[15] another from China,[16] have reported the percentage of Richter's transformation in CLL patients as 9% (17/185) and 10.7% (16/149), respectively. Richter's transformation can present at any time during the course of CLL. Development of Richter's transformation is dependent on intrinsic biological features of the initial CLL clone. In one study (with a uniform biopsy protocol), the cumulative incidence of Richter's transformation at 5 and 10 years exceeded 5% and 10%, respectively, and the median time to development of Richter's transformation was 23 months from the date of diagnosis of CLL.[15]

This review summarizes advances in our understanding of the pathobiology and in the management of Richter's transformation in patients with CLL.

Pathogenesis of Richter's Transformation

As mentioned earlier, the majority of patients with Richter's transformation develop diffuse large
B-cell lymphoma. Multiple immune and genetic factors can influence the development of Richter's transformation. The diffuse large B-cell lymphoma that arises from Richter's transformation is different from de novo diffuse large B-cell lymphoma in both clinical behavior and disease biology.

**Chromosomal aberrations**

Specific cytogenetic abnormalities/translocations are not seen in Richter's transformation. Non-del13q14 abnormalities in CLL cells are considered a risk factor for Richter's transformation. Chromosome 14q32 translocations, commonly seen in other non-Hodgkin's lymphomas (eg, 14;18 in follicular lymphoma and 11;14 in mantle cell lymphoma) are not observed in Richter's transformation.

**Molecular profiling**

In one study, a comprehensive molecular profiling of 84 patients with Richter's transformation was performed.[11] TP53 disruption (47.1%) and c-MYC abnormalities (26.2%) were the most common genetic lesions. Patients with Richter's transformation did not have the common mutations seen in de novo diffuse large B-cell lymphoma (eg, BCL2, BCL6, NF-kB pathway, CD79a and CD79b, and EZH2). The median survival for patients with TP53 mutations was 10 months, compared with 27 months in patients without TP53 mutations, while median survival with TP53 disruptions (deletion or mutations) was 9.4 months, compared with 47.1 months in patients without such disruptions. However, the presence of TP53 mutations at the time of diagnosis of CLL did not predict for a higher risk of Richter's transformation.

**Clonality analysis**

Diffuse large B-cell lymphoma that develops in patients with Richter's transformation can be either clonally related or unrelated to the original CLL clone. Clonally related Richter's transformation and clonally unrelated Richter's transformation differ in many respects—and clonally unrelated Richter's transformation is also different from de novo diffuse large B-cell lymphoma. Figure 1 depicts the outline of the development of clonally related/unrelated diffuse large B-cell lymphoma in patients with CLL.[17] Immunoglobulin heavy chain (IGHV) gene sequencing by polymerase chain reaction (PCR) is useful in determining the clonality in patients with Richter's transformation.[10] Clonally unrelated Richter's transformations have a lower prevalence of TP53 disruption, stereotyped V<sub>H</sub> CDR3, and a higher prevalence of mutated IGHV. Patients with clonally unrelated Richter's transformation have a longer survival than patients with clonally related diffuse large B-cell lymphoma (true Richter's transformation).[11]

**EBV infection**

Some reports have suggested the presence of Epstein-Barr virus (EBV) in the large cells of Richter's transformation patients,[18,19] but conclusive evidence demonstrating a cause-effect relationship is lacking. EBV infection was more commonly associated with Hodgkin's variant Richter's transformation than with the common diffuse large B-cell lymphoma Richter's transformation.[20]

**Activation-induced cytidine deaminase**

This enzyme is responsible for somatic hypermutation and class-switch recombination in B cells. Any defect in somatic hypermutation caused by aberrancy in actions of activation-
induced cytidine deaminase can lead to lymphomagenesis. In Richter's transformation, the pathological relevance of mutations in activation-induced cytidine deaminase is not clear, whereas in de novo diffuse large B-cell lymphoma, activation-induced cytidine deaminase is known to cause aberrant somatic hypermutation, thus activating proto-oncogenes such as \textit{c-MYC}.

**Cell-cycle dysregulation**

The deletion of the \textit{Rb} gene, loss of cell-cycle inhibitors CDKN1A and CDKN2A, and increased copy numbers of the \textit{MYC} gene also contribute to transformations in CLL.

**Predisposing Factors for Richter's Transformation**

Extensive studies of genomic changes occurring in Richter's transformation were reported by Rossi et al.[11,21] Factors that were seen to predispose to Richter's transformation were different from the risk factors associated with CLL progression. Specific guidelines for interventions in patients having risk factors for Richter's transformation are not yet available.

A pilot study reported by Rossi et al in 2008[15] involving 185 CLL patients and paired samples (CLL and Richter's transformation in the same patient) has shown that the following factors[22] predispose to Richter's transformation in a patient with CLL. (Detailed discussions of the pathological mechanisms behind these factors are beyond the scope of this article.)

1. \textit{CD38} expression (CD38 ≥ 30%)
2. Stereotyped B-cell receptor
3. \textit{IGHV4-39} gene usage
4. Telomere length < 5000 base pairs
5. Lymph node size > 3 cm
6. Absence of del13q14

Other studies have reported on polymorphisms with \textit{CD38} and \textit{LRP4} genes. \textit{CD38} GG homozygous patients had a 30.6% increased risk compared with the risk in patients having the GC or CC genotype[23] and patients having the \textit{LRP4} TT genotype (which is related to Wnt signaling pathways in CLL).

\textit{NOTCH1} mutations were recently shown to predict for the development of Richter's transformation, while \textit{SF3B1} mutations did not.[24]

Currently, there is no evidence that treatment with purine analogues (fludarabine, cladribine), alone or in combination with cyclophosphamide and rituximab (Rituxan), can increase the risk of Richter's transformation in patients with CLL.[25]

**Prognostic Factors in Richter's Transformation**

In 2006, one of the largest studies in patients with Richter's transformation (n = 148) proposed a prognostic scoring system (Richter's transformation Score).[14] Five factors that significantly predicted for poor outcome in patients with Richter's transformation were:

- Zubrod performance status > 1
- Elevated lactate dehydrogenase (LDH) levels (> 1.5 times normal)
- Platelet count < 100 × 109/L
- Tumor size > 5 cm
- Prior therapies > 1

Patients were divided into low-, low-intermediate–, high-intermediate–, and high-risk categories based on the number of risk factors at the time of presentation (identified by scores of 0–1, 2, 3, and 4–5, respectively). Median survival of patients in low-, low-intermediate–, high-intermediate–, and high-risk categories was 1.12, 0.9, 0.33, and 0.2 years, respectively (Figure 2).
Survival in 130 Assessable Treated Patients in the Study of Richter's Transformation From Which a Prognostic Scoring System Was Developed

Histopathology of Richter's Transformation

Biopsy of the involved site (core needle/excisional) is necessary to confirm the diagnosis of RT. Morphologically, specimens from Richter's transformation show large atypical cells with centroblastic/immunoblastic morphology. The majority (about 80%) of diffuse large B-cell lymphoma cases in Richter's transformation displays a post-germinal center (GC) phenotype (MUM1/IRF4 expression) and only a few cases will show a GC variety (CD10 and BCL6 expression). CD20 expression is generally bright, while CD5 and CD23 expression may be dim to negative in Richter's transformation. The proliferation marker Ki-67 can be highly expressed in large cells of Richter's transformation. Rarely, Richter's transformation can also present with a Hodgkin's variant with Reed Sternberg (R-S) cells, with expression of CD15 and CD30 by the R-S cells similar to that seen in de novo Hodgkin's disease.[10]

Approach to a Patient With Suspected Richter's Transformation

Suspect Richter's transformation when a patient with CLL presents with a rapidly deteriorating clinical profile and enlargement of lymph nodes, prominent B symptoms (night sweats, weight loss, fever without infection), and extranodal involvement (such as involvement of the central nervous system, skin, stomach, testes, eyes, or lungs).[26] Pancytopenia is common. Elevated LDH levels are common. Hypercalcemia with or without lytic bone lesions and monoclonal gammopathy can also be seen.

Imaging

PET-CT (positron emission tomography–computed tomography) scanning may be quite helpful in diagnosing Richter's transformation. An abnormal increase in uptake of the tracer 18F-FDG (18-fluorodeoxyglucose, a glucose analogue) on PET-CT with standardized uptake value (SUV) > 5 is highly suggestive of the development of Richter's transformation. In a study of 37 patients with CLL,[27] 11 patients developed Richter's transformation, and PET-CT scanning detected Richter's transformation with a sensitivity, a specificity, and positive and negative predictive values of 91%, 80%, 53%, and 97%, respectively. Particular attention to the following factors is needed when examining results from PET-CT scans for evidence of suspected Richter's transformation:

• False-positive results can be caused by granulomas, additional malignancies, or infections.
• A uniform method of calculating SUV from the same instrument must be used.
• Poor scanner quality control can result in false-positives.
• Chemotherapy and other immunotherapies increase the likelihood of false-positive PET results.[28]
• Attention must be paid to the type of chemotherapy administered: one study showed that a negative biopsy following a positive PET-CT scan was fairly common after dose-intense chemotherapy.[29]

• Rigorous quality control must be maintained to compensate for variability in data acquisition and image reconstruction.
• Newer biologic agents may inhibit glucose uptake and thus may reduce SUV.

Routine use of PET-CT in clinical practice to detect Richter's transformation in CLL is not necessary.[28] Nevertheless, PET-CT can indicate a site of Richter's transformation amenable to biopsy, since all nodes may not be involved. Biopsy with a pathologic diagnosis remains the gold standard for diagnosing Richter's transformation. Gallium-67 scanning was used in the past to differentiate Richter's transformation from CLL, but is of limited value in the current era.
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Survival in Patients With Richter’s Transformation Who Underwent Stem-Cell Transplantation, According to Type of Transplant and Disease Status at the Time of Transplant

**Differential Diagnosis**

The clinical presentation of Richter's transformation can easily mimic the conditions listed below. Differentiation of these conditions from Richter's transformation is dependent on proper histopathological evaluation of the involved nodal or extranodal site. It is important to distinguish such conditions from Richter's transformation, since the management and outcomes are different.

**Accelerated CLL**

Proliferation centers are the hallmark of lymphoid tissues involved in CLL. Accelerated CLL is diagnosed when patients exhibit expanded proliferation centers (PC) broader than a 20× field and a high proliferation rate (either > 2.4 mitoses/proliferation center or Ki-67 > 40%/proliferation center). Patients usually have higher LDH levels, and CLL cells express ZAP-70. The median survival of patients with accelerated CLL vs those with Richter's transformation was 34 months and 4.3 months, respectively.[13] Data regarding the treatment options appropriate for accelerated CLL are lacking.

**Hodgkin's variant of Richter's transformation**

This is a rare entity.[6] Most patients have the mixed cellularity variant on biopsy. Hodgkin's variant of Richter's transformation is associated with EBV positivity. The R-S cells in Hodgkin's variant of Richter's transformation have higher CD20 expression. Chemotherapy regimens used in treating Hodgkin's lymphoma are associated with poorer outcomes as compared to the outcomes seen in primary Hodgkin's lymphoma.[30,31]

**Prolymphocytic transformation**

These patients have increased prolymphocytes (> 55%) with positive CD5, CD23 expression, and weak CD22 and CD79b (a feature differentiating this entity from de novo B-cell prolymphocytic leukemia [B-PLL]). The prognosis of prolymphocytic transformation is poor. Therapy usually is similar to that for B-PLL, incorporating alemtuzumab (Campath), rituximab-based purine analogue combinations, and allogeneic stem-cell transplantation (SCT).[12,32]

**EBV-associated lymphoproliferative disorder**

Patients with CLL have inherent immune defects that are compounded by the effects of chemotherapy. Purine analogues and monoclonal antibodies such as alemtuzumab can predispose to the reactivation of EBV in lymphoid tissues. Patients with EBV-associated lymphoproliferative disorder may present with rapidly enlarging lymph nodes and progressive clinical symptoms. Histopathological evaluation mimics that of age-related diffuse large B-cell lymphoma of the elderly[33] or a classical Hodgkin's lymphoma, but these entities can be distinguished from EBV-associated lymphoproliferative disorder by expert hematopathologists (by means of the presence of other markers of diffuse large B-cell lymphoma, such as immunoblastic, centroblastic morphology and MUM1/CD10/bcl2/bcl6 expression in monoclonal B cells). In EBV-associated lymphoproliferative disorder, the morphology is polymorphous, with predominant geographic necrosis. The disease course of EBV-associated lymphoproliferative disorder is highly variable, ranging from spontaneous regression to the need for therapy (eg, single-agent rituximab or arginine butyrate therapy with cidofovir). Of note, misdiagnosis of this entity may lead to unnecessary administration of intensive chemotherapy for diffuse large B-cell lymphoma.[34,35]

**Therapeutic Options**

Richter's transformation in CLL has a rapidly progressive clinical course with extensive tumor burden and widespread or localized extranodal and nodal involvement. Treatment options are usually limited, because of the chemo-refractoriness of the lymphomatous cells (due to TP53 mutations), rapid cell turnover, and poor performance status of the patients.[14]

**Chemotherapy and chemo-immunotherapy**

In the pre-rituximab era, Richter's transformation was treated similarly to high-grade lymphomas—with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-based
regimens, ESHAP (etoposide [Vepesid], methylprednisolone, cytarabine, and cisplatin), FACPGM (fludarabine, cytarabine, cyclophosphamide, cisplatin, and granulocyte macrophage colony-stimulating factor [GM-CSF]),[36] etc. About one-third of patients respond to the foregoing regimens. With the addition of rituximab to HyperCVXD (hyperfractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone), alternating with methotrexate and ara-C, the response rates were similar to the rates achieved with CHOP, other earlier regimens, and HyperCVXD.[37] The complete remission (CR) rate was 38% with HyperCVXD. Similarly, with HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) plus rituximab (R-HyperCVAD) alternating with methotrexate and ara-C, the response rate was 43%, with a CR rate of 27%.[38] In a retrospective single-center study, the response rates seen with chemotherapy and chemo-immunotherapy were not significantly different. Median survival with both chemotherapy and chemo-immunotherapy was less than 10 months. Of note, higher response rates were observed in patients who had a platelet count >100 ×10^9/L, performance status of 0 or 1, a hemoglobin level > 11 g/dL, and β2 microglobulin < 6 mg/L.[14] In 2008, a phase II study reported responses with the OFAR regimen (oxaliplatin, fludarabine, cytarabine, and rituximab) in 20 patients with RT.[39] This combination was developed after preclinical studies showed synergism between oxaliplatin, fludarabine, and cytarabine. The overall response rate (ORR) was 46%. Fifty percent of patients aged > 70 years responded, and grade 3/4 toxicities were minimal. The median duration of response was 10 months. Another study from the same group reported on the OFAR2 regimen in 15 patients with Richter's transformation.[40] In OFAR2, the oxaliplatin dose was increased and the cytarabine dose was decreased. The responses seen with OFAR2 were not superior to the rate achieved with the OFAR regimen. In a small trial of 15 patients with Richter's transformation, R-CHOP (rituximab plus CHOP) produced an ORR of 67% and progression-free survival of 15 months.[41] A smaller series of seven patients with Richter's transformation were given 90Y ibritumomab tiuxetan; no patients responded.[42] Treatment regimens in Richter's transformation are similar to each other in their response rates and have not improved outcomes.

Stem-cell transplantation

Two studies have reported improved outcomes with stem-cell transplantation in patients with Richter's transformation who achieved remission with chemotherapy. In one study of 20 patients who underwent transplantation, the estimated 3-year cumulative survival was 75% for responding patients with Richter's transformation and 21% for patients who received stem-cell transplantation as salvage therapy after failing chemotherapy.[14]

Recently, another study from the European Group for Blood and Marrow Transplantation (EBMT) in 59 patients with Richter's transformation showed that 3-year probabilities of overall survival and relapse-free survival, and the cumulative incidences of relapse and non-relapse mortality were 36%, 27%, 47%, and 26% for allogeneic SCT, and 59%, 45%, 43%, and 12% for autologous SCT, respectively.[43] Thus, stem-cell transplantation can be considered as a consolidation strategy in chemo-sensitive and physically fit patients with Richter's transformation.

Clinical trials

None of the current regimens have improved response rates in Richter's transformation. One ongoing clinical trial in Richter's transformation is testing ofatumumab (Arzerra) in combination with CHOP (O-CHOP) as induction, and ofatumumab as maintenance treatment.

Summary

Richter's transformation is a biologically heterogeneous condition. The clinical course is aggressive, with low response rates and poor outcomes with the currently available chemotherapeutic regimens. Thus, there is no standard of care in the treatment of Richter's transformation. Identification of predictive markers, such as CD38 GG genotype, IGHV mutational status, V_{H}4-39 gene usage, non-del13q chromosomal abnormalities, and bulky disease at the time of diagnosis may help in early identification of patients who are at risk for developing Richter's transformation. Intensive chemo-immunotherapy is used to treat patients after confirming the diagnosis of Richter's transformation. Stem-cell transplantation for responding patients is warranted. The relevance of maintenance therapy in Richter's transformation is unknown. Other directions for future research would be to explore combinations of B-cell receptor inhibitor agents such as ibrutinib (Bruton tyrosine kinase inhibitor) or GS-1101 (phosphoinositol-3 kinase δ inhibitor) with intensive chemotherapy, or to use lenalidomide (Revlimid) and/or rituximab maintenance. The identification of
newer and targetable mechanisms of CLL transformation may pave the way for improving responses in Richter's transformation.

The Approach to a Patient With Suspected Richter's Transformation That We Recommend

1. Keep in mind that rapidly progressive B symptoms; bulky lymphadenopathy; organomegaly; anemia; a low platelet count; and elevated serum LDH, calcium, and β2 microglobulin levels in a patient with CLL can suggest Richter's transformation.
2. Obtain imaging by whole-body PET-CT scan to pinpoint the area for diagnostic biopsy (SUV > 5).
3. Confirm the diagnosis of Richter's transformation by biopsy of lymph nodes, bone marrow, or involved organs.
4. Initiate treatment with chemo-immunotherapy. Although there is no specific evidence to support any specific regimen, we generally recommend rituximab with HyperCVAD.
5. Evaluate for a possible stem-cell transplantation.

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