Seminars in Oncology ▮ (2016) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/ysonc

Richter syndrome: pathogenesis and management

Davide Rossi*, Gianluca Gaidano

Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy

ARTICLE INFO

Keywords:
Richter syndrome
Chronic lymphocytic leukemia
Diffuse large B-cell lymphoma
NOTCH1
Subset 8

ABSTRACT

Richter syndrome (RS) is the development of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL). The incidence rate RS is ~0.5% per year of observation. Two biomarkers (*NOTCH1* mutations and subset 8 configuration of the B-cell receptor) may help identifying CLL patients at risk of RS to be considered for close monitoring and a careful biopsy policy. In the presence of clinical features suspicious of RS, diagnosis of transformation and choice of the site of biopsy may take advantage of fluorine 18 fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET)/computed tomography (CT). Molecular lesions of regulators of tumor suppression (*TP53*), cell cycle (*CDKN2A*), and cell proliferation (*NOTCH1*, *MYC*) overall account for ~90% of RS and may be responsible for the aggressive clinical phenotype observed in this disease because of the combined effect of chemoresistance and rapid disease kinetics. The prognosis of RS is generally highly unfavorable. However, the pattern of survival is not homogeneous and the most important prognostic factor is the clonal relationship between the CLL and the aggressive lymphoma clones. Rituximab-containing polychemotherapy represents the backbone for induction treatment in RS. Younger patients who respond to induction therapy should be offered stem cell transplant (SCT) to prolong survival.

1. Definition of Richter syndrome

The 2008 World Health Organization (WHO) Classification of Hematopoietic Tumors defines Richter syndrome (RS) as the development of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL) [1]. The WHO classification recognizes two distinct pathologic variants of RS, namely the diffuse large B-cell lymphoma (DLBCL) variant and the Hodgkin lymphoma (HL) variant [1].

Morphologically, the DLBCL variant of RS consists of confluent sheets of large neoplastic B lymphocytes resembling either centroblasts (60%–80% of cases) or immunoblasts (20%–40% of cases) [2–4]. Importantly, CLL cases presenting with numerous proliferation centers and an increased proportion of prolymphocytes and paraimmunoblasts, but lacking clear cut features of DLBCL, should not be diagnosed as RS [5]. Phenotypically, tumor cells invariably express CD20, while CD5 expression is present in only a fraction (~30%) of cases, and CD23 expression is even more rare (~15% of cases) [2]. Based on immunophenotypic markers of de novo DLBCL, most cases of the DLBCL variant of RS (90%–95%) have a post-germinal center phenotype (IRF4-positivity), whereas only 5%–10% display a germinal center phenotype (CD10 and/or BCL6 expression) [2–4].

The HL variant of RS can be further subdivided in two pathologic types [6,7]. Type 1 usually mimics the pathologic features of classical HL, being characterized by the presence of mononuclear Hodgkin cells and multinuclear Reed-Sternberg cells residing in a polymorphous background of small T cells, epithelioid histiocytes, eosinophils, and plasma cells. In type 1, the Hodgkin-Reed-Sternberg cells show the typical CD30$^+$/CD15$^+$/CD20$^-$ phenotype. In contrast, type 2 is characterized by the presence of Hodgkin-Reed-Sternberg-like cells in a background of CLL cells lacking the polymorphous reactive infiltrate of classic HL. In type 2 transformation, Hodgkin-Reed-Sternberg-like cells express both CD30 and CD20 but lack CD15.

Based on the analysis of the rearrangement of *IGHV-D-J* genes, most (~80%) of the DLBCL variants of RS are clonally related to the preceding CLL phase, thus representing true transformation [2–4]. In contrast, only a fraction (~40%–50%) of the HL variants of RS are clonally related to CLL [2,8–10]. Consistently, a number of RS (~20% showing a DLBCL morphology and ~50%–60% showing a classical HL morphology) harbor distinct *IGHV-D-J* rearrangements compared to the paired CLL, representing de novo lymphomas arising in a CLL patient [2–4,8–10].

2. Epidemiology of Richter syndrome

Information about the prevalence of RS in unselected CLL populations mainly derives from analyses of retrospective cohorts of patients. The large variation in the prevalence of RS (1%–23%) in

* Corresponding author. Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Via Solaroli 17, 28100 Novara, Italy. Tel.: +39 0321 660 698; fax: +39 0321 620 421.
E-mail address: rossidav@med.unipmn.it (D. Rossi).

http://dx.doi.org/10.1053/j.seminoncol.2016.02.012
0093-7754/

Table 1
Summary of the published reports assessing the frequency of Richter syndrome transformation.

Reference	Study design	CLL patients included in the study	Study population	Treatment	Patients that developed RS	RS prevalence	RS type
Maddocks-Christianson, 2007 [16]	Retrospective	962	Unselected	na	14	1%	Any
Robak, 2004 [14]	Retrospective	1487	Unselected	na	15	1%	Any
Byrd, 2014 [26]	Clinical trial	391	Relapsed	Ibrutinib, ofatumumab	4	1%	Any
Catovsky, 2007 [18]	Clinical trial	777	Progressive untreated	Clb, F, FC	13	2%	Any
Mauro, 1999 [13]	Retrospective	1011	Unselected	na	22	2%	Any
Parikh, 2013 [23]	Observational	1641	Unselected	na	37	2%	DLBCL
O'Brien, 2014 [27]	Clinical trial	29	Progressive untreated	Ibrutinib	1	3%	Any
Tsimberidou, 2006 [17]	Retrospective	3986	Unselected	na	148	4%	Any
Fisher, 2012 [21]	Clinical trial	817	Progressive untreated	FC, FCR	33	4%	Any
Jain, 2015 [30]	Clinical trial	127	Relapsed/refractory	Ibrutinib	7	5%	Any
Alipour, 2008 [19]	Retrospective	465	Unselected	na	24	5%	Any
Tabuteau, 1999 [12]	Retrospective	620	Unselected	na	37	6%	Any
Farooqui, 2015 [29]	Clinical trial	51	17p deleted	Ibrutinib	3	6%	Any
Keating, 1998 [11]	Clinical trial	174	Progressive untreated	F	13	7%	Any
Solh, 2013 [24]	Clinical trial	521	Progressive untreated	Clb, F, Clb+F	34	7%	Any
Byrd, 2013 [22]	Clinical trial	85	Relapsed/refractory	Ibrutinib	7	8%	Any
Benjamini, 2014 [25]	Clinical trial	234	Progressive untreated	FCR	21	9%	Any
Rossi, 2009 [3]	Retrospective	783	Unselected	na	69	9%	DLBCL
Rossi, 2008 [20]	Retrospective	185	Unselected	na	17	9%	DLBCL
Thornton, 2005 [15]	Retrospective	101	Unselected	na	12	12%	Any
Strati, 2014 [28]	Clinical trial	63	17p deleted	Heterogeneous	15	23%	Any
Parikh, 2015 [31]	Observational	3887	Unselected	na	26	0,7%	HL

CLL, chronic lymphocytic leukemia; RS, Richter syndrome; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma, na, not available; Clb, chlorambucil; F, fludarabine; C, cyclophosphamide; R, rituximab

these historical series is due to heterogeneity in patient populations, length of follow up, whether the analysis was restricted to biopsy-proven cases or also included patients with clinically suspected transformation, and how aggressively biopsies were pursued in patients with rapidly progressive lymphadenopathy (Table 1) [3,11–31]. Among CLL patients included in clinical trials, the prevalence of RS ranges from 2%–7%. However, also these rates must be interpreted with caution because they are derived from selected CLL patients who progressed to require treatment, fit the eligibility criteria for trial participation, and in which the therapy used may have influenced the risk of transformation (Table 1). Though not specifically designed towards this aim, one single prospective observational cohort study reported the incidence of biopsy proven RS in unselected CLL, thus providing the more accurate estimation of the risk of this complication. According to this study, the incidence rate of the DLBCL variant of RS is ~0.5% per year of observation, while the incidence rate of the HL variant of RS is 10 fold lower and of ~0.05% per year of observation [23,31]. The median interval between CLL diagnosis and development of the DLBCL variant of RS is ~2 years, indicating that this can be a relatively early complication of CLL which may also occur in previously untreated patients. Conversely, the HL variant of RS occurs later at a median of ~6 years from CLL diagnosis and mainly among previously treated patients [23,31].

3. Risk factors associated with the development of Richter syndrome

Early recognition of RS transformation may be clinically useful in order to avoid the exposure of patients to multiple lines of therapy that, being targeted to CLL progression, are of little efficacy for the transformed clone. This concept prompts the need for a close monitoring of CLL patients harboring risk factors of RS development. Advancements in the field have unraveled a number of characteristics of the tumor, and possibly also of the host, that predispose CLL to subsequently transform into the most common DLBCL variant of RS. Because the incidence of the HL variant of RS is very low, risk factors predisposing to this condition are currently unknown and their identification is limited by the small sample size of the available cohorts.

3.1. Genetic background

Hereditable polymorphisms of the *BCL2* (rs4987852), *CD38* (rs6449182), and low-density lipoprotein receptor-related protein 4 (*LRP4;* rs2306029) genes predispose certain individuals with CLL to subsequent development of RS [32–34]. The risk of RS associated with these variants is modest, an observation that is consistent with the low penetrance of polymorphisms. The precise functional consequences of germline polymorphisms in the pathogenesis of RS remain to be elucidated. Also, the search of risk alleles for RS has so far followed a candidate gene strategy. Genome wide association studies investigating risk alleles on a genomic scale are warranted to unravel germline polymorphisms associated with RS in previously unstudied genes or even in non-coding regions.

3.2. Clinical features of CLL

CLL patients presenting with bulky extensive lymphadenopathy have a 10-fold increased risk of developing RS. Other clinical features commonly used to predict CLL progression, including rapid lymphocyte doubling time, pattern and percentage of bone marrow involvement, elevated β_2- microglobulin, and elevated lactate dehydrogenase (LDH), have not been found to reliably predict subsequent RS [15,16,20,23]. This observation documents that RS development and CLL progression without histologic transformation are distinct clinical events, that require a different, though complementary, diagnostic approach for a comprehensive assessment of the risk category of the individual patient.

3.3. Biological features of CLL

The risk of RS development is strongly affected by the somatically acquired genetic lesions harbored by the CLL clone, in particular by the presence of *NOTCH1* mutations, and by the expression of specific molecules facilitating the interaction