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Biology of Double-Hit B Cell Lymphomas

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Abstract

Purpose of review—Mature B cell lymphomas bearing concurrent chromosomal rearrangement of *MYC*/8q24 and *BCL2*/18q21 are associated with an aggressive clinical course and resistance to conventional chemotherapy. This review summarizes the recent literature regarding the clinical and pathologic features of Double-hit lymphomas and outlines current questions about the most accurate and inclusive definition of the disease.

Recent findings—Comprehensive evaluation of large series of aggressive mature B cell neoplasms reveals recurrent chromosomal aberrations in the majority of cases. A subset of these lymphomas harbors multiple rearrangements, including *MYC*/8q24 in combination with *BCL2*/18q21 and/or *BCL6*/3q27, and displays a particularly aggressive clinical course. Recent data suggest that consideration of additional features, such as copy number alteration, quantitative protein expression, and biologic pathway activation may be important in deriving a more accurate definition of Double-hit lymphoma. Despite the poor prognosis associated with this subset of lymphomas, there remains no evidence for a risk-adapted treatment strategy and no clinical, pathologic, or genetic factors predict response to therapy.

Summary—“Double-hit lymphoma” remains an incompletely characterized disease entity. Large, multicenter studies are needed to define relevant clinical, genetic, and pathologic variables and to characterize appropriate risk-adapted treatment strategies.

Keywords

Lymphoma; double-hit; MYC; BCL2; BCL6

INTRODUCTION

The term ‘double-hit’ lymphoma was initially used to describe mature B cell neoplasms bearing concurrent rearrangements of the *BCL2*/18q21 and *MYC*/8q24 loci. Though relatively rare, double-hit lymphomas have been the subject of intensified investigation due to their aggressive clinical course and resistance to conventional chemotherapy [1–8]. As clinical and molecular evidence accumulates, ‘double-hit lymphoma’ has been broadened to include any aggressive, mature B cell neoplasm with a chromosomal breakpoint affecting the *MYC* locus and one or more additional rearrangements recurrently associated with lymphoma, most commonly *BCL2*, *BCL6* or *CCND1* [9,10]. Moreover, recent analysis of copy number alterations and pathway mutations prompt consideration of an expanded definition of clinically relevant double-hit lesions [8,11*,12, 13**].

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THE INCIDENCE AND EVOLVING DEFINITION OF DOUBLE-HIT LYMPHOMA

Initial case series have proven invaluable in defining double-hit lymphoma as an important disease entity with distinctive clinical behavior. However, recent data from larger series of unselected patients suggest that the true incidence of double-hit lymphomas may be revealed only by comprehensive molecular analysis. Barrans, et al. evaluated the frequency of *MYC*, *BCL2*, and *BCL6* rearrangements in a population-based cohort of 303 patients with previously untreated, *de novo* diffuse large B cell lymphoma, the majority of whom received R-CHOP chemotherapy [14**]. 245 were evaluable at the *MYC* locus and of these 35 (14%) were found to have *MYC*/8q24 rearrangements. Of those with *MYC* rearrangements, 83% (29/35) had concurrent abnormalities of *BCL2*/18q21 and/or *BCL6*/3q27. The majority of multiple-hit cases in this series were ‘classic’ *MYC*/*BCL2* double-hit (19/29), while the remaining were either *MYC*/*BCL6* double-hit (3/29) or *MYC*/*BCL2*/*BCL6* triple-hit (7/29).

Foot and colleagues provided an unbiased assessment of *MYC*/8q24, *BCL2*/18q21, and *BCL6*/3q27 status in a prospective, sequential series of aggressive and high-grade B cell non-Hodgkin lymphomas (n = 162) [13**]. Using comprehensive FISH analysis on formalin-fixed paraffin-embedded tissue sections, they evaluated for rearrangement and increased copy number (ICN), with a 99% technical success rate. Importantly, all new cases of aggressive B cell NHL, regardless of histology, were included in the study, with the exception of those meeting current WHO criteria for Burkitt Lymphoma. The majority of cases were defined per current WHO classification as DLBCL, not otherwise specified (n = 121) with other cases representing a range of histologies, including Intermediate BL/DLBCL (n = 23) and DLBCL as post-transplant lymphoproliferative disorder (n = 9). It should be noted that in this study, all cases of double-hit lymphoma were automatically classified as intermediate BL/DLBCL based on genetic features, independent of morphology.

In this study, abnormalities of *MYC*/8q24, *BCL2*/18q21, or *BCL6*/3q27 were remarkably common, with rearrangements and/or ICN detectable in 74% of cases of cases. Rearrangements involving *MYC*/8q24 (22%) were most frequent, followed by *BCL6*/3q27 (18% conclusive; 5% abnormal but not conclusive) and *IGH-BCL2* (18%). Double-hit lymphomas, defined by concurrent rearrangements of *MYC* and either *BCL2* or *BCL6*, were diagnosed in 14% of cases. The prevalence of copy number increase (3–6 copies) or amplification (>6 copies) was striking, and was found at *MYC*/8q24 in 19% of samples, *BCL2*/18q21 in 31%, and *BCL6*/3q27 in 22%. Since clinical data were not included in this analysis, the clinicopathologic features and prognostic implications of ICN relative to chromosomal rearrangement are unknown. Further, the frequency of cases harboring concurrent copy number alterations at multiple loci or a combination of rearrangement and ICN was not reported.

These studies raise important questions about the most accurate, inclusive, and clinically relevant definition of double-hit lymphoma. Indeed, there is some evidence to suggest that copy number alteration of *MYC*/8q24 and *BCL2*/18q21 may have clinical consequences that are indistinguishable from rearrangements of these loci [8,11*,12]. Increased *MYC* copy number has been correlated with increased mRNA level in DLBCL, suggesting that the functional consequence of enforced *MYC* expression, independent of the specific genetic lesion, is most relevant to disease biology [15].

Results from the recent next generation sequencing studies have raised similarly provocative questions about a more biologic definition of double-hit lymphoma. Using whole exome sequencing followed by targeted resequencing, a number of recurrent point mutations were identified in DLBCL [16*]. Among these, oncogenic mutations in *MYC* (6.3%) and

mutations in *BCL2* (9.0%) were identified, confirming previous results showing accumulation of mutations in *MYC* and other proto-oncogenes [17]. Though mutations in *BCL6* were not reported in this study, 11.7% of cases harbored inactivating mutations in *PRDM1*, a target of *BCL6* repression required for terminal B cell differentiation. Notably, biallelic inactivation of *PRDM1* was found to be mutually exclusive of *BCL6* rearrangement, suggesting a functional equivalence of enforced *BCL6* expression and abrogated *PRDM1* activity.

B cell lymphomas with more than two lymphoma-specific chromosomal abnormalities, so called triple- or quadruple-hit lymphomas have been described [12, 13**,14**,18–20]. In their unselected series, Foot and colleagues reported that among cases with multiple abnormalities (14.4% of total), 30% harbored concurrent aberrancies of *MYC*, *BCL2*, and *BCL6* [13**]. Similarly, Tomita, et al. found additional *BCL6* rearrangements in 26% of cases of *MYC/BCL2* double-hit lymphoma [18].

CLINICOPATHOLOGIC FEATURES

Double-hit lymphomas bearing concurrent rearrangements of *MYC*/8q24 and *BCL2*/18q21 are clinically distinct from Burkitt Lymphoma and DLBCL. The median age of diagnosis of *MYC/BCL2* double-hit lymphomas is in the 6th–7th decade, significantly older than sporadic BL (4th decade) and younger than DLBCL (7th decade) [3,7,8,21]. Across series, *MYC/BCL2* double-hit lymphomas tend to present with advanced stage (Ann Arbor III/IV), high or high-intermediate International Prognostic Index (IPI), and increased LDH. There is a high frequency of extranodal disease, most commonly involving bone marrow/peripheral blood, central nervous system, or pleural effusions. When compared to IPI-matched DLBCL, only younger age (64 vs. 71 years), higher median LDH at presentation (727 U/L vs. 366 U/L), and increased frequency of bone marrow involvement (59% vs. 23%) are significantly associated with *MYC/BCL2* double-hit lymphomas [8].

On routine cytogenetic analysis, double-hit lymphomas nearly always possess complex karyotypes, as defined by >2 numerical and/or structural aberrations [8,11*,18]. This context of chromosomal complexity is thought to be critical in determining the biological and clinical effects of *MYC* rearrangement. In fact, aggressive B cell lymphomas with *MYC* rearrangement and complex karyotype are associated with poor clinical outcomes, independent of documented second-hit lesions [22]. However, a subset of these patients may harbor cryptic second-hit lesions that escape detection by FISH and routine cytogenetics, as suggested by recent RNA-sequencing analysis [23*].

The median proliferation index of double-hit lymphomas approaches 90% [10]. Recent series have confirmed this observation, but noted a wide range of proliferative index (40–100%), even in disease that otherwise behaves in a clinically aggressive manner [11*]. In an unselected series, nearly 20% of samples with *MYC* rearrangements had a proliferative index <80% [13**]. Together, these data suggest that a relatively low proliferative index should not itself deter full evaluation for double-hit lesions.

With increasing recognition of the incidence and prognostic importance of double-hit lymphomas, several groups have performed comprehensive FISH analysis in specific populations of B cell NHL. In a retrospective study of aggressive B cell lymphomas of the GI tract, *MYC* rearrangements were identified in 22% of cases, 61% of which were Burkitt Lymphoma. *MYC* rearrangements were rarely associated with concurrent rearrangement of *BCL6* (8%) and never with *BCL2* [24*], suggesting a restricted distribution of extranodal disease sites in double-hit lymphoma. In a population-based pediatric cohort, *MYC* rearrangements were found in 44% (7/16) of cases not meeting criteria for Burkitt lymphoma, only two of which were found to have concurrent *BCL6* ICN [25*]. No cases

with aberrancies of the *BCL2* locus were identified, consistent with previous reports demonstrating absence of t(14;18)(q32;q21) in pediatric DLBCL [26].

MORPHOLOGIC CLASSIFICATION

Double-hit lymphomas are, in principle, defined genetically and represent a morphologic continuum between Burkitt Lymphoma and DLBCL. In series unselected by histology, between 30–40% of *MYC/BCL2* double-hit lymphomas are classified as DLBCL, with rare cases classified as B-lymphoblastic lymphoma/leukemia or Follicular lymphoma [2,8,11*]. The majority of cases, however, display morphologic or immunophenotypic characteristics inconsistent with established diagnostic entities. In fact, no unifying pathologic features of double-hit lymphomas have been identified. Based on characteristic genetics, adverse clinical outcomes, and ‘gray-zone’ histology, the 2008 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues assigned a new category aimed in part at capturing double-hit lymphomas. This category, *B cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma* (BCLU), comprises a heterogeneous array of lymphomas with variable clinical behavior and a range of genetic lesions [21].

The diagnosis of BCLU is invoked to classify aggressive, mature B cell neoplasms that fail to meet classical morphologic, immunophenotypic, and genetic definitions of Burkitt lymphoma or DLBCL. BCLU includes lymphomas that represent “true biologic” BL, so-called molecular Burkitt Lymphoma (mBL), that are distinguished from “true biologic” DLBCL and double-hit lymphomas by gene expression signature [22]. In their recent BCLU series, Lin and colleagues confirmed that double-hit lymphomas are enriched within this morphologic category, with 46% of cases harboring concurrent *MYC/BCL2* rearrangements. However, 42% of BCLU cases lacked chromosomal aberrancy at the *MYC* locus, precluding a diagnosis of double-hit lymphoma or perhaps suggesting other mechanisms of *MYC* or *BCL2* pathway activation [27*].

Among patients with double-hit lymphoma, morphology alone has not reliably been demonstrated to carry prognostic significance [2,8,11*]. Further, diagnosis of BCLU does not alone warrant intensified therapy, independent of genetics [27*]. The WHO BCLU assignment thus serves primarily as a provisional category upon which to base studies aimed at defining improved therapies and elucidating fundamental disease biology. It should be emphasized that BCLU should not be viewed as a morphologic proxy for double-hit genetics.

ONTOGENY

Most *MYC* rearrangements in mature B cell neoplasms occur as an unwanted consequence of AID-dependent class switch recombination and somatic hypermutation during the germinal center reaction. In Burkitt lymphoma, *IG/MYC* translocation is the primary, transforming event and is not typically associated with other chromosomal abnormalities. By contrast, rearrangement of *MYC* in double-hit lymphomas is thought to be a secondary event, arising in the context of pre-existing, lymphoma-associated lesions and relative chromosomal complexity. The increased frequency of immunoglobulin light chain (IGL) and non-immunoglobulin *MYC* translocation partners in double-hit lymphoma is invoked to support this concept of tumor ontogeny. Whereas the *MYC* translocation partner is within the immunoglobulin heavy chain (IGH) locus in 80–90% of Burkitt Lymphoma [8,22], the majority of *MYC* partners in double-hit lymphoma are at ‘alternative’ sites, such as IGL or non-IG loci [8,11*,13**,22].

MYC/BCL2 double-hit lymphomas commonly display a germinal center B cell (GCB) phenotype, with immunohistochemistry positive for CD10 and BCL6 and negative for MUM1/IRF4 [8,11,14**]. This finding is consistent with the known enrichment of t(14;18) (q32;q21) translocations in the GCB subset of DLBCL [28]. An important caveat, however, is the incomplete clinicopathologic characterization of double-hit lymphomas that harbor second-hit chromosomal aberrancies other than *IGH/BCL2*. Specifically, both *BCL6* rearrangement and increased *BCL2* copy number are found more commonly in large B cell lymphomas of non-GCB origin [13**,29]. As existing evidence suggests that *BCL6* rearrangement and *BCL2* copy number alteration confer an adverse clinical risk similar to conventional *BCL2* rearrangements [8,11*], it remains to be determined whether the prognostic implications of cell of origin assignment in DLBCL also apply to double-hit lymphoma.

Most double-hit lymphomas arise without history or evidence of indolent lymphoma. In fact, 80–85% of double-hit lymphomas represent *de novo* diagnoses, while 15–20% are found in patients with a prior diagnosis of indolent lymphoma, most often follicular lymphoma (FL) [8,11*]. The molecular ontogeny of *MYC*-related transformation of FL is well demonstrated by two recent case reports of patients who developed B cell lymphomas with foci of high-grade “Burkitt-like” morphology in the setting of otherwise histologically low-grade FL [30,31]. In both cases, the high-grade component harbored *MYC*/8q24 and *BCL2*/18q21 rearrangements, while the low-grade component had t(14;18)(q32;q21) alone. In one study, the clonal relationship of the disparate disease morphologies was demonstrated by sequencing of the immunoglobulin heavy chain variable region [31]. These reports are consistent with established data implicating *MYC* as a rare, though prognostically important, progression factor in FL [5,32–34]. Lastly, concurrent *MYC/BCL2* rearrangements have been identified in cases of FL with blastoid morphology and are associated with adverse clinical outcomes [35,36].

TREATMENT OUTCOMES

Double-hit lymphomas are highly resistant to standard chemotherapy, independent of regimen intensity or inclusion of rituximab. Median survival in recently published series ranges widely from 4.5 to 18.5 months [2,4,7,8,11*,14**,18], but is significantly shorter compared to survival of patients with Burkitt lymphoma or IPI-matched DLBCL [8].

In their study of 303 patients with DLBCL, Barrans, et al. showed that overall survival at 2 years was significantly worse in patients with *MYC*/8q24 rearrangements compared to those with unrearranged *MYC*/8q24 (35% vs. 61%) [14**]. Importantly, 83% of patients with *MYC* rearrangements in this series also harbored rearrangement of *BCL2* and/or *BCL6*, suggesting that in this study “*MYC*-rearranged DLBCL” may serve primarily as a surrogate for “double-hit DLBCL”. Patients in this study were treated uniformly with R-CHOP, leaving unanswered the question of whether risk-adapted intensification of therapy may attenuate the observed survival difference.

In a retrospective analysis of 52 patients with *MYC/BCL2* double-hit lymphoma, Li and colleagues reported a median overall survival of 18.6 months. Importantly, no difference in survival was observed between patients with rearranged *MYC* or *BCL2* loci when compared to those with increased copy number. This again suggests that enforced oncogene expression, regardless of genetic mechanism, may be most clinically and biologically relevant. The majority of patients in this study received high-intensity chemotherapy regimens (primarily R-hyper-CVAD), while the remaining received a moderate-intensity regimen (R-CHOP). 21% of patients received consolidation with either allogeneic stem cell transplantation or high-dose chemotherapy with autologous stem cell rescue. While elevated

LDH, >1 extranodal site, and IPI > 2 were associated with shorter survival in univariate analysis, neither intensity of treatment regimen nor stem cell transplantation impacted outcomes [11*].

PROGNOSTIC AND PREDICTIVE FACTORS

Among patients with double-hit lymphomas, few prognostic variables have been identified consistently across studies. As in DLBCL without double-hit lesions, the International Prognostic Index (IPI), LDH, extent of extranodal disease, and performance status are informative regarding prognosis [2,11*]. Several studies have found that in *MYC/BCL2* double-hit lymphoma, non-DLBCL morphology portends shorter survival than DLBCL morphology [2,8], while another found no association between survival and morphology [11*]. There is similar inconsistency regarding the prognostic importance of BCL2 protein expression, non-IG/MYC translocations, and history of indolent lymphoma [2,11*,27*]. Several small series suggest that lymphomas bearing three (*MYC/BCL2/BCL6*) or four (*MYC/BCL2/BCL6/CCND1*) concurrent rearrangements may fare even worse than double-hit lymphomas, but with small numbers and lack of uniform treatment protocols, it is difficult to draw conclusions regarding definitive differences in clinical outcomes [18,20].

Unfortunately, no clinical or pathologic features currently provide prospective guidance regarding risk-adapted intensification (or de-intensification) of therapy. Larger, multicenter studies are required to determine whether specific clinical, pathologic, or genetic variables might offer reliable information about prognosis or predict response to specific therapies.

CONCLUSION

Double-hit B cell lymphomas have a poor prognosis and are associated with early relapse or primary resistance to conventional chemotherapy. In addition to the well-characterized implications of dual rearrangement of *MYC*/8q24 and *BCL2*/18q21, recent studies suggest future analysis should focus on additional loci (i.e. *BCL6*/3q27) and on more diverse mechanisms of pathway dysregulation (i.e. copy number alterations, aberrant protein expression, somatic point mutation, small insertion/deletions). Population-based studies will allow the most accurate and clinically relevant definition of double-hit lymphomas and prospective clinical trials will determine whether intensified therapeutic approaches can improve outcomes.

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Abbreviations

DLBCL	diffuse large B cell lymphoma
ICN	increased copy number
IPI	International Prognostic Index
GCB	germinal center B cell
LDH	lactate dehydrogenase
IGH	immunoglobulin heavy chain
IGL	immunoglobulin light chain
BL	Burkitt lymphoma

FL	follicular lymphoma
BCLU	B cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

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Key points

- Double-hit lymphomas are mature B cell neoplasms with concurrent chromosomal abnormalities affecting *MYC*/8q24 and one or more additional loci that are recurrently affected in lymphoma, most commonly *BCL2*/18q21 or *BCL6*/3q27.
- Double-hit B cell lymphomas have a poor prognosis and are associated with primary resistance to conventional chemotherapy or early disease relapse.
- Recent studies suggest that the incidence of double-hit lymphomas is currently underestimated.
- Prospective clinical trials are required to determine whether intensification of therapy will yield improved clinical outcomes.