

# B-cell lymphomas with *MYC/8q24* rearrangements and *IGH@BCL2/t(14;18)* (q32;q21): an aggressive disease with heterogeneous histology, germinal center B-cell immunophenotype and poor outcome

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**B-cell lymphomas with *MYC/8q24* rearrangement and *IGH@BCL2/t(14;18)*(q32;q21), also known as double-hit or *MYC/BCL2* B-cell lymphomas, are uncommon neoplasms. We report our experience with 60 cases: 52 *MYC/BCL2* B-cell lymphomas and 8 tumors with extra *MYC* signals plus *IGH@BCL2* or *MYC* rearrangement plus extra *BCL2* signals/copies. There were 38 men and 22 women with a median age of 55 years. In all, 10 patients had antecedent/concurrent follicular lymphoma. Using the 2008 World Health Organization classification, there were 33 B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (henceforth referred to as unclassifiable, aggressive B-cell lymphoma), 23 diffuse large B-cell lymphoma, 1 follicular lymphoma grade 3B, 1 follicular lymphoma plus diffuse large B-cell lymphoma, 1 B-lymphoblastic lymphoma, and 1 composite diffuse large B-cell lymphoma with B-lymphoblastic lymphoma. Using older classification systems, the 33 unclassifiable, aggressive B-cell lymphomas most closely resembled Burkitt-like lymphoma ( $n=24$ ) or atypical Burkitt lymphoma with *BCL2* expression ( $n=9$ ). Of 48 cases assessed, 47 (98%) had a germinal center B-cell immunophenotype. Patients were treated with standard ( $n=23$ ) or more aggressive chemotherapy regimens ( $n=34$ ). Adequate follow-up was available for 57 patients: 26 died and 31 were alive. For the 52 patients with *MYC/BCL2* lymphoma, the median overall survival was 18.6 months. Patients with antecedent/concurrent follicular lymphoma had median overall survival of 7.8 months. Elevated serum lactate dehydrogenase level,  $\geq 2$  extranodal sites, bone marrow or central nervous system involvement, and International Prognostic Index  $>2$  were associated with worse overall survival ( $P<0.05$ ). Morphological features did not correlate with prognosis. Patients with neoplasms characterized by extra *MYC* signals plus *IGH@BCL2* ( $n=6$ ) or *MYC* rearrangement with extra *BCL2* signals ( $n=2$ ) had overall survival ranging from 1.7 to 49 months, similar to patients with *MYC/BCL2* lymphomas. We conclude that *MYC/BCL2* lymphomas are clinically aggressive, irrespective of their morphological appearance, with a germinal center B-cell immunophenotype. Tumors with extra *MYC* signals plus *IGH@BCL2* or *MYC* rearrangement plus extra *BCL2* signals, respectively, appear to behave as poorly as *MYC/BCL2* lymphomas, possibly expanding the disease spectrum.**

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Chromosomal translocations involving the immunoglobulin genes are common in B-cell non-Hodgkin lymphomas.<sup>1,2</sup> Two common translocations involve the *BCL2* and *MYC* genes. The t(14;18)(q32;q21) juxtaposes *BCL2* at 18q21 with the immunoglobulin heavy chain (*IGH*) gene enhancer at 14q32, resulting in the overexpression of *BCL2*. The t(14;18)(q32;q21) is characteristic of follicular lymphoma, but also occurs in 20–30% of *de novo* diffuse large B-cell lymphoma.<sup>3</sup> Translocations that involve *MYC*, including t(8;14)(q24;q32), t(2;8)(p12;q24), and t(8;22)(q24;q11), juxtapose *MYC* at 8q24 with the *IGH*,  $\kappa$ , and  $\lambda$  genes, respectively, and upregulate *MYC*.<sup>4,5</sup> *MYC* translocations are a hallmark of Burkitt lymphoma, but are not specific, as they can occur in other B-cell lymphomas. *MYC* rearrangement is observed in 5–10% of diffuse large B-cell lymphoma and up to 50% of high-grade B-cell lymphomas other than Burkitt lymphoma.<sup>6–8</sup> In these tumors, *MYC* translocations also can involve non-IG partners.

B-cell lymphomas with *MYC/8q24* rearrangement and *IGH@BCL2/t(14;18)(q32;q21)* have been referred to by others in the literature as double-hit lymphoma, double-hit B-cell lymphoma, *MYC/BCL2* or M/B lymphoma, or *BCL2 + /MYC +* lymphoma.<sup>9–11</sup> We believe that the term double-hit lymphoma is vague and that specifying the molecular abnormalities has value. For this reason, we will refer to these neoplasms as *MYC/BCL2* lymphomas in this study. In a recent review, Aukema *et al*<sup>11</sup> stated that approximately 200 cases are reported in the literature, many as case reports or small case series.

Despite the number of *MYC/BCL2* lymphomas reported already, questions remain or issues need refinement. Many *MYC/BCL2* lymphomas reported in the literature were classified using older systems, rather than the current 2008 World Health Organization classification. Patients with *MYC/BCL2* lymphoma can present *de novo* or be associated with follicular lymphoma.<sup>9–24</sup> The prognosis of patients with *MYC/BCL2* lymphomas with *de novo* disease has been reported, but patients with antecedent/concurrent follicular lymphoma have received less attention in the literature. We also have encountered rare cases of aggressive B-cell lymphoma that carry extra signals of *MYC* associated with *IGH@BCL2* or *MYC* rearrangement with extra signals of *BCL2*, and the clinical significance of these molecular combinations is uncertain.

In this retrospective study, we reviewed all patients with *MYC/BCL2* lymphomas at our institution to assess their morphological features using the 2008 World Health Organization classification, address potential prognostic factors, including the importance of *de novo* disease vs patients with follicular lymphoma, and to report on the subset of patients with B-cell lymphomas associated with extra signals of *MYC* or *BCL2* associated with *IGH@BCL2* or *MYC* rearrangement, respectively.

## Materials and methods

### Case Selection

The database of our institution was searched for cases of B-cell lymphoma associated with *MYC/8q24* rearrangement and *IGH@BCL2/t(14;18)(q32;q21)* from 1 April 1995 to 15 May 2011. The presence of translocations was confirmed by conventional cytogenetic analysis and/or fluorescence *in situ* hybridization analysis. A subset of 12 cases was reported previously by Kanungo *et al*,<sup>18</sup> and one case referred to our institution was published as a case report by the submitting institution.<sup>24</sup> Eight additional cases were identified that did not meet the classical definition of *MYC/BCL2* lymphoma, but had both *MYC* and *BCL2* abnormalities. These patients had B-cell lymphoma associated with extra signals of *MYC* and *IGH@BCL2/t(14;18)(q32;q21)* ( $n=6$ ) or *MYC/8q24* rearrangement with extra signals/copies of *BCL2* ( $n=2$ ). The clinicopathological features and overall survival of these eight patients were analyzed separately.

Corresponding medical records were reviewed to obtain clinical information, including prior history of lymphoma, number and sites of involvement, Ann Arbor stage, International Prognostic Index, treatment regimens, response to therapy, overall survival, and progression-free survival. Morphological, immunophenotypic, and cytogenetic data were reviewed to confirm the diagnosis and classify the neoplasms according to the current World Health Organization classification, which includes the new category designated B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma.<sup>25</sup> All neoplasms in this category were also classified using the 1994 Revised European–American Lymphoma classification and the 2001 World Health Organization classification, in an attempt to further distinguish subsets of these neoplasms for this study.

### Immunophenotyping

Immunohistochemical stains were performed using formalin-fixed, paraffin-embedded tissue sections either at the time of diagnosis or retrospectively for this study, as described previously.<sup>18</sup> The panel of monoclonal antibodies used was variable over time, but included reagents specific for CD3, CD5, CD10, CD20, *BCL2*, *BCL6* and Ki-67 (MIB-1) (DAKO, Carpinteria, CA, USA). Flow cytometry immunophenotyping was performed using standard multi-color analysis, three-color in the distant past and four- to eight-color more recently. Analysis was performed using either a FACScanto II or FACS-Calibur cytometer (Becton-Dickinson Biosciences, San Jose, CA, USA) as described previously.<sup>26</sup> Lymphocytes were gated for analysis using CD45 expression and side scatter. The panel of antibodies

used was variable over the years, but usually included CD3, CD4, CD5, CD7, CD10, CD13, CD19, CD20, CD23, CD33, CD34, CD38, and immunoglobulin  $\kappa$  and  $\lambda$  light chains. All antibodies were obtained from Becton-Dickinson Biosciences, except for TdT that was obtained from Supertech (Bethesda, MD, USA).

### Conventional Cytogenetic Studies

Conventional G-band karyotype analysis was performed on 21 cases using cell suspensions of lymph node, extranodal tissue biopsy, or bone marrow aspirate specimens using methods described previously.<sup>27</sup> The karyotypes were reported according to the 2009 International System for Human Cytogenetic Nomenclature.<sup>28</sup>

### Fluorescence *In Situ* Hybridization

Fluorescence *in situ* hybridization analysis was performed on 53 cases using an LSI *MYC* dual-color break-apart probe (Vysis, Downers Grove, IL, USA). In 50 cases, an LSI *IGH@BCL2* dual-color, dual-fusion translocation probe was used (Vysis). *BCL6* rearrangement was tested in 16 cases using dual-color, break-apart probe (Abbott Laboratories, Des Plaines, IL, USA) following the manufacturer's instructions.

For bone marrow aspirate specimens, fluorescence *in situ* hybridization was performed by using a freshly dropped slide from a harvested bone marrow aspirate specimen or a G-banded slide for metaphase mapping according to the manufacturer's instructions. For formalin-fixed, paraffin-embedded tissue samples, fluorescence *in situ* hybridization was performed on 4- $\mu$ m tissue sections and fixed onto slides as per the manufacturer's protocols. The signals from 200 nuclei were analyzed. The sample was considered positive for *MYC*, *BCL2*, or *BCL6* rearrangement if more than 3.8%, 0.1%, or 8% of nuclei showed positive signals, respectively.

### Statistical Analysis

Overall survival was calculated from the date of diagnosis to the date of death or last follow-up. Progression-free survival was calculated from the date of diagnosis to the date of progression or last follow-up. Patient survival was analyzed using the Kaplan–Meier method and compared using the log-rank test (SAS-9.1 software). A *P*-value less than 0.05 was considered statistically significant.

## Results

### Cases of *MYC/BCL2* Lymphoma

#### Clinical characteristics

There were 52 patients with neoplasms associated with *MYC/8q24* rearrangement and *IGH@BCL2/*

**Table 1** Clinicopathological, immunophenotypic and genetic features of patients with *MYC/BCL2* lymphomas

Feature	n = 52	%
<b>Sex</b>		
Male	33	64
Female	19	36
<b>Age range (median)</b>		
> 60 years	25/52	48
<i>De novo</i>	42/52	81
Previous or concurrent FL	10/52	19
BM positive	27/47	57
CSF positive	7/30	23
High serum LDH	37/45	82
Stage III or IV	37/50	74
Extranodal sites > 2	27/46	55
IPI > 2	30/48	63
<b>WHO classification</b>		
DLBCL	19/52	36
Unclassifiable <sup>a</sup>	29/52	56
Other	4/52	8
<b>Immunophenotype</b>		
CD10	47/48	98
BCL6	22/23	96
BCL2	40/46	87
Ki-67 (%)	40–99%	
<b>Karyotype</b>		
Complex	21/21	100
IG partner in translocation	18/21	86
Non-IG partner in translocation	3/21	14
<b>Fluorescence <i>in situ</i> hybridization</b>		
<i>MYC</i>	46/46	100
<i>IGH@BCL2</i>	46/46	100
<i>BCL6</i>	0/16	0

BM, bone marrow; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; WHO, World Health Organization.

<sup>a</sup>B-cell lymphoma, unclassifiable, with features intermediate between diffuse B-cell lymphoma and Burkitt lymphoma.

t(14;18)(q32;q21). There were 33 men and 19 women, with a median age of 55 years (range, 18–76 years). In all, 42 (81%) patients presented with *de novo* disease and 10 (19%) patients had a history or concurrent low-grade follicular lymphoma. Of 45 patients with available data, 37 (82%) had an elevated serum lactate dehydrogenase level. Twenty-seven of 45 (55%) patients had two or more extranodal sites of disease. Involved extranodal sites included bone marrow, central nervous system, abdomen, gastrointestinal tract (stomach, small intestine, or colon), liver, spleen, lung, pleural fluid, testis, prostate, mediastinum, ovaries, ear, skin, and peripheral blood. Bone marrow involvement was observed in 27 of 47 (57%) patients. Thirty patients underwent spinal tap and cerebrospinal fluid analysis; 7 (23%) cases were positive. Thirty-seven of 50 patients (74%) had advanced Ann Arbor stage (III/IV) disease and 30 of 48 (63%) patients had an International Prognostic Index > 2 (Table 1).

*Morphological and immunophenotypic features*

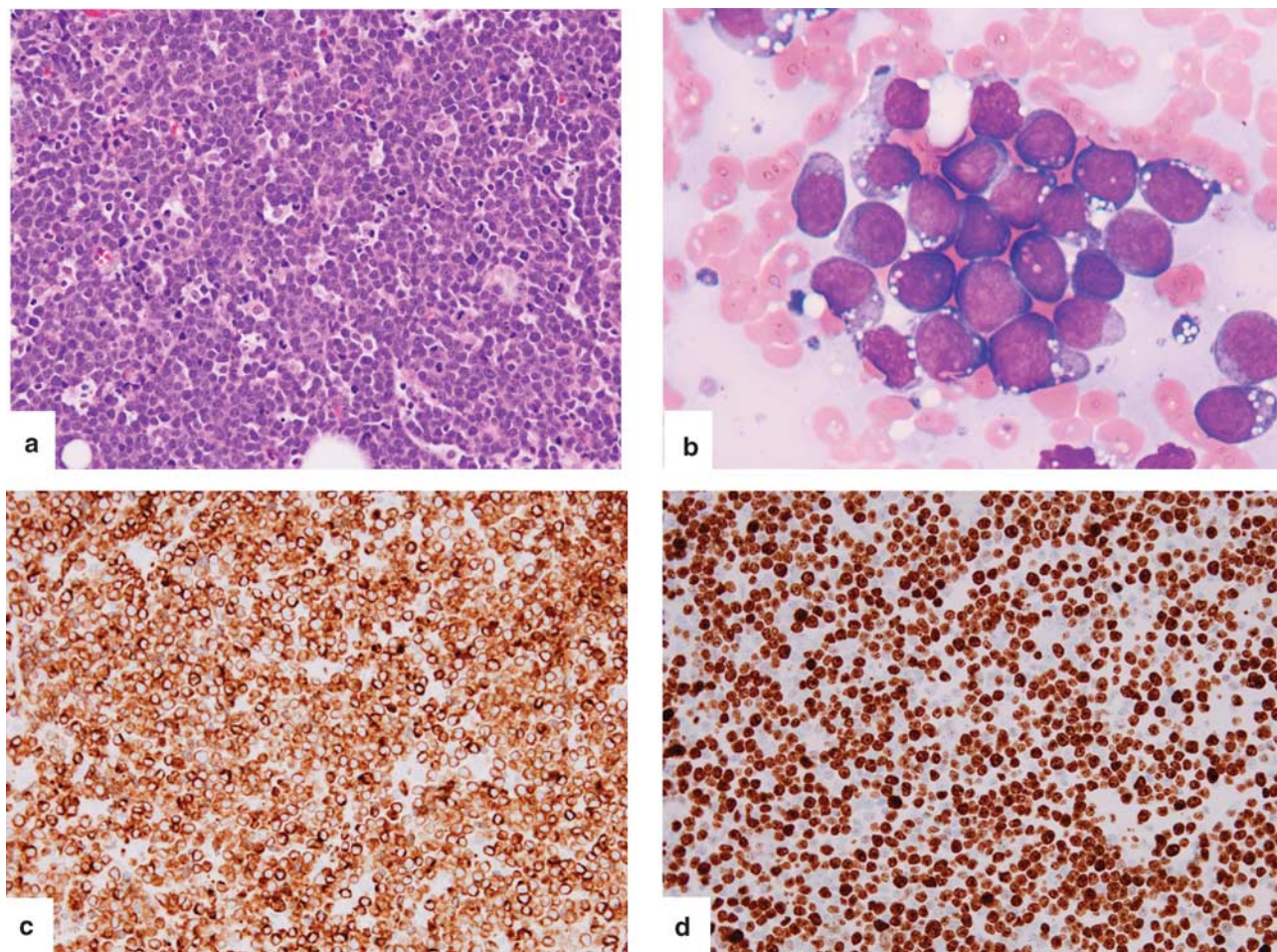
Using the 2008 World Health Organization classification, the 52 *MYC/BCL2* lymphomas were classified as follows: 29 (56%) unclassifiable aggressive B-cell lymphoma, 19 (36%) diffuse large B-cell lymphoma, 1 (2%) follicular lymphoma grade 3B, 1 (2%) follicular lymphoma grade 3B with diffuse large B-cell lymphoma, 1 (2%) B-lymphoblastic lymphoma, and 1 (2%) composite diffuse large B-cell lymphoma with B-lymphoblastic lymphoma (Figures 1 and 2).

We also assessed the unclassifiable, aggressive B-cell lymphoma category using the Revised European–American Lymphoma and 2001 World Health Organization classifications. In total, 20 tumors could be classified as high-grade B-cell lymphoma, Burkitt-like (or unclassifiable using the 2001 World Health Organization). Nine other tumors fit the designation of atypical Burkitt lymphoma (all were BCL2+). One case classified as B-lymphoblastic lymphoma presented in the bone marrow with

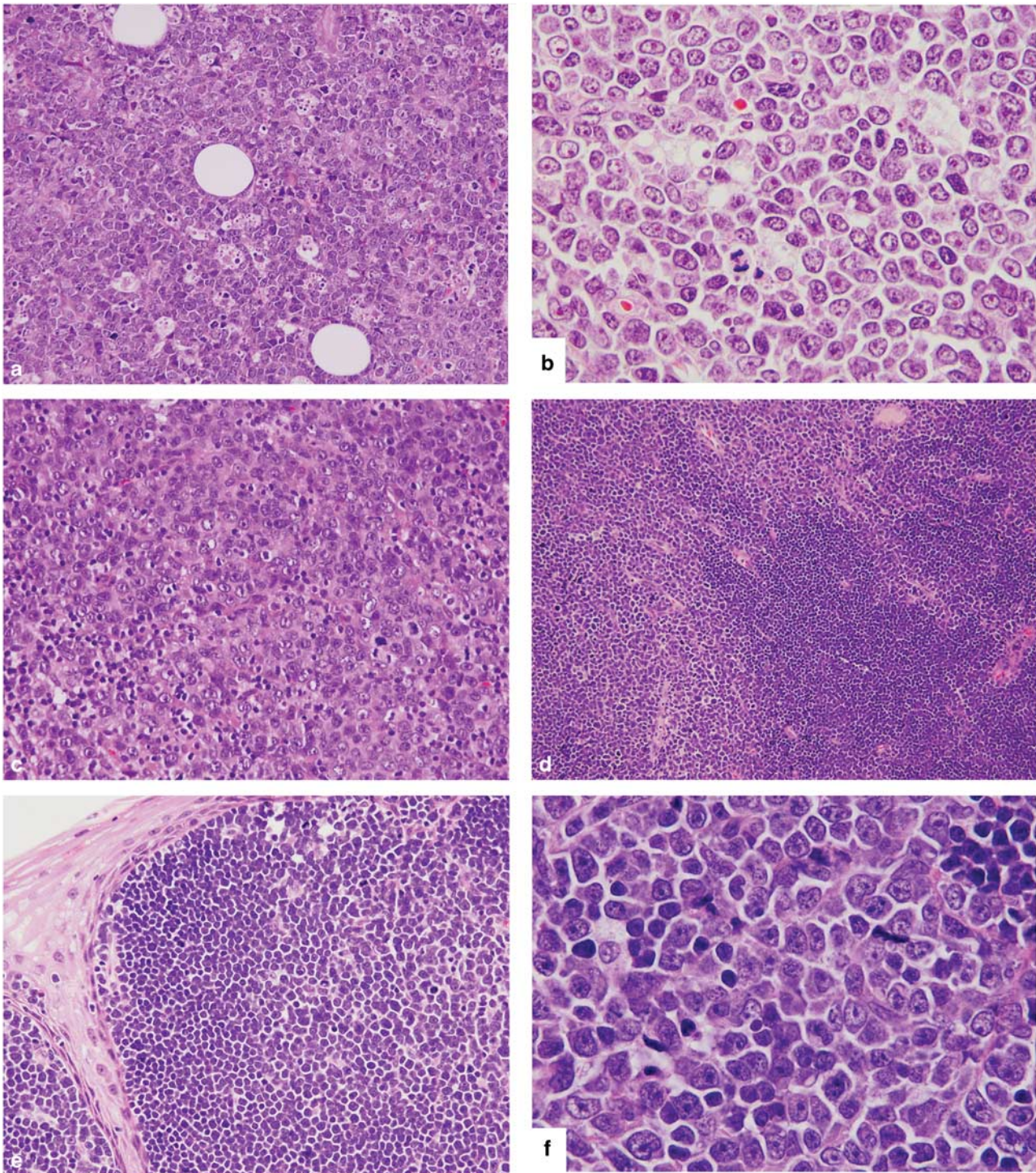
numerous blasts, of L1 type, as described in the French–American British classification.

The *MYC/BCL2* tumors were assessed using a combination of paraffin section immunohistochemistry and flow cytometry immunophenotyping. All tumors were of B-cell lineage, positive for one or more pan-B-cell antigens and negative for pan-T-cell antigens. CD10 was positive in 47 of 48 (98%), BCL6 in 22 of 23 (96%), and BCL2 in 40 of 46 (87%) cases assessed. These results support a germinal center B-cell immunophenotype in 47 (98%) cases. The case of composite diffuse large B-cell lymphoma and B-lymphoblastic lymphoma had corresponding differences in the immunophenotype: the lymphoblastic areas were CD20 dim+ to negative and TdT+, and the large cell areas were CD20 bright+ and TdT– (Figure 2).

The proliferation (Ki-67) rate in these tumors was variable, ranging from 40 to 50% up to >99% (Figure 1). There was some correlation with morphological features. Cases of unclassifiable,



**Figure 1** Morphological and immunophenotypic features of a case of *MYC/BCL2* lymphoma that fit within the category of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma in the current World Health Organization classification. This neoplasm also had features of atypical Burkitt lymphoma. (a) Omental mass (hematoxylin–eosin  $\times 400$ ); (b) bone marrow smear (Wright–Giemsa,  $\times 1000$ ); (c) the neoplasm was strongly positive for BCL2; and (d) Ki-67 highlighted >90% cells (c and d: immunohistochemistry with hematoxylin counterstain,  $\times 400$ ).



**Figure 2** Morphological spectrum of four cases of *MYC/BCL2* lymphoma classified using the current World Health Organization classification. (a) B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (hematoxylin–eosin,  $\times 400$ ). (b) Diffuse large B-cell lymphoma. This field shows high mitotic and apoptotic activity (hematoxylin–eosin,  $\times 1000$ ). (c) Diffuse large B-cell lymphoma. This neoplasm had many immunoblasts (hematoxylin–eosin,  $\times 400$ ). (d–f) A case of composite lymphoma composed of B-lymphoblastic lymphoma and diffuse large B-cell lymphoma (d) Low-power magnification showing both components (hematoxylin–eosin,  $\times 200$ ). (e) B-lymphoblastic lymphoma (hematoxylin–eosin,  $\times 400$ ). This component was CD20 dim+ to – and TdT+ (not shown). (f) Diffuse large B-cell lymphoma (hematoxylin–eosin,  $\times 400$ ). This component was CD20+ and TdT– (not shown).

aggressive B-cell lymphoma that resembled atypical Burkitt lymphoma had a proliferation rate from 80 to virtually 100%, and most cases were  $>95\%$ .

Cases of unclassifiable, aggressive B-cell lymphoma with Burkitt-like features had a Ki-67 range from 60 to 70% up to virtually 100% with a median Ki-67 of

90%. Cases of diffuse large B-cell lymphoma had a Ki-67 range of 40–50% up to virtually 100%, with a median of approximately 80%.

#### Cytogenetic and molecular genetic characteristics

Conventional cytogenetic analysis was performed on 21 MYC/BCL2 lymphomas. All neoplasms had a complex karyotype with  $\geq 3$  numerical and/or structural aberrations (Table 2). The 8q24 locus was involved in translocations in each case, including 9 (43%) with t(8;22)(q24;q11), 7 (33%) with t(8;14)(q24;q32), 2 (10%) with t(2;8)(q24;p11), and 3 (14%) with non-IG loci. Fluorescence *in situ* hybridization analysis performed on 15 cases also assessed by conventional cytogenetic analysis confirmed the presence of MYC and BCL2 rearrangement.

Fluorescence *in situ* hybridization was also performed on 31 MYC/BCL2 lymphomas not analyzed by conventional cytogenetics. All cases showed

MYC rearrangement and IGH@BCL2. The partner of MYC was not assessed in these studies. Analysis for BCL6 rearrangements was performed by fluorescence *in situ* hybridization on 16 cases; no case showed rearrangement of BCL6.

#### Treatment and response

In all, 49 patients with MYC/BCL2 lymphoma were treated with combination chemotherapy: 19 patients with rituximab, cyclophosphamide, daunorubicin, vincristine, prednisone (R-CHOP) and 30 patients with more aggressive regimens. The aggressive regimens included 28 rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine (R-hyper-CVAD), 1 cyclophosphamide, cytarabine, doxorubicin, leucovorin, methotrexate, and vincristine (CODOX), and 1 rituximab plus fludarabine, mitoxantrone, and dexamethasone. A total of

**Table 2** Conventional cytogenetic findings in MYC/BCL2 lymphomas

Case	Cytogenetics
3	51–53,XY,+X,del(2)(q32),add(4)(p16),+5, t(8;22)(q24;q11), +11,+12, t(14;18)(q32;q21), -15,+22,+2-3mar[9]/46,XY[11]
4	46,XY,t(1;3)(p32;q26.2),del(b)(q21),t(8;22)(q24;q11),add(14)(q32),t(14;18)(q32;q21),+1-3mar[4]/metaphases exhibiting random breakage[10]/46,XY[22]
5	39–52,XY,+X,-1,t(2;17)(q13;q21),+3,+4,+5,+6, +7, +8, -8,t(8;22)(q24;q11),+12,dup(12)(q13q24),-13,-13,+14, t(14;18)(q32;q21),+der(14)t(14;18),+16, +18, +19,+20,+21,+22,-22,+mar[cp17]/64,XY,+X, t(2;17)(q13;q21), -3,-4,-4,+5,+8,t(8;22)(q24;q11), -9,-10,-10,-10,dup(12)(q13q24),-13,der(14)t(14;18)x2,+16,-18,-18,+3mar[1]
6	48X,-Y,t(1;14), t(2;9), -3, -4, -5, del(6)(q13;q23), +7(q22), t(14;18)(q32;q21),+16(p11.2), +18, +22
9	46,XX,add(5)(p13),t(8;14)(q24;q32),t(14;18)(q32;q21)[8]/46,XX,idem,der(17)t(10;17)(q22;q10)[1]/46,XX[10]
10	47,XX,+1,t(1;9)(p34.1;p22),add(8)(p23),t(8;22)(q24;q11),del(9)(q21),t(14;18)(q32;q21.3)[7]/46,XX[10]
11	47,Y,add(X)(p22.3),del(1)(q23),add(2)(p25),-4,del(5)(p13), add(6)(p25),-7,t(8;14)(q24;q32), der(8)t(8;14)t(14;18)(q32;q21), +ider(8)(q10) del(8)(q12q22),der(14)t(8;14),+add(14)(q32),add(15)(q26), i(17)(q10),+der(18)t(14;18)[3]/51,Y, add(X)(p22.3),del(1)(q23),add(2)(p25),-4,-5, del(5)(p23),add(6)(p25),-7,t(8;14)(q24;q32), der(8)t(8;14)t(14;18)(q32;q21), +ider(8)(q10) del(8)(q12q22),add(11)(q25),+12, der(14)t(8;14), +add(14)(q32)x2,add(15)(q26),-17,i(17)(q10), +der(18)t(14;18),-19,+del(20)(q11.2), del(22)(q11.2), +3-5mar[cp3]/46,XY[12]
12	48,XX,+X,-2,der(7)t(7;8)(q36q22)x2,-8,del(10)(q24), add(12)(q24.3)x2,t(14;18)(q32q21),+mar
14	48–51,XY,del(4)(21),idic(6)(p10),+7,+8, t(8;22)(q24;q11) t(14;18)(q32;q21),+18,+der(?), t(4;?)q22;?)mar with other numerical changes[20]
15	50,XY,t(2;8)(p11.2;q24.3),t(3;5)(p12;q12),+7, +8,inv(9)(p11q12),+11,t(14;18)(q32;q21), add(17)(p11),+19[16]
16	47,XY,del(6)(q14),+7,t(8;22)(q24;q11.2),inv(9)(p11q12), t(14;18)(q32;q21)[19]/47,idem,+1, der(1;14)(q10;q10)[1]
17	47,XX,t(8;14)(q24.1;q23),+12,t(14;18)(q23;q21)[12]/46,XX[8]
18	42–45,X,-X,dup(2)(p16p21),del(6)(q21q23), t(8;14)(q24;q32),del(10)(q23q25),dup(12)(q13q24), t(14;18)(q32;q21),-16,der(22)t(1;22)(q31;q13),+mar[cp7]
23	45,XY,t(2;8)(p11.2;q24.1),del(13)(q14q32),t(14;18)(q32;q21),16,der(16)t(11;16)(q13 ;p11.2),Add(17)(p11.2)[cp5]/46,idem, -add(17),+del(7)(p11.2),mar [cp14]/46,XY[cp1]
26	72–81 < 3n >,XXX,+X,+X,+del(1)(p22p36.1)x2,i(6)(p10), t(8;22)(q24.1;q11.2),+der(8)t(8;22), del(11)(q13q23), +12,+13,+14, t(14;18)(q32;q21.3)x2,-15,-17,+18,add(19)(q13.3),+21,+22,+2-8mar[cp18]
29	46,XX,add(1)(p36.3),del(4)(q12q21),der(8)t(8;14)(q24.1;q32)t(14;18)(q32;q21.3),der(14)t(8;14),der(18)t(14;18)[19]/46,XX[1]
30	48,XY,+Y,add(3)(q29),del(6)(q13q25),t(8;14)(q24.1;q32),add(9)(p22),del(9)(q22),del(13)(q12q14), t(14;18)(q32;q21.3),+der(18)t(14;18)[19]
31	46,XY,dup(1)(q12q32),t(8;22)(q24.1;q11.2), t(14;18)(q32;q21.3), add(21)(q22)[19]
34	46–48,XX,add(1)(p36.1), der(8)t(8;22)(q24.1;q11.2), +ider(8)(q10)t(8;22),-9,t(14;18)(q32;q21.3), add(16)(q24),i(17)(q10),-20,+22,+22,del(22)(q11.2),der(22)t(9;22)(q11;p13)del(22)(q11.2)[cp18]/46,XX[1]
39	48,XX,+7,add(8)(q24),del(9)(p21),+12,del(13)(q12q14), t(14;18)(q32;q21),der(14)t(14;18)[19]
48	84-91-46,XXY,del(X)(p22.1),dup(1)(q12q25),der(1) add(1)(p13)dup(1),-2,add(3)(q12)x2,-4,-6,+7,+7,-7,der(8)t(8;14)(q24.1;q32)t(14;18)(q32;q21)x2,add(10)(q22)der(14)t(8;14)x2, der(14)del(14)(q11.2q24),-15,-18,+17,add(17)(p11.2)x3,der(18)t(14;18)x2,-22,-22,marx2[cp14]/46,XY[1].

**Table 3** Univariate analysis of clinicopathological features predictive of survival in patients with MYC/BCL2 lymphoma

Features	Overall survival		Progression-free survival	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Age (>60 vs ≤60 years)	0.651	1.22 (0.51–2.91)	0.659	1.22 (0.51–2.91)
Gender (male vs female)	0.804	0.88 (0.32–2.37)	0.987	1.01 (0.37–2.78)
History of FL	0.065	3.67 (0.92–14.55)	0.212	2.21 (0.64–7.66)
LDH (high vs normal)	0.036	3.03 (1.07–8.49)	0.037	3.01 (1.07–8.51)
BM involvement	0.021	2.36 (1.00–5.61)	0.086	2.13 (0.90–5.03)
Extranodal site ≥2	0.003	3.79 (1.60–9.00)	0.002	4.07 (1.71–9.67)
CNS involvement	0.007	7.08 (1.70–29.45)	0.008	6.80 (1.65–28.05)
BCL2 protein (+ vs –)	0.157	2.14 (0.74–6.17)	0.16	2.14 (0.74–6.18)
Morphology (DLBCL vs non-DLBCL)	0.154	1.89 (0.79–4.)	0.401	1.46 (0.60–3.52)
Stage (III/IV vs I/II)	0.057	2.46 (0.97–6.23)	0.048	2.55 (1.01–6.42)
IPI (>2 vs ≤2)	0.002	4.18 (1.71–10.22)	0.001	4.38 (1.78–10.75)
Chemo (+HCVAD vs –HCVAD)	0.54	1.28 (0.51–3.20)	0.393	1.29 (0.51–3.24)
Stem cell transplant	0.733	0.83 (0.29–2.37)	0.79	0.91 (0.31–2.66)

BM, bone marrow; CI, confidence interval; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

13 patients received intrathecal methotrexate. Three patients in this study were diagnosed recently and therapeutic decisions are not complete.

Of 29 patients, 17 (58%) with unclassifiable, aggressive B-cell lymphoma were treated with R-hyper-CVAD (or CODOX in 1 patient) and 9 of 19 (47%) diffuse large B-cell lymphoma patients received R-hyper-CVAD. The patient with grade 3B follicular lymphoma was treated initially with R-CHOP and subsequently with R-hyper-CVAD. The patient with B-lymphoblastic lymphoma was treated with R-hyper-CVAD as was the patient with follicular lymphoma grade 3B associated with diffuse large B-cell lymphoma. The patient with composite lymphoma with diffuse large B-cell lymphoma and B-lymphoblastic lymphoma components was treated with R-CHOP. Overall, there was no statistical significant difference in median overall survival and progression-free survival between patients who were or were not treated with R-hyper-CVAD (Table 3 and Figure 3). In all, 11 patients also received autologous or allogeneic stem cell transplant. There was no statistically significant difference in survival between patients who received or did not receive stem cell transplant.

#### Prognostic factors

We analyzed prognostic factors for 49 patients with MYC/BCL2 lymphoma with adequate clinical follow-up. After a median follow-up of 44 months (range, 1.6–82.1 months), 22 patients died. The median overall survival was 18.6 months and the 1-year survival rate was 58%.

In a univariate analysis (Table 3 and Figure 3) that evaluated 13 clinical and pathological parameters elevated serum lactate dehydrogenase, ≥2 extranodal sites of disease, bone marrow involvement, central nervous system involvement, and International Prognostic Index >2 were associated with a worse overall

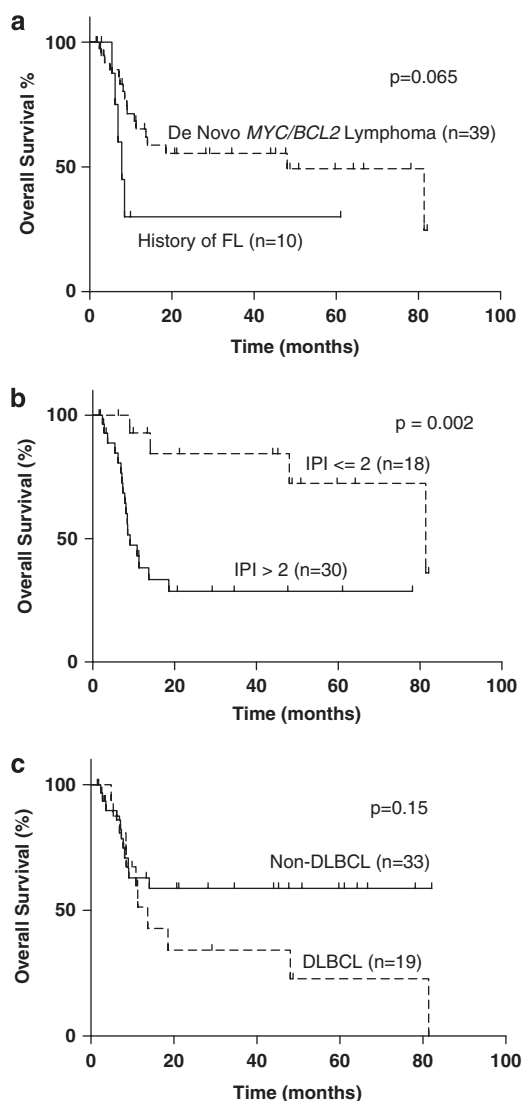
survival ( $P < 0.05$ ) and all of these factors except bone marrow involvement were associated with progression-free survival ( $P < 0.05$ ). Previous history or concurrent follicular lymphoma and stage were marginally associated with a worse overall survival ( $P = 0.065$  and  $0.057$ , respectively). The median overall survival of patients with a history of follicular lymphoma was 7.8 months compared with 48 months for patients with *de novo* disease.

All factors predictive of overall survival by univariate analysis were entered for multivariate analysis. After model selection, only International Prognostic Index >2 was significantly associated with shorter overall survival ( $P = 0.017$ , hazard ratio 6.81, 95% confidence interval of hazard ratio 1.4–32.7). Elevated serum lactate dehydrogenase ( $P = 0.042$ , hazard ratio 5.31, 95% confidence interval of hazard ratio 1.1–26.5) and International Prognostic Index >2 ( $P = 0.010$ , hazard ratio 7.70, 95% confidence interval of hazard ratio 1.6–36.5) were significantly associated with worse progression-free survival.

#### Lymphomas with Extra MYC Signals and IGH@BCL2/t(14;18)(q32;q21) or MYC/8q24 Rearrangements and Extra BCL2 Signals

Eight additional patients had coexistent MYC and BCL2 abnormalities, although they did not fit the classical description of MYC/BCL2 lymphoma. Six patients had lymphoma associated with extra MYC signals and IGH@BCL2, but without evidence of MYC rearrangement. Two patients had lymphoma associated with MYC rearrangement and extra BCL2 signals or extra chromosome 18 copies, but without IGH@BCL2. The clinicopathological features of these eight patients are summarized in Table 4.

Six patients had lymphomas associated with extra MYC signals and IGH@BCL2/t(14;18)(q32;q21).



**Figure 3** Overall survival of patients with MYC/BCL2 lymphoma. (a) Patients with *de novo* tumors vs patients with previous or concurrent low-grade follicular lymphoma (FL). (b) All patients subdivided according International Prognostic Index (IPI) of >2 or ≤2. (c) All patients subdivided into those classified as diffuse large B-cell lymphoma (DLBCL) or non-DLBCL.

There were four men and two women, 32–71 years of age (Table 4). Five patients had stage IV disease, and one patient had stage II disease. Four patients had >2 extranodal sites of disease and three had bone marrow involvement. The central nervous system was not involved in three patients assessed by cytological examination of cerebrospinal fluid. Serum lactate dehydrogenase level was elevated in four of five patients, ranging from 997 to 9973 U/l (normal range, 330–618 U/l). The International Prognostic Index could be calculated for five of six patients (1 had incomplete information) and was: 3 in 3 patients, 2 in 1 patients, and 1 in 1 patient. Morphologically, these neoplasms were classified as: 4 diffuse large B-cell lymphoma and 2 unclassifiable, aggressive B-cell lymphoma. The immunophenotype

was virtually identical to MYC/BCL2 lymphomas. Ki-67 immunostain was available for five patients and the proliferation rates ranged from 60 to 70% to virtually 100%. The extra MYC signals numbered from 3 to 8. The patients were treated with R-hyper-CVAD ( $n=3$ ) or R-CHOP ( $n=3$ ). The overall survival of these patients was 1.4, 2.3, 12.2, 13.3, 14.8, and 49.1 months, and was similar to that of patients with MYC/BCL2 lymphomas.

Two patients had lymphomas associated with MYC/8q24 rearrangements and extra BCL2 signals/copies. This group included two patients with stage II or IV disease (Table 4); both patients had bone marrow involvement and one patient had >2 extranodal sites of disease. The cerebrospinal fluid was negative in one patient assessed. Serum lactate dehydrogenase was elevated at 2171 U/l in one patient. The International Prognostic Index was 2 for both patients. Both patients had unclassifiable, aggressive B-cell lymphomas. The immunophenotype was very similar to MYC/BCL2 lymphomas and the proliferation rates were 80 and 90–95%. Conventional cytogenetics in one patient showed extra chromosome 18 and fluorescence *in situ* hybridization in the other patient showed four BCL2 signals. Both patients received R-hyper-CVAD chemotherapy and had an overall survival of 1.7 and 9.7 months.

## Discussion

B-cell lymphoma with MYC/8q24 rearrangement and IGH@BCL2/t(14;18)(q32;q21) is uncommon, representing <1% of all lymphomas and approximately 4% of high-grade B-cell lymphomas.<sup>11,29,30</sup> In this study, we retrospectively reviewed our experience with these neoplasms.

As shown by others, the morphological findings of MYC/BCL2 lymphomas show a spectrum, with most cases fitting best within the current World Health Organization system category of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (for convenience referred to here as unclassifiable, aggressive B-cell lymphoma).<sup>11,25</sup> However, a substantial subset of cases can be classified as diffuse large B-cell lymphoma and rare cases can be classified as follicular lymphoma, B-lymphoblastic lymphoma, and composite lymphoma. Since the World Health Organization category of unclassifiable, aggressive B-cell lymphoma is morphologically heterogeneous, and neoplasms can qualify for this category in a number of ways, we also classified these lymphomas using older classification systems in an attempt to derive more information. Most of the cases in this study fit into the Revised European–American Lymphoma classification category of high-grade B-cell lymphoma, Burkitt-like lymphoma due to the heterogeneous mixture of intermediate and slightly larger cells.



**Table 4** Clinicopathological features of eight patients with extra *MYC* signals plus *IGH@BCL2* or *MYC* translocation with extra *BCL2* signals

No.	FISH		Cytogenetics	Age/sex	LDH	Morphology	Ki-67 (%)	BM	CNS	Therapy	Stage	IPI	OS (M)	Alive/dead
	MYC	IGH@BCL2												
1	<i>MYC</i> × 8	+	NA	37/M	2065	DLBCL	70–90	NA	NA	R-CHOP, ESHAP	IVE	3	12.2	Dead
2	<i>MYC</i> × 3	+	47,XY,del(6)(q21q25),+8,t(14;18)(q32;q21)[19]/46,XY[1]	49/M	8143	U	60–70	Yes	No	R-HCVAD	IVB	2	14.8	Alive
3	<i>MYC</i> × 6	+	47X,-X,add(2)(p23),add(3)(q29), t(14;18)(q32;q21), del(17)(p11.2),+20,+21, add(21)(p11.2)[4]/46,X,-X, add(1)(q44), add(2)(p23),der(3)inv(3)(p21p25)add(3)(q29), t(14;18)(q32;q21),del(17)(p11.2),+20[3]	32/F	997	DLBCL	90	No	No	R-CHOP, RICE	IV	3	2.3	Alive
4	<i>MYC</i> × 3	+	NA	71/M	393	DLBCL	NA	No	NA	R-CHOP, SCT-auto	II	1	49.1	Dead
5	<i>MYC</i> × 4	+	70-73,XXY,dup(1)(q21q44),-4,del(4)(q25q31.3), -5,i(6)(p10),+i(6)(p10),-8,der(9)t(8;9)(q24.1;p13), +der(9)t(8;9)x2,-10,del(13)(q12q22),t(14;18)(q32;q21.3), der(18)t(14;18),+der(18)t(14;18),+19,+20,+2-3mar[cp10]	44/M	9973	U	100	Yes	No	R-HCVAD-M	IV E	3	1.4	Dead
6	Extra copies	+	NA	44/F	NA	DLBCL	70–80	Yes	NA	R-CHOP	IV		13.3	Alive
	MYC translocation		BCL2											
7	+	BCL2 × 4	72,XX,-Y,der(1)t(1;1)(p34;q21)add(1)(q32), der(1)dup(1)(q21q23)t(1)(1;1)(q23;?),del(3)(p14p21),-4,ins(5)(q12;?)+7, t(8;14)(q24.1;q32)x2, inv(11)(q21q23),+12, +13,-15, add(16)(p13.3), +21,+21, +mar[3 ]/73, sl,+18[5]/73,sl,+11[2]	18/M	510	U	90–95	Yes	No	R-CHOP, HCVAD, SCT-auto	IV	2	9.7	Dead
8	+	NA	48,XX,dup(1)(q32q21),t(3;7)(q29;q32),t(8;14)(q24q32), del(13)(q12q22),del(15)(q11.2q15),+18,+18[19]/46,XX[1]	72/F	2172	U	80	Yes	NA	HCVAD-M	II	2	1.7	Alive

BM, bone marrow; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ESHAP, etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C) and cisplatin; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase (normal ≤618 IU/l); M, intrathecal methotrexate-cytarabine; NA, not applicable; OS, overall survival; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HCVAD, hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone alternating with methotrexate and cytarabine; SCT-auto, autologous stem cell transplant; RICE, rituximab, ifosfamide, carboplatin, etoposide; U, unclassifiable B-cell lymphoma, with features between DLBCL and Burkitt lymphoma.

Other cases could be designated using 2001 World Health Organization terminology as atypical Burkitt lymphoma; however, these tumors were BCL2+. Unlike the findings of Johnson *et al*,<sup>10</sup> in this study morphological features did not correlate with prognosis. A comparison of patients with diffuse large B-cell lymphoma vs non-diffuse large B-cell lymphoma tumors showed no significant difference in survival. Similarly, a comparison of patients with diffuse large B-cell lymphoma vs Burkitt-like lymphoma vs atypical Burkitt lymphoma showed no differences in survival.

Others have shown that MYC/8q24 translocation in cases of MYC/BCL2 lymphoma can partner with all IG loci as well as non-IG loci. In the study by Johnson *et al*,<sup>10</sup> karyotypes available in 30 cases showed involvement of IGH in 53%,  $\lambda$  in 37%, and  $\kappa$  in 10%. Combining conventional karyotyping with fluorescence *in situ* hybridization, approximately 44% MYC/BCL2 lymphomas partnered with a non-IG locus, and this occurrence was associated with diffuse large B-cell lymphoma morphology. In this study, karyotypes were available for 21 cases. The partners of MYC were  $\lambda$  in 9 (43%), IGH in 7 (33%),  $\kappa$  in 2 (10%), and a non-IG locus in 3 (14%). The frequency of MYC translocations involving  $\lambda$  and  $\kappa$  is very similar to that reported by Johnson *et al*,<sup>10</sup> but we cannot explain the lower frequency of MYC partnering with non-IG loci in this study.

In an earlier and smaller study by our group, all MYC/BCL2 lymphomas reported were BCL2+,<sup>18</sup> but this was not the experience of others in subsequent studies.<sup>10,12,16</sup> The data in this large study show that approximately 15% of MYC/BCL2 lymphomas are negative for BCL2 by immunostaining, in agreement with other studies. One potential explanation is that this subset of neoplasms truly expresses BCL2, but mutations in BCL2 preclude recognition with the commonly used anti-BCL2 antibody (monoclonal antibody 124; DAKO) that was used in this study. This has been shown to be the case in a subset of BCL2- MYC/BCL2 lymphomas by others.<sup>10</sup> Alternatively, these tumors are truly negative for BCL2 expression. Others have reported a better overall survival for patients with BCL2- versus BCL2+ MYC/BCL2 lymphomas. Our results show a similar trend, with median overall survival of 48 months in BCL2- cases vs 13.7 months in BCL2+ cases, but this did not reach statistical significance.

It is not entirely clear if MYC/8q24 rearrangement and IGH@BCL2 occur concurrently or sequentially in *de novo* MYC/BCL2 lymphomas. Others have suggested that frequent involvement of IG light chain and a non-IG gene as partners of MYC indicates that MYC rearrangement is a secondary event.<sup>11</sup> However, Snuderl *et al*.<sup>22</sup> reported a case of follicular lymphoma associated with t(14;18)(q32;q21) that also had blastoid morphological features and MYC translocation. In this study, MYC/BCL2 lymphomas arose shortly after or nearly coincided with the diagnosis of low-grade follicular lymphoma in 6 of 10 cases,

suggesting that a subset of tumor cells already carried MYC translocation in otherwise morphologically low-grade follicular lymphoma. In support of this idea, one case reported by Kanungo *et al*.<sup>18</sup> was morphologically low-grade B-cell lymphoma and yet had MYC rearrangement and IGH@BCL2. Alternatively, as suggested by others, MYC/BCL2 lymphomas may arise in two ways: from a clinically overt or subclinical follicular lymphoma, or directly from B cells with IGH@BCL2 that have not attained malignant potential.<sup>11</sup>

We also report eight B-cell lymphomas that carried MYC/8q24 and BCL2 abnormalities, and yet did not meet the classical definition of MYC/BCL2 lymphoma. Six patients had 3–8 MYC signals associated with IGH@BCL2. These patients had aggressive clinical or laboratory findings, including high International Prognostic Index and high to very high serum lactate dehydrogenase levels. Three of six patients died within 1.4–49 months. Two patients had MYC rearrangement and extra BCL2 signals or an extra chromosome 18. These patients had similar aggressive clinical or laboratory findings and one patient died in <1 year. Relatively little information is available in the literature for cases such as these eight cases reported here. Snuderl *et al*.<sup>22</sup> described one patient with histologically aggressive B-cell lymphoma associated with MYC translocation and eight BCL2 copies and this patient did poorly. The authors included this case in their study of 20 MYC/BCL2 lymphomas and our data support this approach. We suggest that the eight cases we report appear to fit within the spectrum of MYC/BCL2 lymphomas; however, confirmation of this hypothesis after analysis of a larger number of cases is needed.

Despite intensive chemotherapy, the median overall survival for patients in this study was 18.6 months. Although prognosis was poor, however, patients in this study had relatively better survival compared with that of patients with MYC/BCL2 lymphomas reported in the literature, in which the median overall survival has been reported in the range of 4.5–6 months, with 1-year survival <30%.<sup>10,22</sup> The reasons for this discrepancy are unclear. Perhaps the better overall survival can be attributed to the fact that nearly two-thirds of patients received high-intensity chemotherapy and that nearly all patients received rituximab. Previous studies have shown that addition of rituximab might improve the outcome of patients with MYC/BCL2 lymphoma (overall survival 1.4 years in R-CHOP group vs 0.4 years in CHOP group).<sup>10,29</sup> However, it is difficult to comment on the impact of different therapies in this study as the patients were not treated in a standardized manner. It seems reasonable to conclude that the overall poor outcome of patients with MYC/BCL2 lymphoma, regardless of the individual study, indicates that novel therapeutic approaches are required.

As shown in earlier studies,<sup>9,10,18,21,22</sup> patients with MYC/BCL2 lymphomas have a number of

poor prognostic features. Most patients in this study had a high serum lactate dehydrogenase level. There was a high frequency of bone marrow involvement and many patients had multiple extranodal sites of involvement. Central nervous system disease was also common, although the frequency of involvement in our cohort is lower than that reported in an earlier study.<sup>22</sup> Most patients in this study had a high International Prognostic Index and patients with antecedent/concurrent low-grade follicular lymphoma had a poor prognosis. This feature has not received much attention in the literature to date. In a univariate analysis, elevated serum lactate dehydrogenase level,  $\geq 2$  extranodal sites of involvement, bone marrow involvement, central nervous system involvement, advanced Ann Arbor stage (III/IV) disease, International Prognostic Index  $> 2$ , and antecedent/concurrent low-grade follicular lymphoma (*vs de novo* disease) correlated with overall survival. In a multivariate analysis, International Prognostic Index score was an independent predictor for overall survival, and serum lactate dehydrogenase level and International Prognostic Index were independent predictors of progression-free survival.

In conclusion, *MYC/BCL2* lymphomas are clinically aggressive neoplasms that exhibit a spectrum of morphological findings and are associated with a poor prognosis. In this study, stratification into World Health Organization classification categories did not correlate with prognosis. Patients with tumors that had extra *MYC* signals associated with *IGH@BCL2* or *MYC* rearrangement associated with extra *BCL2* signals had morphological and immunophenotypic features similar to classical *MYC/BCL2* lymphomas, and also had a poor prognosis. Therefore, we suggest that these cases may expand the spectrum *MYC/BCL2* lymphomas. In addition to the many poor prognostic features described by others, antecedent/concurrent low-grade follicular lymphoma appears to identify a subset of patients with a poor prognosis.

## Disclosure/conflict of interest

The authors declare no conflict of interest.

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