VOLUME 28 · NUMBER 17 · JUNE 10 2010

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Prognostic Factors in Follicular Lymphoma

Thomas Relander, Nathalie A. Johnson, Pedro Farinha, Joseph M. Connors, Laurie H. Sehn, and Randy D. Gascoyne

From the Departments of Pathology & Laboratory Medicine and the Division of Medical Oncology, British Columbia Cancer Agency and the University of British Columbia, Vancouver, British Columbia, Canada.

Submitted September 14, 2009; accepted December 17, 2009; published online ahead of print at www.jco.org on April 12, 2010.

Supported by grants from the Crafoord Foundation (T.R.), The Gunnar Nilsson Cancer Foundation (T.R.), The Michael Smith Foundation (01793; N.A.J.), the Canadian Institute of Health Research (53912; N.A.J., P.F.), Fundação para la Ciência e Tecnologia (BD13230/2003; P.F.), Genome Canada (J.M.C., R.D.G.), The Terry Fox Foundation (019001; J.M.C., R.D.G.), and the National Cancer Institute of Canada (019005; N.A.J.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Randy D. Gascoyne, MD, FRCPC, Department of Pathology, British Columbia Cancer Agency, 600 W 10th Ave, Vancouver, British Columbia V5Z 4E6, Canada; e-mail: rgascoyn@bccancer.bc.ca.

0732-183X/10/2817-2902/$20.00

DOI: 10.1200/JCO.2009.26.1693

ABSTRACT

Follicular lymphoma (FL) is one of the most common types of non-Hodgkin's lymphoma. It is usually diagnosed at an advanced stage, for which many treatment options exist, however, no curative standard therapy has been identified. The outcome is highly variable with a median survival of approximately 10 years. The life expectancy of patients with FL has been extended with the use of rituximab, a monoclonal antibody targeting the CD20 antigen on FL cells, but there remains a group of patients who fail to respond to chemoimmunotherapy and die early of their disease. Transformation of FL to an aggressive histology is an important event with high morbidity and mortality. The Follicular Lymphoma International Prognostic Index has become the clinically useful prognostic tool, but gives only a rough estimate of expected outcome. There is a need for useful biomarkers for prediction of the disease course of single patients to individualize therapy, especially in the new era of chemoimmunotherapy.

J Clin Oncol 28:2902-2913. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Follicular lymphoma (FL) constitutes approximately 20% of all newly diagnosed lymphoma cases,[1] making it the second most common subtype of non-Hodgkin's lymphoma worldwide and the most common subtype seen in North America.[2] It is characterized by an indolent clinical course, typical morphology, and the presence of a chromosomal translocation, t(14;18)(q32;q21) or variant in 85% of patients. This chromosomal aberration results in the juxtaposition of the immunoglobulin heavy chain gene (*IGH*) on chromosome 14 with the *BCL2* oncogene on chromosome 18 leading to constitutive, and therefore inappropriate, expression of the BCL2 protein. Overexpression of *BCL2* confers relative resistance to apoptosis, thus giving the cells a survival advantage that may facilitate the acquisition and retention of secondary genetic abnormalities.

FL is a heterogeneous entity with some patients developing progressive or transformed disease early and 15% dying within 2 years from diagnosis, while others remain alive for decades without need for treatment. This variability in outcome underscores the necessity to gain further insight into the biology and clinical behavior of the disease to enable individualized therapy.

TREATMENT AND CLINICAL COURSE

The median age at diagnosis of FL is 59 years with a male to female ratio of 1:1.7.[3] FL is typically diagnosed in the advanced stages, with only 26% to 33% of patients presenting with stage I to II disease.[3,4] With conventional chemotherapy, even if combined with radiotherapy, advanced-stage FL is incurable. It is characterized by an indolent course with patients developing slowly progressive lymphadenopathy over many years, with or without constitutional B symptoms (eg, fever, weight loss > 10%, drenching night sweats). Temporary, spontaneous regressions occur in 20% of patients managed without initial therapy.[5] Historically, median survival has ranged from 6 to 10 years.[4-7]

Transformation to an aggressive lymphoma occurs at a rate of 3% per year and is associated with substantial morbidity and mortality.[8,9] Transformation is defined as the development of a more aggressive histology lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL), that is thought to be clonally related to the original FL.

Limited-stage FL treated with external-beam radiotherapy results in prolonged remission in 30% to 50% of patients and an apparent plateau on the disease-free survival curve after 15 to 20 years.[10,11] Two randomized studies showed that deferred initial treatment in asymptomatic advanced-stage patients does not compromise long-term outcome or risk of transformation.[7,12] FL is highly sensitive to antineoplastic agents early, but grows increasingly resistant with successive lines of therapy.[4]

The chimeric anti-CD20 monoclonal antibody rituximab has significant activity alone[13] and in combination with chemotherapy.[14] The addition of

rituximab to chemotherapy has resulted in a higher rate of complete remission (CR) and prolonged remission duration without increasing clinically relevant toxicity.[15] Several studies have confirmed an improvement in overall survival (OS) with immunochemotherapy as the initial treatment for FL.[15-17] Furthermore, rituximab as maintenance therapy after induction therapy for relapse improves progression-free survival (PFS) and OS.[18] However, an improved survival for patients diagnosed with FL has been noted over the past 25 years,[19] an effect at least in part predating the introduction of rituximab, likely explained by improved diagnosis and supportive care.

CLINICAL PARAMETERS

Multiparameter Indices

The International Prognostic Index (IPI), originally developed for aggressive lymphoma, identifies four risk groups based on age, tumor stage, serum lactate dehydrogenase (LDH) level, performance status, and number of extranodal sites of disease.[20] The IPI also reliably identifies risk groups among FL[21-23]; however, it only classifies a small proportion of patients into the highest-risk category.

Three prognostic indices have been developed specifically for FL. The Italian Lymphoma Intergroup (ILI) index identifies three risk groups with 10-year survival rates of 65%, 54%, and 11% based on six clinical parameters (advanced age, male sex, number of extranodal sites of disease, B symptoms, serum LDH level, and erythrocyte sedimentation rate).[24]

In 2004, the Follicular Lymphoma International Prognostic Index (FLIPI) was published resulting from a multicenter effort.[25] It includes five parameters: age (> 60 *v* ≤ 60 years), stage (III-IV *v* I-II), anemia (hemoglobin < 120 *v* ≥ 120 g/L), number of involved nodal areas (> 4 *v* ≤ 4), and serum LDH (elevated *v* normal), and classifies patients into three groups with 10-year OS rates of 71%, 51%, and 36%, respectively. The FLIPI is predictive in patients treated with immunochemotherapy,[26] can be applied in first relapse,[27] and predicts transformation.[28] The IPI, FLIPI, and ILI indices have been directly compared, all identifying somewhat different risk groups.[29] Recently, the FLIPI-2 index was published, incorporating beta-2 microglobulin, lymph node size larger than 6 cm, bone marrow involvement, anemia, and age older than 60 years (Table 1).[25,30,36] All of these clinical indices are robust, easy to use in clinical practice, and of value for stratification in clinical trials; however, marked variations in outcome remain within each risk group.

Biomarkers in Blood and Bone Marrow

There are conflicting reports regarding the prognostic impact of bone marrow (BM) involvement by FL. BM involvement was associated with decreased survival in several investigations including those of the ILI and the FLIPI.[24,25,32,33] In contrast, others have not found BM involvement in itself to affect survival,[34] but rather the histologic pattern[35] or degree of marrow involvement.[36] Importantly, BM status at the time of diagnosis has been included in the FLIPI-2.[30]

The characteristic t(14;18)(q32;q21) generates a *BCL2-IGH* fusion gene, which can be used as a marker of disease detectable by polymerase chain reaction (PCR).[37] This technique is highly sensitive and can routinely detect one translocation-positive cell in 10^6 cells in peripheral blood (PB) or BM. PCR has been used for detecting minimal residual disease (MRD) after therapy.[38] Three different break points within the *BCL2* gene have been identified in FL.[39-41] However, the value of molecular monitoring in FL has not yet been established. Despite attaining a CR after chemotherapy, the BM remained positive by PCR in all or most patients without clear prognostic impact in some reports,[42-44] whereas others have found molecular CRs to be common.[45] Rambaldi et al[46] reported that the degree of BM involvement by lymphoma by quantitative real-time PCR before rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy was predictive of outcome and that patients attaining molecular CR experienced a prolonged freedom from relapse.

Currently, the implication of the presence of t(14;18)-positive cells detected by PCR remains unknown. Not all PCR-positive patients relapse, and some convert to PCR negativity without therapy.[47] Furthermore, t(14;18)-positive cells have been found in patients in long-term remission after therapy for FL[48,49] and *BCL2* translocations have been detected by PCR in PB from healthy individuals and from autopsies from patients without lymphoma.[50,51]

Other Biomarkers in Blood

Biomarkers readily measurable from the PB that have been correlated with outcome in FL are summarized in Table 2.[52-67] Beta-2 microglobulin has reached wide acceptance as a prognostic marker and is included in FLIPI-2,[31] but is not universally available in retrospective cohorts.[24,25] LDH is a robust prognostic factor in several types of lymphoma; however, in FL it is elevated in only 20% of patients.[24,25] Serum angiogenic factors have been analyzed in heterogeneous groups of patients with lymphoma with partly conflicting results.[59,60,61,63,68] Interestingly, polymorphisms leading to high expression of tumor necrosis factor may influence outcome in non-Hodgkin's lymphoma, pointing to the importance of host factors.[62,64-66]

Table 1. Adverse Factors in the FLIPI and the FLIPI2 Indices

FLIPI[25]	FLIPI2[30]
Age > 60 years	Age > 60 years
Stage III-IV	Bone marrow involvement
Anemia (Hb < 120g/L)	Anemia (Hb < 120 g/L)
Number of involved nodal areas > 4	Nodes > 6 cm
LDH > ULN	β2-microglobulin > ULN

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper level of normal.

PATHOLOGIC PARAMETERS

FL is a neoplasm of germinal center B cells that mimic the architecture of normal secondary lymphoid follicles. Benign and malignant follicles contain a heterogeneous mixture of non-neoplastic cells including T cells, benign B cells, follicular dendritic cells (FDC), and macrophages. The majority of patients with FL manifest two major types of neoplastic B cells: small centrocytes and larger centroblasts. Histologic grading of FL is based on the relative proportions of these two cell types.

Histologic Grade

The current WHO classification recognizes three histologic grades (grades 1 to 3) of FL.[69] Grading of FL is poorly reproducible

Table 2. Peripheral Blood Biomarkers and Prognosis in FL

Biomarker	Effect on OS	Other Effects	Comment
Absolute lymphocyte count	Longer if ↑ [52]		
Beta-2 microglobulin		Poor response and short TTF if ↑ [15,53]	
	Shorter if ↑ [54]		
	Shorter if ↑ [55]		FL grade 3
	Shorter if ↑ [56]	Shorter FFP if ↑	FL grade 3
		Shorter FFP in first relapse if ↑ [57]	
LDH	Shorter if ↑ [24,25,33]		
	No effect[58]		Stage I-II
Albumin			
Serum	Shorter if ↓ [24,25]		
Urine		Poor response and short PFS if ↑ [58]	
VEGF	Shorter if ↑ [59]	Associated with other poor prognosis factors	Only 13% FL
FGF	Shorter if ↑ [60]	Strong prognostic factor	Only 14% FL
VEGF + FGF	Shorter if ↑ [61]	Combination independent of IPI	Only 14% FL
	No effect[62]		30% FL
Endostatin	Shorter if ↑ [63]	Associated with VEGF ↑	Only 16% FL
TNF	Shorter if ↑ [64,65]	Shorter PFS if ↑	Combined with receptor levels; 40% indolent lymphoma
TNF + sCD23		Poor response if ↑ [66]	Indolent lymphoma
sICAM-1	Shorter if ↑ [67]	Correlated to advanced disease and B-symptoms	Minority FL

Abbreviations: FL, follicular lymphoma; OS, overall survival; TTF, time-to-treatment failure; FFP, freedom from progression; LDH, lactate dehydrogenase; PFS, progression-free survival; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; IPI, International Prognostic Index; TNF, tumor necrosis factor; sICAM-1, soluble inter-cellular adhesion molecule-1.

among pathologists, calling into question studies that report prognostic impact based solely on this variable. Similarly, subtle architectural variations, such as the presence of diffuse areas, have not been well annotated in most FL studies. Immunostaining for FDCs has been infrequently performed, making it difficult to accurately determine true follicle formation in most reported studies.[70,71] Several studies have suggested a correlation between grade and survival in FL.[23,69,72,73] Although there is no OS difference between patients with grade 1 or 2 FL, there remains controversy about an inferior OS correlating with FL grade 3. This may reflect that grade 3 FL itself is heterogeneous. Anthracycline-based therapy has been claimed to be beneficial when treating patients with grade 3 FL[69] and to have a potential for cure; however, this remains controversial.[23,55,56,74,75] Miller et al[76] found no plateau in the survival curve or difference in OS between patients receiving aggressive therapy for FL of different grades. In a retrospective analysis, Chau et al[73] found no difference in survival among FL grades 1 to 3. Patients with FL grade 3 were similarly at risk for late relapses as for grades 1 and 2.

The WHO classification subdivides FL grade 3 into FL grade 3A, made up of a mixture of centroblasts and centrocytes, and FL grade 3B, in which the centroblasts are distributed in confluent sheets.[69] Potentially, FL grade 3A may lie within the spectrum of disease with FL grades 1 to 2, while FL grade 3B may behave similarly to de novo DLBCL. Similar to FL grades 1 to 2, FL grade 3A is more likely to be CD10 positive and t(14;18) positive compared with FL grade 3B.[71] Furthermore, chromosomal aberrations involving 3q27 (*BCL6*) occur in a similar frequency in FL grade 3B and DLBCL.[71,77] However, in one report comprising 190 patients with FL grade 3, no difference in event-free survival or OS was found between patients classified as grade 3A and grade 3B,[70] which is supported by Chau et al.[73] Thus, the relevance of distinguishing between FL grade 3A and 3B remains unclear. Identifying areas of diffuse disease,[70] likely a harbinger of transformation, may be more clinically relevant.

Immunophenotype: Neoplastic Cells

Proliferation index. The proliferation index has prognostic value in FL.[23,78] It correlates with the number of large cells and thus with histologic grade and with OS in univariate analysis but not in multivariate analysis.[79]

BCL2 and BCL2 family proteins. The family of BCL2-related proteins plays a central role in the surveillance of mitochondrial integrity by balancing between pro- and antiapoptotic members. Only a few of these proteins have been studied in relationship to prognosis in FL and no consistent correlation has been found.[80] As a possible exception, a high number of MCL1-positive centroblasts has been correlated with poor OS.[81] Similarly, expression of the long RNA isoform of $BCLX_L$ has been correlated with prognosis in FL,[82] however, expression of the protein did not.[83]

Using reverse-phase protein microarrays, when microdissected follicles from reactive lymph nodes were compared with follicles with FL, most proapoptotic and antiapoptotic proteins except for BCL2 were present at comparable levels in BCL2-positive and BCL2-negative tumors with activation of the AKT/BAD signaling pathway.[84] Gulmann et al[85] also used a proteomic approach to analyze apoptotic pathways in FL. They found phosphorylation of AKT to be frequent in FL suggesting that it may act as an antiapoptotic agent along with BCL2. High ratios of BCL2/BAK and BCL2/BAX were associated with early death from disease. The expression patterns of other proapoptotic members of the BCL2 family have largely unknown clinical impact.[86] Future studies on the role of BCL2 family proteins in FL are

needed as they may identify patients who will benefit from novel BH3 mimetics, small molecules that specifically target BCL2 proteins.[87,88]

Germinal center–related markers. *BCL6* encodes a zinc finger transcription factor involved in germinal center formation. CD10 is a membrane metalloendopeptidase expressed in the germinal center. In FL, these two markers of germinal center origin are expressed in more than 95% and 75% of cases, respectively.[89] Although their prognostic significance is established in DLBCL,[90] their relevance in FL is less clear. Using immunohistochemical scoring systems to combine the percentage of positive malignant cells and their intensity of expression, the expression level of BCL6 has been correlated with favorable prognosis in FL.[91] PU.1 is an ETS-domain transcription factor essential for the development of myeloid and B lymphoid cells. Constitutive PU.1 expression inhibits the earliest B-cell development, and low levels of PU.1 expression in hematopoietic progenitor cells are instrumental in promoting B-cell fate determination.[92] Torlakovic et al[93] studied the clinical impact of proteins associated with the germinal center in FL and found PU.1 protein expression, but not CD10 or BCL6, to be a favorable marker of OS independent of the FLIPI.

Cell cycle regulators. *TP53* mutations have been reported in FL at diagnosis and are associated with an inferior survival.[94] The presence of mutations leading to overexpression of the TP53 protein has been associated with transformation.[95,96] Expression of TP53 protein is only moderately correlated with the presence of mutations (64%) and similarly with the expression of key regulators of TP53, such as CDKN1A or MDM2.[97] The latter have also been shown to correlate with transformation.[97,98] A gene expression profiling study of 57 patients with FL established a set of 14 genes that were highly expressed in patients with a favorable response to CHOP; however, only expression of *CYCLIN B1* mRNA and protein level had prognostic impact independent of the FLIPI.[99]

Others. SOCS3 is a cytokine suppressor that inhibits cytokine signaling by Janus kinase (ie, the JAK-STAT pathway). Overexpression of SOCS3 has been reported to be an independent unfavorable prognostic factor in FL.[100] Overexpression of Ying-Yang 1, a zinc-finger protein regulating *IL4* gene expression, has also been linked with shorter survival in FL.[101]

Cytogenetics and Molecular Genetics

Classical karyotyping. Cytogenetic analysis of FL reveals a wide range of recurrent, nonrandom chromosomal alterations. FL is characterized by the overexpression of the antiapoptotic protein BCL2 as a result of the t(14;18)(q32;q21) or its rare variants t(2;18) and t(18;22). t(14;18) is present in approximately 85% of grade 1 and 2 FL and although it is considered insufficient on its own to cause FL, it provides these B cells with a survival advantage leaving them prone to accumulate additional genomic abnormalities.[102] However, in a study of FL cases lacking the t(14;18), Horsman et al[103] found distinct patterns of recurrent chromosomal alterations. In another report, FLs lacking the t(14;18) were less likely to express CD10 or BCL2, were more likely to arise at extranodal sites and had a better OS. Recently, Katzenberger et al[104] described t(14;18)-negative FL characterized by a predominantly diffuse growth pattern, presenting clinically with large but localized inguinal tumors. The majority of FL patients without a t(14;18) have a deletion in 1p36.

The malignant cells in FL have an average of four to six different cytogenetic changes in addition to the *BCL2* translocation.[105,106] Only 5% of FL have t(14;18) as the sole detectable abnormality. The most common abnormalities are break points in chromosome 1, deletions in the long arm of chromosome 6 (6q−), trisomy 7 (+7), trisomy 12 (+12), presence of a derivative of chromosome 18 (der(18), and duplication of X (+X).[106]

Early studies suggested that the number of abnormalities and presence of certain alterations (6q−, +7, +X, +21) were associated with an inferior survival.[107] However, as karyotypic complexity increases after therapy,[108] there is an inherent selection bias if biopsies

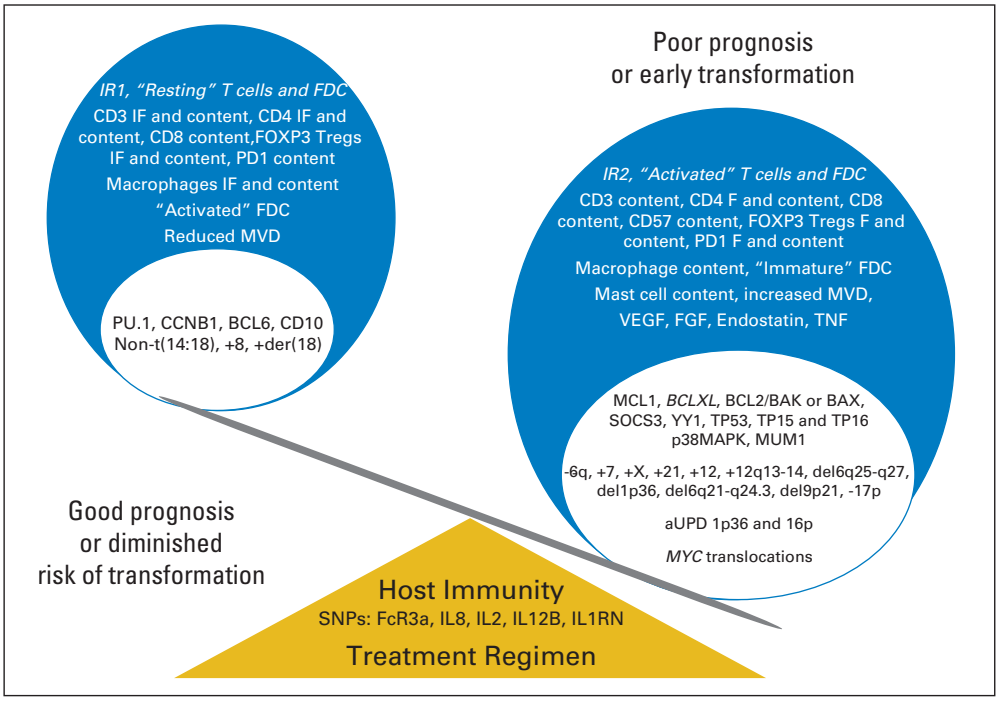

Fig 1. Biomarkers impacting survival or transformation in follicular lymphoma (FL). Some biomarkers are controversial, resulting from treatment heterogeneity. Larger circle: features of nonmalignant cells. Inner circle: tumor cells. IR, immune response; FDC, follicular dendritic cells; IF, interfollicular; F, follicular; MVD, microvessel density; VEGF, vascular endothelial growth factor; EGF, endothelial growth factor; TNF, tumor necrosis factor; aUPD, acquired uniparental disomy; SNPs, single nucleotide polymorphisms.

taken at the time of progression or relapse are used for analysis. Tilly et al[109] reviewed 66 FL biopsies taken at the time of diagnosis and found deletion 6q to be associated with an inferior survival. Höglund et al[110] reviewed the karyotypes of 336 cases of FL and, using principle components analysis, postulated distinct pathways of clonal evolution of chromosomal changes arising in a temporal order with early changes being 1q+, +7, +8,+12, and +der(18) and later 2p−, 10p−, −15, 17p−, and 17q−. Based on the clinical data on 165 patients, +12 and 17p− were correlated with an adverse outcome. In contrast, we recently reviewed 210 karyotypes from FL biopsies taken at diagnosis and found no association between the number or type of cytogenetic abnormalities with clinical outcome.[111]

Comparative genomic hybridization. Comparative genomic hybridization (CGH) can be performed by hybridizing tumor DNA against normal chromosomes (chromosomal CGH) or by using microarray platforms with spotted DNA probes (array CGH).[112] Viardot and colleagues[113] analyzed 124 samples of FL using chromosomal CGH and reported a number of recurrent alterations. In a subset analysis of 82 patients, loss of chromosomal material at 6q25-27 was a strong independent predictor of inferior survival. Cheung et al[114] identified two genomic regions, deletions in 1p36.22-p36.33 and 6q21-q24.3, to be highly associated with transformation and inferior OS in patients with FL using array CGH. Recently, Schwaenen et al[115] reported a large number of recurring genomic aberrations in FL as analyzed by array CGH, of which deletions in 9p21 (*CDKN2A/B*), 6q25, and 6q26 were associated with inferior survival.

Single nucleotide polymorphism arrays. Copy-neutral loss of heterozygosity, undetectable by previously available methods, can be identified using single nucleotide polymorphism (SNP) arrays. This phenomenon, termed acquired uniparental disomy (aUPD), results from mitotic recombination or nondisjunction and has been described in FL.[112,116] In a recent report, a number of recurring aUPDs were described in FL, of which aUPD on 1p36 correlated with shortened OS and aUPD on chromosome 16 was predictive of transformation.[117]

Host Constitutional Genetics

SNPs are changes in the DNA sequence by one base pair. Recent studies have suggested that SNPs in the *FcγR* genes may significantly alter the binding affinity between the Fc portion of rituximab and the Fc receptors on macrophages.[118,119] Cartron et al[120] found a correlation between the *FcRIIIA* genotype and response to single-agent rituximab in untreated FL. Patients homozygous for −158VV *FcRIIIA* polymorphism did significantly better than the heterozygotes −158VF. In a study of recurrent FL, Weng and

Table 3. Morphologic, Immunophenotypic, and Gene Expression Biomarkers in FL

Biomarker	Impact on Survival	Risk of Transformation
Morphology		
Tumor cells		
Histologic grade[70,74]	Therapy-dependent, increasing grade associated with worse OS; effect possibly mitigated by doxorubicin-containing regimens	No effect
Grade 3A *v* 3B[22,55,70,71,76,77]	No effect	Typically already present in grade 3B
Architecture (diffuse)[26,71]	Controversial	Increased
Proliferative rate[22,78,79,133,174,175]	Controversial	No effect
Microenvironment		
Microvessel density[129-131]	Controversial	Not studied
Macrophages[83,127,135-137]	Unfavorable	No effect
FDC[102,135,176]	Unfavorable if immature phenotype of FDCs	Increased; associated with FDC disruption
$CD4^+$ T cells[83,102,136,140,142,149,177-179]	Controversial	No effect
$CD8^+$ T cells[136,142,146,147]	Controversial	Controversial
Regulatory T cells[136,140-142,177]	Controversial	Not studied
Single gene (RNA and/or protein)		
BCL6 and *CD10*[91]	Favorable	Not studied
BCL2 and *BCL2/BAX* or *BAK*[80,86]	High ratio favoring *BCL-2* associated with early death	Not studied
MCL1[81]	High *MCL-1* associated with worse outcome	Not studied
$BCLX_L$[82]	High $BCL\text{-}X_L$ associated with inferior survival	Not studied
MUM1[180,181]	Expression of *MUM1* may be associated with inferior survival	Not studied
PU.1[93]	Favorable	Not studied
SOCS3[100]	Unfavorable	Not studied
YY.1[101]	Unfavorable	Not studied
Multigene		
IR-1 and *IR-2*[127]	Variable; *IR-1* associated with favorable OS, while *IR-2* predicts for inferior OS	Not studied
81-gene predictor[128]	No effect; strongly predictive of immediate clinical behavior	No effect

Abbreviations: FL, follicular lymphoma; OS, overall survival; FDC, follicular dendritic cells; IR, immune response signature.

colleagues[121] confirmed these findings and identified a second polymorphic site related to the duration of response (*FcRIIA* 131 histidine/arginine). Similarly, Ghielmini et al[122] reported that *FcRIIIA* V/V was a predictive factor for event-free survival in rituximab monotherapy in FL. In contrast, Maloney et al and others[123,124] did not find that *FcRIIIA* or *RIIA* polymorphisms correlated with outcome in a study of R-CHOP.

Recently, Cerhan et al[125] analyzed the impact of immune response SNPs in FL. Germline DNA was analyzed from patients with FL and a final set of four prognostically relevant immune response SNPs was identified (interleukin [*IL*] *-8*, *IL2*, *IL12B,* and *IL1RN*). An outcome predictor was built using clinical and demographic factors combined with the four deleterious SNPs, which identified three risk groups with 5-year OS estimates of 96%, 72%, and 58%, respectively. These patients were treated in an era before the use of rituximab. Although these four genes strongly predict outcome in patients with FL, none of them has been shown to be associated with the risk of developing FL.[125,126] Together with the gene expression profiling (GEP) data below,[127] these results suggest that the composition and functional status of the immune cells in the tumor microenvironment of FL may largely be driven by the genetics of the host.

Non-Neoplastic Cells of the Microenvironment

Lymph nodes involved with FL contain an admixture of non-neoplastic T cells, FDCs, macrophages, and other cells. A renewed interest in the microenvironment in FL followed the Leukemia Lymphoma Molecular Profiling Project (LLMPP) study in 2004[127] in which GEP of whole-section frozen lymph nodes from 191 cases of FL demonstrated that the tumor microenvironment was the most important predictor of patient outcome. Two signatures of gene expression were identified that best correlated with survival prediction. The immune-response 1 (IR-1) signature included genes encoding for T-cell markers and some genes that are highly expressed in monocytes/macrophages, and predicted a favorable outcome. The IR-2 signature included genes preferentially expressed in macrophages or dendritic cells, and predicted an unfavorable outcome. When patients were grouped into quartiles based on their survival-predictor scores, median survival rates ranged from 3.9 years to 13.6 years. These data highlighted the dominant prognostic role of the microenvironment in FL and suggested that the critical determinants of outcome might already be present at diagnosis.

After the LLMPP study, Glas et al[128] performed GEP in a series of patients with FL who were grouped according to outcome and transformation. They defined an 81-gene predictor that correlated with immediate clinical behavior but not with long-term survival or risk of transformation. Interestingly, the genetic profile of patients with early transformation exhibited an activated status of T cells, FDCs, and macrophages characterized by genes that were present in the favorable IR-1 signature of the LLMPP study. Differences in experimental design, patient selection, gene expression platforms, and data analysis may explain the different conclusions between these two studies.

Microvessel density. Despite evidence for a vital role of angiogenesis in supporting tumorigenesis,[129] some reports have suggested that increased vessel density correlates with better prognosis in FL.[130] Intriguing results by Streubel et al[131] demonstrated that endothelial cells of the microvasculature share the *BCL2* rearrangement characteristic of FL, implying an intimate relationship between the two.

FDC meshwork "immaturity." In addition to presenting antigens, FDCs comprise the scaffolding of both benign and malignant follicles, their dendritic processes providing structural support for B cells and non-neoplastic cells. An immature FDC phenotype is typified by expression of low-affinity nerve growth factor and CNA.42, accompanied by absence of mature FDC markers such as CD21, CD35, CD23, and CXCL13. This phenotype typifies undifferentiated fibroblastic cells and has been reported to correlate with progression

Table 4. Molecular Genetic Biomarkers in FL

Gene	Impact on Survival	Risk of Transformation
BCL2[165,182-186]	No clear survival difference between t(14;18)-positive FL and t(14;18) negative; suggestion that *BCL2* breakpoint may affect survival, but unconfirmed by later studies	Somatic mutations of *BCL2* gene on the translocated allele may rarely underlie transformation
MYC[161-163,170]	Translocations of *MYC* rarely encountered at diagnosis; tend to confer an inferior survival	Infrequently associated with transformation, but when found they are associated with markedly inferior post-transformation survival
CDKN2A/B[160,187]	Tumor suppressor genes on chromosome 9p21; only rarely found at diagnosis and not definitively associated with survival	Paired sample studies clearly show loss of *CDKN2A/B* through deletion, mutation, or hypermethylation is associated with histologic transformation
TP53[95-97]	Loss of *TP53* tumor suppressor only rarely seen at diagnosis; mutation is closely correlated with protein expression in FL	Loss of *TP53* was the first gene implicated in transformation of FL; LOH not typically associated with 17p13 deletion
MDM2[97,99]	None	Expression correlated with transformation, but not obviously correlated with TP53 gene status; found within the amplified region of chromosome 12q13-14 frequently associated with transformation
BCL6[164,184,188]	No clear affect on survival in FL	Postulated to increase risk of transformation, but studies documenting the presence of translocations were based exclusively on inverse LD-PCR
CCNB1[99]	Increased expression of cyclin B1 associated with improved survival after CHOP chemotherapy	

Abbreviations: FL, follicular lymphoma; LOH, loss of heterozygosity; LD, long-distance; PCR, polymerase chain reaction; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

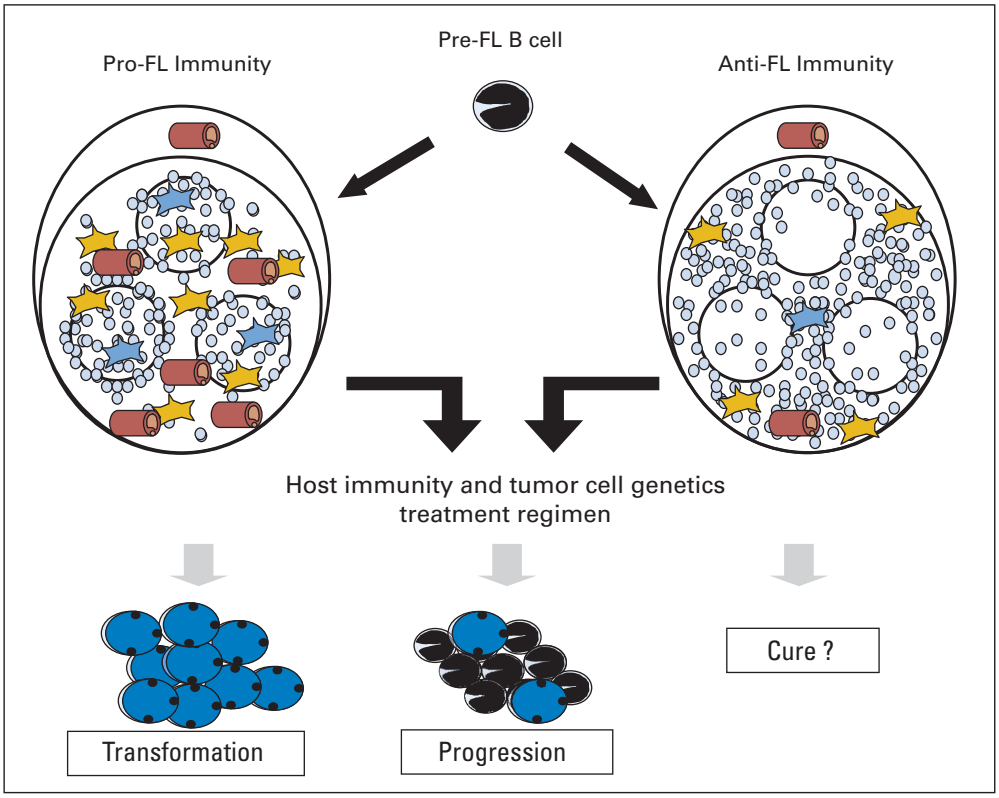

Fig 2. Model of how non-neoplastic cells in the microenvironment might impact survival and transformation in follicular lymphoma (FL). Left: follicular polarization of CD4+ cells, especially forkhead box protein P3–positive regulatory T cells (blue circles), increased numbers of vessels (red tubes), mast cells (blue stars), or macrophages (gold stars): local immunity supports tumor growth. Right: an antilymphoma immune response.

and/or transformation,[132] but not in all studies.[83] These changes correlate with loss of normal T-cell infiltration within follicles and might reflect a reduced cross-talk between these two cell types. Disruption of the tight FDC meshwork that characterizes FL has been associated with early transformation.[133]

Macrophages. Tumor-associated macrophages have been described in a number of cancers, with increased numbers of benign macrophages typically associated with inferior survival. Farinha and colleagues[83] demonstrated that the small subset of FL cases with high macrophage content experienced markedly decreased OS and PFS independent of the IPI. These data appear consistent with the LLMPP GEP study, with high macrophage content being a surrogate for the IR-2 signature.[127] Alvaro et al[134] reported opposite results finding that increased macrophages were associated with indolent clinical behavior. In a related study, these same authors found that 30% of macrophages express STAT1 protein and that presence of this subset of cells was associated with inferior survival.[135] In two recent trials, a high macrophage content was associated with poor survival after chemotherapy, but not if combined with rituximab.[136,137]

Macrophage plasticity has been well described, as these cells can be broadly separated into helper (M1) and healer (M2 or activated) cell types.[138] In most tumors, tumor-associated macrophages are polarized to a M2 phenotype and appear to create a trophic environment that favors the tumor cells.[139] A pan-macrophage marker (CD68) cannot capture these distinctions and may explain the discordant results.

T-cell subsets. T cells comprise a majority of the non-neoplastic cells in FL biopsies and play an important role in FL. Subsets include helper CD4-positive T cells, cytotoxic CD8-positive T cells, CD57-positive follicular helper T cells, and immunosuppressive regulatory T cells (Treg), but the exact role played by these subsets is not completely understood. Studies investigating the roles of CD4-positive and CD8-positive T cells in FL utilize different methodologies and have conflicting results.[133,134,140-144] Tregs are a subset mostly with a CD4-positive CD25-positive forkhead box protein P3-positive[145] immunophenotype that serve a critical role in regulating CD4 and CD8 effector functions by suppressing proliferation and cytokine production of these cells.[146] In epithelial malignancies, Tregs have been implicated in creating an immunosuppressed microenvironment that allows the tumor cells to escape the host immune response.[147] Some investigators have reported that an increased number of Tregs was associated with favorable clinical behavior in FL,[134,141] while others claim that the T-cell distribution may be more relevant.[143,148] Recently, a low number of tumor-infiltrating programmed cell death 1–positive was associated with transformation and with inferior survival.[149] Still, the precise role of T-cell subsets in FL biology remains unclear. The clinical impact of these cells in the microenvironment may be largely influenced by the characteristics of the patient and the treatments received.[145] Specific therapies may have different effects on neoplastic cells versus cells within the microenvironment. Moreover, the role of host genetics influencing the immune microenvironment has only recently been explored.[125]

Transformation

Histologic transformation is often heralded by a sudden change in clinical behavior, such as a rise in serum LDH or development of unusual extranodal sites of disease. It is a dominant clinical event, associated with shortened survival and relative resistance to therapy. The reported frequency varies dramatically ranging from 5% to 60%

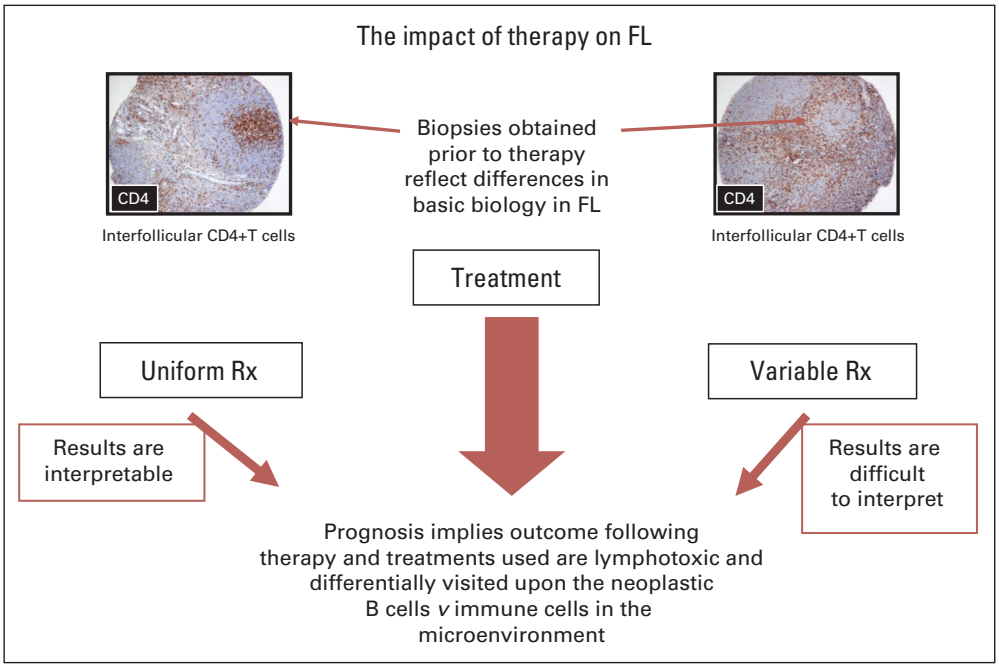

Fig 3. Treatment influences prognostic markers. Biopsies stained for CD4. Left, T cells within neoplastic follicles; right, in the interfollicular region. Importantly, treatments differentially visit toxicity on tumor cells versus cells in the microenvironment. The prognostic role of any factor must be interpreted with caution if treatment varies. FL, follicular lymphoma; Rx, therapeutic regimens.

of patients with FL.[5,8,150-156] Since risk of transformation is time dependent, approximately 3% per year, this variation probably reflects differing durations of follow-up. The length of time that patients are followed and the rigor with which biopsies are obtained at progression heavily affect the reported frequency. Biomarkers that predict for survival do not necessarily correlate with those that predict risk of transformation.

An association between increased FLIPI score and frequency of transformation has been noted.[9,28] Morphologic features associated with transformation risk include the presence of diffuse areas and disruption of the FDC meshwork.[132,157] The presence of grade 3B FL and increased intrafollicular CD4-positive T cells have also been linked to early transformation.[133]

Studies using paired samples (FL and subsequent DLBCL) have demonstrated that transformation is a molecularly heterogeneous event, including loss of *TP53*, loss of the *CDKN2A* tumor suppressor, or acquisition of *MYC* translocations, leading to upregulation of *MYC* or its target genes.[95,96,98,158-163] Other molecular alterations include mutations of the coding region of *BCL2* and translocations involving *BCL6*.[164,165] Cytogenetic studies of paired samples have revealed candidate chromosomal alterations, including +7, +12q13-14, and −6q16-21.[166-170] Lastly, a number of small studies using gene expression profiling of paired samples have been published.[160,170-173] These demonstrate the molecular heterogeneity underlying transformation, implicating upregulation of *p38 MAP KINASE*, upregulation of *MYC* and its target genes, and a generic increase in the mitotic machinery.

Recent data suggest that FL may comprise two major patient subgroups; those destined to develop transformation and those who will not.[9] Distinguishing between these two clinical risk groups might have major implications for therapy.

Translation Into the Clinic

A summary of factors associated with outcome in FL is shown in Figure 1. As presented in Tables 2, 3, and 4,[174-188] consensus on which biomarkers to use in clinical practice and how these might impact treatment decisions is still lacking. Most prognostic markers were studied before the introduction of rituximab and require validation in the current era of chemoimmunotherapy. At this time, disease behavior and robust indices, such as the FLIPI and FLIPI-2, remain the basis for clinical decision making. The key elements in the interaction of host immunogenetics, tumor microenvironment, and therapy in FL are still not well understood (Fig 2). The inclusion of correlative science into clinical trials should help to determine the precise role of biomarkers in predicting survival and transformation risk in FL. Prospective randomized clinical trials will be instrumental in defining future prognostic factors in FL, as uniform treatment groups can be compared (Fig 3). If patients who respond poorly to standard therapy can be identified and the mechanism(s) underlying their inferior outcome determined, these patients could reasonably be considered candidates for novel therapies with the potential for improved outcome avoiding toxicity from ineffective therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Randy D. Gascoyne, Roche Canada (C), Genentech (C), Celgene (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Joseph M. Connors, Hoffmann-La Roche; Randy D. Gascoyne, Roche Canada **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Thomas Relander, Pedro Farinha, Randy D. Gascoyne
Administrative support: Randy D. Gascoyne
Provision of study materials or patients: Randy D. Gascoyne
Collection and assembly of data: Randy D. Gascoyne
Data analysis and interpretation: Thomas Relander, Nathalie A. Johnson, Pedro Farinha, Joseph M. Connors, Laurie H. Sehn, Randy D. Gascoyne
Manuscript writing: Thomas Relander, Nathalie A. Johnson, Pedro Farinha, Joseph M. Connors, Laurie H. Sehn, Randy D. Gascoyne
Final approval of manuscript: Thomas Relander, Nathalie A. Johnson, Pedro Farinha, Joseph M. Connors, Laurie H. Sehn, Randy D. Gascoyne

REFERENCES

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 89:3909-3918, 1997

2. Anderson JR, Armitage JO, Weisenburger DD: Epidemiology of the non-Hodgkin's lymphomas: Distributions of the major subtypes differ by geographic locations: Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 9:717-720, 1998

3. Armitage JO, Weisenburger DD: New approach to classifying non-Hodgkin's lymphomas: Clinical features of the major histologic subtypes: Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 16:2780-2795, 1998

4. Gallagher CJ, Gregory WM, Jones AE, et al: Follicular lymphoma: Prognostic factors for response and survival. J Clin Oncol 4:1470-1480, 1986

5. Horning SJ, Rosenberg SA: The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 311:1471-1475, 1984

6. Horning SJ: Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol 20:75-88, 1993

7. Ardeshna KM, Smith P, Norton A, et al: Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: A randomised controlled trial. Lancet 362:516-522, 2003

8. Al-Tourah AJ, Gill KK, Chhanabhai M, et al: Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 26:5165-5169, 2008

9. Montoto S, Davies AJ, Matthews J, et al: Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. J Clin Oncol 25:2426-2433, 2007

10. Mac Manus MP, Hoppe RT: Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 14:1282-1290, 1996

11. Wilder RB, Jones D, Tucker SL, et al: Long-term results with radiotherapy for stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 51:1219-1227, 2001

12. Brice P, Bastion Y, Lepage E, et al: Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: A randomized study from the Groupe d'Etude des Lymphomes Folliculaires: Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 15:1110-1117, 1997

13. McLaughlin P, Grillo-Lopez AJ, Link BK, et al: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. J Clin Oncol 16:2825-2833, 1998

14. Czuczman MS, Grillo-Lopez AJ, White CA, et al: Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 17:268-276, 1999

15. Marcus R, Imrie K, Belch A, et al: CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 105:1417-1423, 2005

16. Herold M, Haas A, Srock S, et al: Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: An East German Study Group Hematology and Oncology Study. J Clin Oncol 25:1986-1992, 2007

17. Hiddemann W, Kneba M, Dreyling M, et al: Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 106:3725-3732, 2005

18. van Oers MH, Klasa R, Marcus RE, et al: Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial. Blood 108:3295-3301, 2006

19. Swenson WT, Wooldridge JE, Lynch CF, et al: Improved survival of follicular lymphoma patients in the United States. J Clin Oncol 23:5019-5026, 2005

20. Shipp MA, Harrington DP, Anderson JR, et al: A predictive model for aggressive NHL: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329:987-994, 1993

21. McManus BM, Gascoyne RD: Pathology and laboratory medicine. JAMA 277:1887-1889, 1997

22. Lopez-Guillermo A, Montserrat E, Bosch F, et al: Applicability of the International Index for aggressive lymphomas to patients with low-grade lymphoma. J Clin Oncol 12:1343-1348, 1994

23. Martin AR, Weisenburger DD, Chan WC, et al: Prognostic value of cellular proliferation and histologic grade in follicular lymphoma. Blood 85:3671-3678, 1995

24. Federico M, Vitolo U, Zinzani PL, et al: Prognosis of follicular lymphoma: A predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi. Blood 95:783-789, 2000

25. Solal-Celigny P, Roy P, Colombat P, et al: Follicular lymphoma international prognostic index. Blood 104:1258-1265, 2004

26. Buske C, Hoster E, Dreyling M, et al: The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. Blood 108:1504-1508, 2006

27. Montoto S, Lopez-Guillermo A, Altes A, et al: Predictive value of Follicular Lymphoma International Prognostic Index (FLIPI) in patients with follicular lymphoma at first progression. Ann Oncol 15:1484-1489, 2004

28. Gine E, Montoto S, Bosch F, et al: The Follicular Lymphoma International Prognostic Index (FLIPI) and the histological subtype are the most important factors to predict histological transformation in follicular lymphoma. Ann Oncol 17:1539-1545, 2006

29. Perea G, Altes A, Montoto S, et al: Prognostic indexes in follicular lymphoma: A comparison of different prognostic systems. Ann Oncol 16:1508-1513, 2005

30. Federico M, Bellei M, Marcheselli L, et al: Follicular Lymphoma International Prognostic Index 2: A new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 27:4555-4562, 2009

31. Reference deleted

32. Bastion Y, Berger F, Bryon PA, et al: Follicular lymphomas: Assessment of prognostic factors in 127 patients followed for 10 years. Ann Oncol 2:123-129, 1991 (suppl 2)

33. Lopez-Guillermo A, Cabanillas F, McLaughlin P, et al: Molecular response assessed by PCR is the most important factor predicting failure-free survival in indolent follicular lymphoma: Update of the MDACC series. Ann Oncol 11:137-140, 2000 (suppl 1)

34. Dana BW, Dahlberg S, Nathwani BN, et al: Long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherapy. J Clin Oncol 11:644-651, 1993

35. Canioni D, Brice P, Lepage E, et al: Bone marrow histological patterns can predict survival of patients with grade 1 or 2 follicular lymphoma: A study from the Groupe d'Etude des Lymphomes Folliculaires. Br J Haematol 126:364-371, 2004

36. Romaguera JE, McLaughlin P, North L, et al: Multivariate analysis of prognostic factors in stage IV follicular low-grade lymphoma: A risk model. J Clin Oncol 9:762-769, 1991

37. Lee MS, Chang KS, Cabanillas F, et al: Detection of minimal residual cells carrying the t(14;18) by DNA sequence amplification. Science 237:175-178, 1987

38. Berinstein NL, Reis MD, Ngan BY, et al: Detection of occult lymphoma in the peripheral blood and bone marrow of patients with untreated early-stage and advanced-stage follicular lymphoma. J Clin Oncol 11:1344-1352, 1993

39. Albinger-Hegyi A, Hochreutener B, Abdou MT, et al: High frequency of t(14;18)-translocation breakpoints outside of major breakpoint and minor cluster regions in follicular lymphomas: Improved polymerase chain reaction protocols for their detection. Am J Pathol 160:823-832, 2002

40. Cleary ML, Galili N, Sklar J: Detection of a second t(14;18) breakpoint cluster region in human follicular lymphomas. J Exp Med 164:315-320, 1986

41. Cleary ML, Sklar J: Nucleotide sequence of a t(14;18) chromosomal breakpoint in follicular lymphoma and demonstration of a breakpoint-cluster

region near a transcriptionally active locus on chromosome 18. Proc Natl Acad Sci U S A 82:7439-7443, 1985

42. Gribben JG, Freedman A, Woo SD, et al: All advanced stage non-Hodgkin's lymphomas with a polymerase chain reaction amplifiable breakpoint of bcl-2 have residual cells containing the bcl-2 rearrangement at evaluation and after treatment. Blood 78:3275-3280, 1991

43. Hirt C, Dolken G: Quantitative detection of t(14;18)-positive cells in patients with follicular lymphoma before and after autologous bone marrow transplantation. Bone Marrow Transplant 25:419-426, 2000

44. Johnson PW, Price CG, Smith T, et al: Detection of cells bearing the t(14;18) translocation following myeloablative treatment and autologous bone marrow transplantation for follicular lymphoma. J Clin Oncol 12:798-805, 1994

45. Lopez-Guillermo A, Cabanillas F, McLaughlin P, et al: The clinical significance of molecular response in indolent follicular lymphomas. Blood 91: 2955-2960, 1998

46. Rambaldi A, Carlotti E, Oldani E, et al: Quantitative PCR of bone marrow BCL2/IgH+ cells at diagnosis predicts treatment response and long-term outcome in follicular non-Hodgkin lymphoma. Blood 105:3428-3433, 2005

47. Gribben JG, Neuberg D, Freedman AS, et al: Detection by polymerase chain reaction of residual cells with the bcl-2 translocation is associated with increased risk of relapse after autologous bone marrow transplantation for B-cell lymphoma. Blood 81:3449-3457, 1993

48. Price CG, Meerabux J, Murtagh S, et al: The significance of circulating cells carrying t(14;18) in long remission from follicular lymphoma. J Clin Oncol 9:1527-1532, 1991

49. Finke J, Slanina J, Lange W, et al: Persistence of circulating t(14;18)-positive cells in long-term remission after radiation therapy for localized-stage follicular lymphoma. J Clin Oncol 11:1668-1673, 1993

50. Liu Y, Hernandez AM, Shibata D, et al: BCL2 translocation frequency rises with age in humans. Proc Natl Acad Sci U S A 91:8910-8914, 1994

51. Summers KE, Goff LK, Wilson AG, et al: Frequency of the Bcl-2/IgH rearrangement in normal individuals: Implications for the monitoring of disease in patients with follicular lymphoma. J Clin Oncol 19:420-424, 2001

52. Siddiqui M, Ristow K, Markovic SN, et al: Absolute lymphocyte count predicts overall survival in follicular lymphomas. Brit J Haematol 134:596-601, 2006

53. Litam P, Swan F, Cabanillas F, et al: Prognostic value of serum beta-2 microglobulin in low-grade lymphoma. Ann Intern Med 114:855-860, 1991

54. Seymour JF, Pro B, Fuller LM, et al: Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol 21:2115-2122, 2003

55. Ganti AK, Weisenburger DD, Smith LM, et al: Patients with grade 3 follicular lymphoma have prolonged relapse-free survival following anthracycline-based chemotherapy: The Nebraska Lymphoma Study Group Experience. Ann Oncol 17:920-927, 2006

56. Wendum D, Sebban C, Gaulard P, et al: Follicular large-cell lymphoma treated with intensive chemotherapy: An analysis of 89 cases included in the LNH87 trial and comparison with the outcome of diffuse large B-cell lymphoma: Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 15:1654-1663, 1997

57. Montoto S, Lopez-Guillermo A, Ferrer A, et al: Survival after progression in patients with follicular lymphoma: Analysis of prognostic factors. Ann Oncol 13:523-530, 2002

58. Pedersen LM, Sorensen PG: Urinary albumin excretion is a predictor of response to treatment and disease progression in low-grade non-Hodgkin's lymphoma. Leuk Lymphoma 45:547-551, 2004

59. Salven P, Teerenhovi L, Joensuu H: A high pretreatment serum basic fibroblast growth factor concentration is an independent predictor of poor prognosis in non-Hodgkin's lymphoma. Blood 94: 3334-3339, 1999

60. Bono P, Teerenhovi L, Joensuu H: Elevated serum endostatin is associated with poor outcome in patients with non-Hodgkin lymphoma. Cancer 97:2767-2775, 2003

61. Salven P, Teerenhovi L, Joensuu H: A high pretreatment serum vascular endothelial growth factor concentration is associated with poor outcome in non-Hodgkin's lymphoma. Blood 90:3167-3172, 1997

62. Salles G, Bienvenu J, Bastion Y, et al: Elevated circulating levels of TNFalpha and its p55 soluble receptor are associated with an adverse prognosis in lymphoma patients. Br J Haematol 93:352-359, 1996

63. Giles FJ, Vose JM, Do KA, et al: Clinical relevance of circulating angiogenic factors in patients with non-Hodgkin's lymphoma or Hodgkin's lymphoma. Leuk Res 28:595-604, 2004

64. Warzocha K, Salles G, Bienvenu J, et al: Prognostic significance of TNF alpha and its p55 soluble receptor in malignant lymphomas. Leukemia 11:441-443, 1997

65. Warzocha K, Ribeiro P, Bienvenu J, et al: Genetic polymorphisms in the tumor necrosis factor locus influence non-Hodgkin's lymphoma outcome. Blood 91:3574-3581, 1998

66. Zinzani PL, Baccini C, Zaccaria A, et al: Clinical implications of serum levels of soluble CD23 and tumor necrosis factor alpha in low-grade non-Hodgkin's lymphoma. Eur J Haematol 57:335-340, 1996

67. Christiansen I, Gidlof C, Kalkner KM, et al: Elevated serum levels of soluble ICAM-1 in non-Hodgkin's lymphomas correlate with tumour burden, disease activity and other prognostic markers. Br J Haematol 92:639-646, 1996

68. Salven P, Orpana A, Teerenhovi L, et al: Simultaneous elevation in the serum concentrations of the angiogenic growth factors VEGF and bFGF is an independent predictor of poor prognosis in non-Hodgkin lymphoma: A single-institution study of 200 patients. Blood 96:3712-3718, 2000

69. Swerdlow SH, Campo E, Lee Harris N, et al: World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press 2008

70. Hans CP, Weisenburger DD, Vose JM, et al: A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. Blood 101:2363-2367, 2003

71. Ott G, Katzenberger T, Lohr A, et al: Cytomorphologic, immunohistochemical, and cytogenetic profiles of follicular lymphoma: 2 types of follicular lymphoma grade 3. Blood 99:3806-3812, 2002

72. Warnke RA, Kim H, Fuks Z, et al: The coexistence of nodular and diffuse patterns in nodular non-Hodgkin's lymphomas: Significance and clinicopathologic correlation. Cancer 40:1229-1233, 1977

73. Chau I, Jones R, Cunningham D, et al: Outcome of follicular lymphoma grade 3: Is anthracycline necessary as front-line therapy? Br J Cancer 89:36-42, 2003

74. Bartlett NL, Rizeq M, Dorfman RF, et al: Follicular large-cell lymphoma: Intermediate or low grade? J Clin Oncol 12:1349-1357, 1994

75. Rodriguez J, McLaughlin P, Hagemeister FB, et al: Follicular large cell lymphoma: An aggressive lymphoma that often presents with favorable prognostic features. Blood 93:2202-2207, 1999

76. Miller TP, LeBlanc M, Grogan TM, et al: Follicular lymphomas: Do histologic subtypes predict outcome? Hematol Oncol Clin North Am 11: 893-900, 1997

77. Bosga-Bouwer AG, van Imhoff GW, Boonstra R, et al: Follicular lymphoma grade 3B includes 3 cytogenetically defined subgroups with primary t(14;18), 3q27, or other translocations: T(14;18) and 3q27 are mutually exclusive. Blood 101:1149-1154, 2003

78. Hall PA, Richards MA, Gregory WM, et al: The prognostic value of Ki67 immunostaining in non-Hodgkin's lymphoma. J Pathol 154:223-235, 1988

79. Swerdlow SH, Westermann CD, Pelstring RJ, et al: Growth fraction in centrocytic and follicular center cell lymphomas: Assessment in paraffin sections with a proliferating cell nuclear antigen antibody and morphometric correlates. Hum Pathol 24:540-546, 1993

80. Logsdon MD, Meyn Jr RE, Besa PC, et al: Apoptosis and the Bcl-2 gene family – patterns of expression and prognostic value in stage I and II follicular center lymphoma. Int J Radiat Oncol Biol Phys 44:19-29, 1999

81. Michels J, Foria V, Mead B, et al: Immunohistochemical analysis of the antiapoptotic Mcl-1 and Bcl-2 proteins in follicular lymphoma. Br J Haematol 132:743-746, 2006

82. Zhao WL, Daneshpouy ME, Mounier N, et al: Prognostic significance of bcl-xL gene expression and apoptotic cell counts in follicular lymphoma. Blood 103:695-697, 2004

83. Farinha P, Masoudi H, Skinnider BF, et al: Analysis of multiple biomarkers shows that lymphoma-associated macrophage (LAM) content is an independent predictor of survival in follicular lymphoma (FL). Blood 106:2169-2174, 2005

84. Zha H, Raffeld M, Charboneau L, et al: Similarities of prosurvival signals in Bcl-2-positive and Bcl-2-negative follicular lymphomas identified by reverse phase protein microarray. Lab Invest 84:235-244, 2004

85. Gulmann C, Espina V, Petricoin III E, et al: Proteomic analysis of apoptotic pathways reveals prognostic factors in follicular lymphoma. Clin Cancer Res 11:5847-5855, 2005

86. Agarwal B, Naresh KN: Bcl-2 family of proteins in indolent B-cell non-Hodgkin's lymphoma: Study of 116 cases. Am J Hematol 70:278-282, 2002

87. Oltersdorf T, Elmore SW, Shoemaker AR, et al: An inhibitor of Bcl-2 family proteins induces regression of solid tumours. Nature 435:677-681, 2005

88. Paoluzzi L, Gonen M, Gardner JR, et al: Targeting Bcl-2 family members with the BH3 mimetic AT-101 markedly enhances the therapeutic effects of chemotherapeutic agents in in vitro and in vivo models of B-cell lymphoma. Blood 111:5350-5358, 2008

89. Dogan A, Bagdi E, Munson P, et al: CD10 and BCL-6 expression in paraffin sections of normal lymphoid tissue and B-cell lymphomas. Am J Surg Pathol 24:846-852, 2000

90. Hans CP, Weisenburger DD, Greiner TC, et al: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275-282, 2004

91. Bilalovic N, Blystad AK, Golouh R, et al: Expression of bcl-6 and CD10 protein is associated with longer overall survival and time to treatment failure in follicular lymphoma. Am J Clin Pathol 121:34-42, 2004

92. Zou GM, Chen JJ, Yoder MC, et al: Knockdown of Pu. 1 by small interfering RNA in CD34+ embryoid body cells derived from mouse ES cells turns cell fate determination to pro-B cells. Proc Natl Acad Sci U S A 102:13236-13241, 2005

93. Torlakovic EE, Bilalovic N, Golouh R, et al: Prognostic significance of PU. 1 in follicular lymphoma. J Pathol 209:352-359, 2006

94. O'Shea D, O'Riain C, Taylor C, et al: The presence of TP53 mutation at diagnosis of follicular lymphoma identifies a high-risk group of patients with shortened time to disease progression and poorer overall survival. Blood 112:3126-3129, 2008

95. Sander CA, Yano T, Clark HM, et al: p53 mutation is associated with progression in follicular lymphomas. Blood 82:1994-2004, 1993

96. Lo Coco F, Gaidano G, Louie DC, et al: p53 mutations are associated with histologic transformation of follicular lymphoma. Blood 82:2289-2295, 1993

97. Davies AJ, Lee AM, Taylor C, et al: A limited role for TP53 mutation in the transformation of follicular lymphoma to diffuse large B-cell lymphoma. Leukemia 19:1459-1465, 2005

98. Moller MB, Nielsen O, Pedersen NT: Frequent alteration of MDM2 and p53 in the molecular progression of recurring non-Hodgkin's lymphoma. Histopathology 41:322-330, 2002

99. Bjorck E, Ek S, Landgren O, et al: High expression of cyclin B1 predicts a favorable outcome in patients with follicular lymphoma. Blood 105:2908-2915, 2005

100. Krishnadasan R, Bifulco C, Kim J, et al: Overexpression of SOCS3 is associated with decreased survival in a cohort of patients with de novo follicular lymphoma. Brit J Haematol 135:72-75, 2006

101. Sakhinia E, Glennie C, Hoyland JA, et al: Clinical quantitation of diagnostic and predictive gene expression levels in follicular and diffuse large B-cell lymphoma by RT-PCR gene expression profiling. Blood 109:3922-3928, 2007

102. Kuppers R: Mechanisms of B-cell lymphoma pathogenesis. Nat Rev Cancer 5:251-262, 2005

103. Horsman DE, Okamoto I, Ludkovski O, et al: Follicular lymphoma lacking the t(14;18)(q32;q21): Identification of two disease subtypes. Brit J Haematol 120:424-433, 2003

104. Katzenberger T, Kalla J, Leich E, et al: A distinctive subtype of t(14;18)-negative nodal follicular non-Hodgkin lymphoma characterized by a predominantly diffuse growth pattern and deletions in the chromosomal region 1p36. Blood 113:1053-1061, 2009

105. Horsman DE, Connors JM, Pantzar T, et al: Analysis of secondary chromosomal alterations in 165 cases of follicular lymphoma with t(14;18). Genes Chromosomes Cancer 30:375-382, 2001

106. Johansson B, Mertens F, Mitelman F: Cytogenetic evolution patterns in non-Hodgkin's lymphoma. Blood 86:3905-3914, 1995

107. Yunis JJ, Frizzera G, Oken MM, et al: Multiple recurrent genomic defects in follicular lymphoma: A possible model for cancer. N Engl J Med 316:79-84, 1987

108. Offit K, Jhanwar SC, Ladanyi M, et al: Cytogenetic analysis of 434 consecutively ascertained specimens of non-Hodgkin's lymphoma: Correlations between recurrent aberrations, histology, and exposure to cytotoxic treatment. Genes Chromosomes Cancer 3:189-201, 1991

109. Tilly H, Rossi A, Stamatoullas A, et al: Prognostic value of chromosomal abnormalities in follicular lymphoma. Blood 84:1043-1049, 1994

110. Hoglund M, Sehn L, Connors JM, et al: Identification of cytogenetic subgroups and karyotypic pathways of clonal evolution in follicular lymphomas. Genes Chromosomes Cancer 39:195-204, 2004

111. Johnson NA, Al-Tourah A, Brown CJ, et al: Prognostic significance of secondary cytogenetic alterations in follicular lymphomas. Genes Chromosomes Cancer 47:1038-1048, 2008

112. Ross CW, Ouillette PD, Saddler CM, et al: Comprehensive analysis of copy number and allele status identifies multiple chromosome defects underlying follicular lymphoma pathogenesis. Clin Cancer Res 13:4777-4785, 2007

113. Viardot A, Moller P, Hogel J, et al: Clinicopathologic correlations of genomic gains and losses in follicular lymphoma. J Clin Oncol 20:4523-4530, 2002

114. Cheung KJ, Shah SP, Steidl C, et al: Genome-wide profiling of follicular lymphoma by array comparative genomic hybridization reveals prognostically significant DNA copy number imbalances. Blood 113:137-148, 2009

115. Schwaenen C, Viardot A, Berger H, et al: Microarray-based genomic profiling reveals novel genomic aberrations in follicular lymphoma which associate with patient survival and gene expression status. Genes Chromosomes Cancer 48:39-54, 2009

116. Fitzgibbon J, Iqbal S, Davies A, et al: Genome-wide detection of recurring sites of uniparental disomy in follicular and transformed follicular lymphoma. Leukemia 21:1514-1520, 2007

117. O'Shea D, O'Riain C, Gupta M, et al: Regions of acquired uniparental disomy at diagnosis of follicular lymphoma are associated with both overall survival and risk of transformation. Blood 113:2298-2301, 2009

118. Cartron G, Watier H, Golay J, et al: From the bench to the bedside: Ways to improve rituximab efficacy. Blood 104:2635-2642, 2004

119. Maloney DG, Smith B, Rose A: Rituximab: Mechanism of action and resistance. Semin Oncol 29:2-9, 2002

120. Cartron G, Dacheux L, Salles G, et al: Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. Blood 99:754-758, 2002

121. Weng WK, Levy R: Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol 21:3940-3947, 2003

122. Ghielmini M, Rufibach K, Salles G, et al: Single agent rituximab in patients with follicular or mantle cell lymphoma: Clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: A study of the Swiss Group for Clinical Cancer Res (SAKK). Ann Oncol 16:1675-1682, 2005

123. Maloney DG, Pender-Smith B, Unger JM, et al: FcR gamma polymorphisms do not influence progression free survival of follicular NHL patients treated with CHOP followed by rituximab (SWOG 9800). Blood 104, 2004 (abstr 589)

124. Boettcher S, Pott C, Ritgen M, et al: Evidence for FcR gamma receptor IIIA-independent rituximab effector mechanisms in patients with follicular lymphoma treated with combined immunochemotherapy. Blood 104, 2004 (abstr 590)

125. Cerhan JR, Wang S, Maurer MJ, et al: Prognostic significance of host immune gene polymorphisms in follicular lymphoma survival. Blood 109: 5439-5446, 2007

126. Rothman N, Skibola CF, Wang SS, et al: Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: A report from the InterLymph Consortium. Lancet Oncol 7:27-38, 2006

127. Dave SS, Wright G, Tan B, et al: Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med 351:2159-2169, 2004

128. Glas AM, Kersten MJ, Delahaye LJ, et al: Gene expression profiling in follicular lymphoma to assess clinical aggressiveness and to guide the choice of treatment. Blood 105:301-307, 2005

129. Folkman J: Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1:27-31, 1995

130. Koster A, van Krieken JH, Mackenzie MA, et al: Increased vascularization predicts favorable outcome in follicular lymphoma. Clin Cancer Res 11: 154-161, 2005

131. Streubel B, Chott A, Huber D, et al: Lymphoma-specific genetic aberrations in microvascular endothelial cells in B-cell lymphomas. N Engl J Med 351:250-259, 2004

132. Shiozawa E, Yamochi-Onizuka T, Yamochi T, et al: Disappearance of CD21-positive follicular dendritic cells preceding the transformation of follicular lymphoma: Immunohistological study of the transformation using CD21, p53, Ki-67, and P-glycoprotein. Pathol Res Pract 199:293-302, 2003

133. Glas AM, Knoops L, Delahaye L, et al: Gene-expression and immunohistochemical study of specific T-cell subsets and accessory cell types in the transformation and prognosis of follicular lymphoma. J Clin Oncol 25:390-398, 2007

134. Alvaro T, Lejeune M, Salvado M-T, et al: Immunohistochemical patterns of reactive microenvironment are associated with clinicobiologic behavior in follicular lymphoma patients. J Clin Oncol 24:5350-5357, 2006

135. Alvaro T, Lejeune M, Camacho FI, et al: The presence of STAT1-positive tumor-associated macrophages and their relation to outcome in patients with follicular lymphoma. Haematologica 91:1605-1612, 2006

136. Canioni D, Salles G, Mounier N, et al: The poor prognosis value of high intra-tumoral macrophage count in follicular lymphoma patients requires selection of appropriate cut-off and can be circumvented by rituximab therapy. Blood 108, 2006 (abstr 822)

137. Taskinen M, Karjalainen-Lindsberg ML, Nyman H, et al: A high tumor-associated macrophage content predicts favorable outcome in follicular lymphoma patients treated with rituximab and cyclophosphamide-doxorubicin-vincristine-prednisone. Clin Cancer Res 13:5784-5789, 2007

138. Mantovani A, Sica A, Sozzani S, et al: The chemokine system in diverse forms of macrophage

activation and polarization. Trends Immunol 25:677-686, 2004

139. Bingle L, Brown NJ, Lewis CE: The role of tumour-associated macrophages in tumour progression: Implications for new anticancer therapies. J Pathol 196:254-265, 2002

140. Ai WYZ, Czerwinski DK, Horning S, et al: Tumor-infiltrating T cells are not predictive of clinical outcome in follicular lymphoma. Blood 108, 2006 (abstr 824)

141. Carreras J, Lopez-Guillermo A, Fox BC, et al: High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma. Blood 108:2957-2964, 2006

142. Farinha P, Han J, Al-Tourah A, et al: The tumor microenvironment measured by flow cytometry predicts overall survival and transformation risk in follicular lymphoma. Blood 108, 2006 (abstr 2406)

143. Lee AM, Clear AJ, Calaminici M, et al: Number of CD4+ cells and location of forkhead box protein P3-positive cells in diagnostic follicular lymphoma tissue microarrays correlates with outcome. J Clin Oncol 24:5052-5059, 2006

144. Strickler JG, Copenhaver CM, Rojas VA, et al: Comparison of "host cell infiltrates" in patients with follicular lymphoma with and without spontaneous regression. Am J Clin Pathol 90:257-261, 1988

145. de Jong D, Koster A, Hagenbeek A, et al: Impact of the tumor microenvironment on prognosis in follicular lymphoma is dependent on specific treatment protocols. Haematologica 94:70-77, 2009

146. Zou W: Regulatory T cells, tumour immunity and immunotherapy. Nature reviews 6:295-307, 2006

147. Curiel TJ, Coukos G, Zou L, et al: Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 10:942-949, 2004

148. Farinha P, Campo E, Banham A, et al: The architectural pattern of FOXP3+ T cells is an independent predictor of survival in patients with follicular lymphoma (FL). Mod Pathol 19:1043a, 2006

149. Carreras J, Lopez-Guillermo A, Roncador G, et al: High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J Clin Oncol 27:1470-1476, 2009

150. Acker B, Hoppe RT, Colby TV, et al: Histologic conversion in the non-Hodgkin's lymphomas. J Clin Oncol 1:11-16, 1983

151. Cullen MH, Lister TA, Brearley RI, et al: Histological transformation of non-Hodgkin's lymphoma: A prospective study. Cancer 44:645-651, 1979

152. Ersboll J, Schultz HB, Pedersen-Bjergaard J, et al: Follicular low-grade non-Hodgkin's lymphoma: Long-term outcome with or without tumor progression. Eur J Haematol 42:155-163, 1989

153. Garvin AJ, Simon RM, Osborne CK, et al: An autopsy study of histologic progression in non-Hodgkin's lymphomas: 192 cases from the National Cancer Institute. Cancer 52:393-398, 1983

154. Hubbard SM, Chabner BA, DeVita Jr VT, et al: Histologic progression in non-Hodgkin's lymphoma. Blood 59:258-264, 1982

155. Oviatt DL, Cousar JB, Collins RD, et al: Malignant lymphomas of follicular center cell origin in humans. V. Incidence, clinical features, and prognostic implications of transformation of small cleaved cell nodular lymphoma. Cancer 53:1109-1114, 1984

156. Qazi R, Aisenberg AC, Long JC: The natural history of nodular lymphoma. Cancer 37:1923-1927, 1976

157. Muller-Hermelink HK, Zettl A, Pfeifer W, et al: Pathology of lymphoma progression. Histopathology 38:285-306, 2001

158. Elenitoba-Johnson KS, Gascoyne RD, Lim MS, et al: Homozygous deletions at chromosome 9p21 involving p16 and p15 are associated with histologic progression in follicle center lymphoma. Blood 91:4677-4685, 1998

159. Lossos IS: Molecular pathogenesis of diffuse large B-cell lymphoma. J Clin Oncol 23:6351-6357, 2005

160. Lossos IS, Alizadeh AA, Diehn M, et al: Transformation of follicular lymphoma to diffuse large-cell lymphoma: Alternative patterns with increased or decreased expression of c-myc and its regulated genes. Proc Natl Acad Sci U S A 99:8886-8891, 2002

161. Lossos IS, Levy R: Higher grade transformation of follicular lymphoma: Phenotypic tumor progression associated with diverse genetic lesions. Semin Cancer Biol 13:191-202, 2003

162. Macpherson N, Lesack D, Klasa R, et al: Small noncleaved, non-Burkitt's (Burkitt-Like) lymphoma: Cytogenetics predict outcome and reflect clinical presentation. J Clin Oncol 17:1558-1567, 1999

163. Yano T, Jaffe ES, Longo DL, et al: MYC rearrangements in histologically progressed follicular lymphomas. Blood 80:758-767, 1992

164. Akasaka T, Lossos IS, Levy R: BCL6 gene translocation in follicular lymphoma: A harbinger of eventual transformation to diffuse aggressive lymphoma. Blood 102:1443-1448, 2003

165. Matolcsy A, Warnke RA, Knowles DM: Somatic mutations of the translocated bcl-2 gene are associated with morphologic transformation of follicular lymphoma to diffuse large-cell lymphoma. Ann Oncol 8:119-122, 1997

166. Berglund M, Enblad G, Thunberg U, et al: Genomic imbalances during transformation from follicular lymphoma to diffuse large B-cell lymphoma. Mod Pathol 20:63-75, 2007

167. Bernell P, Jacobsson B, Liliemark J, et al: Gain of chromosome 7 marks the progression from indolent to aggressive follicle centre lymphoma and is a common finding in patients with diffuse large B-cell lymphoma: A study by FISH. Br J Haematol 101:487-491, 1998

168. Boonstra R, Bosga-Bouwer A, Mastik M, et al: Identification of chromosomal copy number changes associated with transformation of follicular lymphoma to diffuse large B-cell lymphoma. Hum Pathol 34:915-923, 2003

169. Hough RE, Goepel JR, Alcock HE, et al: Copy number gain at 12q12-14 may be important in the transformation from follicular lymphoma to diffuse large B cell lymphoma. Br J Cancer 84:499-503, 2001

170. Martinez-Climent JA, Alizadeh AA, Segraves R, et al: Transformation of follicular lymphoma to diffuse large cell lymphoma is associated with a heterogeneous set of DNA copy number and gene expression alterations. Blood 101:3109-3117, 2003

171. de Vos S, Hofmann WK, Grogan TM, et al: Gene expression profile of serial samples of transformed B-cell lymphomas. Lab Invest 83:271-285, 2003

172. Elenitoba-Johnson KS, Jenson SD, Abbott RT, et al: Involvement of multiple signaling pathways in follicular lymphoma transformation: P38-mitogen-activated protein kinase as a target for therapy. Proc Natl Acad Sci U S A 100:7259-7264, 2003

173. Davies AJ, Rosenwald A, Wright G, et al: Transformation of follicular lymphoma to diffuse large B-cell lymphoma proceeds by distinct oncogenic mechanisms. Br J Haematol 136:286-293, 2007

174. Koster A, Tromp HA, Raemaekers JM, et al: The prognostic significance of the intra-follicular tumor cell proliferative rate in follicular lymphoma. Haematologica 92:184-190, 2007

175. Wang SA, Wang L, Hochberg EP, et al: Low histologic grade follicular lymphoma with high proliferation index: Morphologic and clinical features. Am J Surg Pathol 29:1490-1496, 2005

176. Chang KC, Huang X, Medeiros LJ, et al: Germinal centre-like versus undifferentiated stromal immunophenotypes in follicular lymphoma. J Pathol 201:404-412, 2003

177. Hilchey SP, De A, Rimsza LM, et al: Follicular lymphoma intratumoral CD4+CD25+GITR+ regulatory t cells potently suppress CD3/CD28-costimulated autologous and allogeneic CD8+CD25- and CD4+CD25- T Cells. J Immunol 178:4051-4061, 2007

178. Porter DL, Levine BL, Bunin N, et al: A phase 1 trial of donor lymphocyte infusions expanded and activated ex vivo via CD3/CD28 costimulation. Blood 107:1325-1331, 2006

179. Wahlin BE, Sander B, Christensson B, et al: CD8+ T-cell content in diagnostic lymph nodes measured by flow cytometry is a predictor of survival in follicular lymphoma. Clin Cancer Res 13:388-397, 2007

180. Karube K, Guo Y, Suzumiya J, et al: CD10-MUM1+ follicular lymphoma lacks BCL2 gene translocation and shows characteristic biologic and clinical features. Blood 109:3076-3079, 2007

181. Naresh KN: MUM1 expression dichotomises follicular lymphoma into predominantly, MUM1-negative low-grade and MUM1-positive high-grade subtypes. Haematologica 92:267-268, 2007

182. Horsman DE, Okamoto I, Ludkovski O, et al: Follicular lymphoma lacking the t(14;18)(q32;q21): Identification of two disease subtypes. Br J Haematol 120:424-433, 2003

183. Iqbal S, Jenner MJ, Summers KE, et al: Reliable detection of clonal IgH/Bcl2 MBR rearrangement in follicular lymphoma: Methodology and clinical significance. Br J Haematol 124:325-328, 2004

184. Johnson NA, Al-Tourah A, Horsman DE, et al: Insights into disease evolution of transformed follicular lymphoma derived from cytogenetics. Blood 106, 2005 (abstr 180)

185. Lopez-Guillermo A, Cabanillas F, McDonnell TI, et al: Correlation of bcl-2 rearrangement with clinical characteristics and outcome in indolent follicular lymphoma. Blood 93:3081-3087, 1999

186. Martinka M, Comeau T, Foyle A, et al: Prognostic significance of t(14;18) and bcl-2 gene expression in follicular small cleaved cell lymphoma and diffuse large cell lymphoma. Clin Invest Med 20: 364-370, 1997

187. Pinyol M, Cobo F, Bea S, et al: P16(INK4a) gene inactivation by deletions, mutations, and hypermethylation is associated with transformed and aggressive variants of non-Hodgkin's lymphomas. Blood 91:2977-2984, 1998

188. Bastard C, Deweindt C, Kerckaert JP, et al: LAZ3 rearrangements in non-Hodgkin's lymphoma: Correlation with histology, immunophenotype, karyotype, and clinical outcome in 217 patients. Blood 83:2423-2427, 1994

CORRECTIONS

Author Corrections

The January 10, 2010, article by Oktay et al, entitled, "Association of *BRCA1* Mutations With Occult Primary Ovarian Insufficiency: A Possible Explanation for the Link Between Infertility and Breast/Ovarian Cancer Risks" (J Clin Oncol 28: 240-244, 2010), contained an error.

The primary institutional affiliation for David Barad was inadvertently omitted and should have been listed as The Center for Human Reproduction, New York, NY.

The authors apologize to the readers for the mistake.

DOI: 10.1200/JCO.2010.32.8278

The July 10, 2010, article by Sargent et al, entitled, "Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer" (J Clin Oncol 28:3219-3226, 2010), contained errors.

In Table 2 and Table 4, the univariate and multivariate results (HR, 95% CI, and *P* values) for DFS and OS were presented for dMMR and pMMR patients who were not treated, whereas they should have been given for patients who were treated.

The authors apologize to the readers for the mistakes.

DOI: 10.1200/JCO.2010.32.8286

Journal Corrections

The June 10, 2010, article by Thurlow et al, entitled, "Spectral Clustering of Microarray Data Elucidates the Roles of Microenvironment Remodeling and Immune Responses in Survival of Head and Neck Squamous Cell Carcinoma" (J Clin Oncol 28:2881-2888, 2010), contained an error.

In Table 1, under Primary Tumors, the value for FA (KEGG) in the column "*P* Reduced Multivariate" was inadvertently omitted and should have been $< .001$.

Journal of Clinical Oncology apologizes to the authors and readers for the mistake.

DOI: 10.1200/JCO.2010.32.8252

The June 10, 2010, review article by Relander et al, entitled, "Prognostic Factors in Follicular Lymphoma" (J Clin Oncol 28:2902-2913, 2010), contained an error.

The left-hand image in Figure 3 was identified as "Interfollicular CD4+T cells," whereas it should have been "Intrafollicular CD4+T cells."

Journal of Clinical Oncology apologizes to the authors and readers for the mistake.

DOI: 10.1200/JCO.2010.32.8260

