Molecular and clinical progress in follicular lymphoma lacking the t(14;18) translocation (Review)

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Received August 2, 2019; Accepted October 25, 2019

DOI: 10.3892/ijo.2019.4917

Abstract. Although the majority of patients with follicular lymphoma (FL) harbor the t(14;18)(q32;q21) *IGH/BCL2* gene rearrangement that leads to the overexpression of BCL2 protein, approximately 20% of FL cases lack t(14;18)(q32;q21). It is considered that *BCL2* overexpression underscores the development of the majority of cases of FL and their transformation to more aggressive lymphoma [known as transformed FL (tFL)]. However, FL cases lacking the t(14;18)(q32;q21) translocation exhibit symptoms analogous to their t(14;18)-positive counterparts. An important goal of recent research on FL has been to clarify the distinctions between the two different forms of FL. Numerous studies have shed light onto the genetic and molecular features of t(14;18)-negative FL and the related clinical manifestations. In this review, we summarize the current knowledge of t(14;18)-negative FL occurring in the lymph nodes with an emphasis on the underlying molecular and clinical features. In addition, novel treatment directions are discussed.

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Key words: follicular lymphoma, t(14;18)-negative follicular lymphoma, IGH, BCL2, chromosome translocation, BCL6, R-CHOP

Contents

1. Introduction

Follicular lymphoma (FL) is one of the most common hematological neoplasms. It is an indolent type of non-Hodgkin lymphoma that typically grows and spreads at a slow rate. In normal B cell development, resting follicular B cells are exposed to antigens and may eventually develop into memory B cells (Fig. 1A); in FL, neoplastic germinal center B cells accumulate to form neoplastic follicles (Fig. 1B). These follicles are usually composed of a mixture of cleaved centrocytes and noncleaved centroblasts (1,2). FL is the second most common form of nodal lymphoma, following diffuse large B-cell lymphoma (DLBCL) (3). It is diagnosed at a median age of 60 years, with life expectancy ranging from 6 to 10 years following initial diagnosis (3-5). However, in 20-60% of patients, histological transformation to DLBCL [transformed FL (tFL)] may occur, which reduces life expectancy to 1.2 years (4,6,7).

The genetic hallmark of FL is the t(14;18)(q32;q21) chromosomal aberration, identifiable in 80-90% of FL cases (8,9). This translocation juxtaposes the *BCL2* gene on chromosome 18 to the enhancer sequences of the immunoglobulin heavy chain gene (*IGH*) promoter region on chromosome 14 (9-11), leading to the overexpression of BCL2 in B cells (12) (Fig. 1B). BCL2 normally inhibits apoptosis. BCL2 overexpression resulting from t(14;18) translocation contributes to the development of FL by preventing the apoptosis of neoplastic cells (2,13-16)

However, the t(14;18) translocation can also be detected at a low level in the blood of healthy individuals (17), indicating that the translocation alone is insufficient for the development of FL. Numerous genetic alterations (Table I), many affecting tumor suppressor genes (*TSG*s), are additional factors in the pathogenesis of FL (Fig. 1B) (18) Chromatin modifiers, such as MLL2 and the transcription factor, interferon regulatory factor 4 (IRF4), can be mutated or deleted, affecting the molecular structure and transcription of DNA. Alterations in cell cycle regulators, such as CDKN2A, which activates the p53 and pRb pathways, can also occur. Signal transduction processes can also be affected by mutations in genes such as *FAS*, which also plays a role in apoptosis (18).

While the majority of FL cases are t(14;18)-positive, 10-20% of FL cases lack the translocation (19,20). Several recent studies have focused on the biology and clinical features of t(14;18)-negative FL. Apart from BCL2, the role of other transcription factors or regulators, such as BCL6 expression, has been investigated (21,22). This review summarizes the current knowledge of the molecular characteristics of t(14;18)-negative FL. The review also describes the diagnosis and grading of t(14;18)-negative FL and summarizes the clinical features of the various subtypes.

2. Molecular characterization of t(14;18)-negative FL

Grading of FL. Cases of FL are generally classified into 1 of 3 grades based on the guidelines of the World Health Organization (WHO) (23). The grading of FL is based on the average number of centroblasts in 10 randomly selected microscopic x40 high power fields (HPFs). In grade 1 FL, up to 5 centroblasts per HPF are present; grade 2 FL has 6 to 15 centroblasts per HPF, and grade 3 FL has >15 centroblasts per HPF. Grade 3 is further subdivided into 3A, in which some centrocytes are present, and 3B with no centrocytes (24). Approximately 25% of FL patients are in grade 1, 25-50% in grade 2, and ≥50% in grade 3 (25). FL grades 1 and 2 are considered low grade and affected patients do not necessarily require chemotherapy. For grade 3 FL, chemotherapy is often prescribed (24). Approximately 10% of cases of low-grade FL lack t(14;18). However, approximately 30-40 and 70-85% of grades 3A and 3B FL, respectively, are t(14;18)-negative (26,27).

Unlike grade 3A FL, grade 3B FL is less often found to be BCL2-positive by immunostaining and is associated with an increased p53 and MUM1/IRF expression (28). Grade 3B FL is positive for CD10, also known as common acute lymphocytic leukemia antigen (CALLA), in approximately 50% of cases (29), and is associated with translocations in the 3q27 locus, which affects BCL6 expression (30). In these respects, grade 3B FL more closely resembles DLBCL than the other grades of FL (3,26,27,30,31).

Presence of the t(14;18) translocation in varying grades of FL. Vaandrager *et al* (32) used a FISH assay to detect sequences flanking the *BCL2* gene and found that the absence of t(14;18) was more common in FL grades 2 and 3. Swerdlow *et al* (23) also found that a lack of BCL2 overexpression was particularly common in grade 3 FL. Grade 3B FLs are composed entirely of centroblasts and are typically associated with a lack of t(14;18) (5,27,30). However, results on the frequencies of different grades in t(14;18)-negative FL have been somewhat contradictory. Perhaps owing to small sample sizes, studies, such as those by Weinberg *et al* (33) and Horsman *et al* (21) have found that t(14;18)-negative FLs were more likely to be grades 1 and 2 than grade 3.

BCL2 expression in t(14;18)-negative FL. The t(14;18) translocation leads to the overexpression of BCL2. However, in t(14;18)-negative FL, BCL2 overexpression is more variable (22,32,34-37). Leich *et al* (34,35) studied nodal FL grades 1, 2 and 3A, and found that t(14;18)-positive and t(14;18)-negative FL were morphologically indistinguishable. A small subset of t(14;18)-negative FL samples exhibit evidence of BCL2 overexpression, indicating that factors other than the t(14;18) translocation regulate its expression. The majority of t(14;18)-negative FL cases in this previous study (34) expressed BCL6, CD10, and IRF8. In the study by Horsman *et al* (21) 49 t(14;18)-negative FL cases were analyzed by immunohistochemistry. These researchers found that BCL2 was expressed in 33% of cases. In t(14;18)-negative FLs without BCL2 expression, Leich *et al* (35) performed microRNA expression analysis and found a decreased expression of T cell leukemia/lymphoma 1A (*TCL1A*), supporting the hypothesis that this subtype of FL has a late germinal center B cell phenotype.

BCL6 expression in t(14;18)-negative FL. In addition to BCL2, BCL6 is also frequently expressed in FL (37). While an absence of BCL2 overexpression is a consistent finding in t(14;18)-negative FL, BCL6 expression often accompanies the lack of BCL2 expression (38). In the study by Horsman *et al* (21), only 33% of 49 t(14;18)-negative FL cases expressed BCL2; however, in the majority of cases, a t(3;14) translocation was present and *BCL6* was overexpressed. Jardin *et al* (39) examined a group of patients with t(14;18)-negative FL who had a 3q27/*BCL6* gene rearrangement. Tumor cells in that study were generally negative for CD10, BCL2, CD5, CD23 and CD43, and positive for CD20 and BCL6. In that sample, follicles were significantly larger than those found in t(14;18)-positive FL. Leich *et al* also found that their sample of grades 1-3A t(14;18)-negative FL lacked CD10 expression (34). Jardin *et al* (39) speculated that an anti-apoptotic function of BCL6 may act as a surrogate for BCL2 in this group. Gollub *et al* (40) also found that their samples of t(14;18)-negative FLs with *BCL6* translocations were more common in higher grade FL. A total of 60% of their sample of 5 t(14;18)-negative FLs with *BCL6* translocations were positive for CD10. However, 100% of their sample of t(14;18)-positive FLs with *BCL6* translocations also expressed CD10. In the study by Gollub *et al* (40), t(14;18)-negative FLs with *BCL6* translocations involved the bone marrow less often and did not infiltrate the lymph node capsule as often when compared to t(14;18)-positive FLs. *BCL6* translocations in that study affected the phenotype only when they were not accompanied by *BCL2* translocations.

Gu *et al* (19) also found that *BCL6* rearrangement was more common in t(14;18)-negative FL than in t(14;18)-positive FL and that *BCL6* rearrangements were present in all grades of FL, but were more common in FL grade 3. Pan *et al* (41) also found that the *BCL6* translocation was related to high-grade FL. These studies indicate that *BCL6* rearrangement may

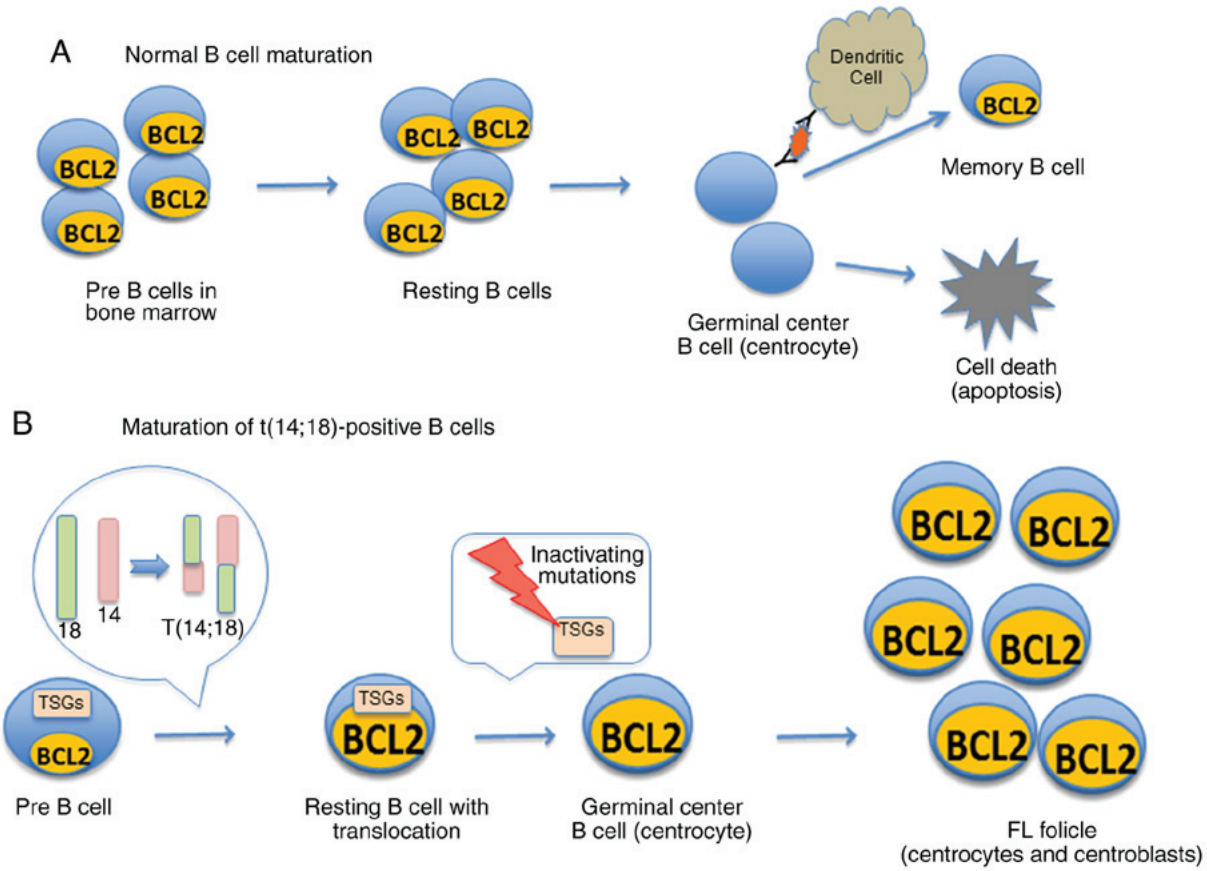

Figure 1. Role of BCL2 protein expression and mutations in tumor suppressor genes (*TSGs*) in the development of t(14;18)-positive follicular lymphoma (FL). (A) In normal developmental conditions, BCL2 is expressed until the B cells enter the germinal center. In the germinal center, the B cells die by apoptosis unless they are rescued by exposure to an antigen, eventually leading to creation of Memory B cells. (B) In t(14;18)-positive FL, B cells continue to express BCL2 after entering the germinal center. Secondary mutation of tumor suppressor genes leads to proliferation of neoplastic follicle center cells and tumor formation.

play a similar role to *BCL2* rearrangement in cases where that does not occur. A summary of genes mutated or abnormally expressed in t(14;18)-negative FL is shown in Table II.

Molecular features of atypical forms of t(14;18)-negative FL. An atypical form of FL lacking the *BCL2* rearrangement that differs from other examples of t(14;18)-negative FL was reported by Karube *et al* (42) This FL subtype exhibited an increased expression of IRF4/MUM1, a protein involved in plasma cell differentiation. The samples were also negative for CD10. Patients with $CD10^{-}MUM1^{+}$ FL were likely to be more elderly than typical FL patients, and more often had grade 3A or 3B morphology and diffuse proliferation. Additionally, 88% of these FLs exhibited *BCL6* translocation or amplification.

In a study on the molecular features of t(14;18)-negative FL, Gagyi *et al* (43) found that t(14;18)-negative FL exhibited no difference when compared to t(14;18)-positive FL in the presence of somatic hypermutations of *IGHV* genes and the levels of expression of activation-induced cytidine deaminase (AID). This supported a germinal center origin and differentiation in both groups of FL. Additionally, there were no differences in somatic hypermutations of the *MYC*, *RhoH*, or *PAX5* genes between the 2 groups. These results led Gagyi *et al* to the conclusion that t(14;18)-positive and t(14;18)-negative should be considered as a single entity. The authors state that, in some cases of t(14;18)-negative FL, BCL2 can be overexpressed by genetic events other than translocation, and other cases of t(14;18)-negative FL, rearrangement of the *BCL6* gene could provide the basis of substitution for the lack of BCL2 expression (43).

Another distinct form of t(14;18)-negative FL is pediatric-type FL (44-47). This form of FL is characterized by highly proliferative follicles, which often have blastoid follicular center cells instead of classic centroblasts (44). These cases are negative for *BCL2*, *BCL6*, and *MYC* rearrangements (45). In this form of FL, dissemination beyond the skin is uncommon, and the cases usually have a good clinical prognosis (46). Although previously associated with a primarily pediatric population, there are occurrences in adults (44,47). The study by Martin-Guerrero *et al* (45) demonstrated that mutations of tumor necrosis factor receptor superfamily 14 (TNFRSF14) accompanied by copy-number neutral loss of heterozygosity (CNN-LOH) at the 1p36 site were more common in pediatric-type FL than in a comparison group with non-pediatric t(14;18)-negative FL. Thus, genetic alterations at the 1p36 site may underlie pathogenesis in pediatric-type FL. The variations in symptomology and gene rearrangements within the t(14;18)-negative FL patient population underscores the diversity of the disease and difficulties related to a coherent classification. These issues suggest that better diagnostic methods are warranted.

Table I. Genes altered in follicular lymphoma.

Gene	Pathway affected	(Refs.)
ARID1A	Transcription regulation; member of the SWI-SNF family	(75,76)
BCL2	Apoptosis regulator protein	(11)
BCL6	Apoptosis regulator protein	(77)
CDKN2A	Activation of p53 and pRb pathways	(75,78-84)
CREBBP	Activation of transcription	(85,86)
DAPK1	Gamma-interferon induced apoptosis	(87)
EBF1	Transcription factor	(75,86)
EP300	Regulation of transcription by chromatin remodeling	(82,88)
EPHA7	Protein tyrosine kinase family	(81)
EZH2	DNA methylation and transcriptional regulation	(89)
TNFRSF6	Apoptosis	(82,90)
FLCN	mTOR; tumor suppressor	(91)
FOXO1	Transcription factor	(82)
HIST1H1E	Nuclear protein involved in nucleosome structure	(76,82)
IGHV, IGLV	Immunoglobulin heavy chains	(92,93)
KMT2D (MLL2)	Trithorax-group histone methyltransferase	(85,88,89)
PAX5	Transcription factor involved in neoplastic transformation	(82)
PRDM1	Repressor of β-interferon gene expression	(75)
RB1	Tumor suppression	(81)
PTPN6 (SHP1)	Protein tyrosine phosphatase family	(94-96)
SOCS1	STAT inhibition	(79,82,86,97-99)
TNFAIP3	Inhibition of NF-κB activation and TNF-mediated apoptosis	(75,82,86)
TNFRSF14	Member of TNF-receptor superfamily; component of pathways involved in activation of the immune response	(82,100,101)
TP53	Tumor suppression	(75,82,102,103)

3. Genetic abnormalities recently identified through next-generation sequencing

Through the use of next-generation sequencing techniques in recent years, researchers have concluded that epigenetic mechanisms of gene regulation play an important role in the development of FL (48). Among the most important and consistent results from these next-generation sequencing studies has been the identification of an important role for histone methyltransferases KMT2D and EZH2 in epigenetic mutations (Table I) (48,49). Next-generation sequencing has also been used to identify the important role of *TNFRSF14*, which is abnormally expressed in about 40% of FL patients (50). *TNFRSF14* encodes a gene termed herpes virus entry mediator, which acts to limit T-cell activation (Table I) (50).

4. Treatment and clinical outcomes

Clinical staging of lymphomas. Various treatment regimens exist for FL, and the appropriate treatment strategy depends upon the grade and clinical characteristics of the disease. A clinical staging system for lymphomas was published by the Committee on Hodgkin's Disease Staging Classification (51). In this system, stage I indicates the involvement of a single lymph node region or a single extranodal site in the cancer. Stage II indicates the involvement of two or more separate lymph node regions on the same side of the diaphragm. Stage III indicates the involvement of lymph node regions on both sides of the diaphragm. Stage IV indicates diffuse or disseminated involvement of one or more extralymphatic organs. Stage IV also includes localized involvement of liver, bone marrow, or nodular involvement of the lungs.

Approximately 26-33% of FL patients are in stage I or II (52). Approximately 20% of patients with FL undergo spontaneous remission without any treatment (53). In approximately 30-40% of patients with FL, a histological transformation to DLBCL occurs, and the majority patients with histological transformation succumb to the disease within a year (54). In terms of histological transformation and the overall survival of patients, there are no reliably documented differences between patients with t(14;18)-positive and t(14;18)-negative FL (55). As no reliable correlation between *BCL2* gene rearrangement status and clinical outcome has been reported, the t(14;18) translocation has not been used as a prognostic marker (56). Furthermore, the results of numerous studies have suggested that a similar set of morphologic, immunophenotypic, and clinical characteristics develop in FL regardless of the presence or absence of a *BCL2* rearrangement in FL grades 1-3A. Thus, the generally accepted opinion of these grades of FL is that they constitute a homogenous group with some distinct but many common molecular pathways (43). A depiction of the major targets of drug treatments in t(14;18)-positive and

Table II. Genes mutated or abnormally expressed in t(14;18)-negative follicular lymphoma.

Gene	Expression level	Samples (%)	(Refs.)
BCL2	No expression	64.7-100	(34,35,70-72)
BCL2	Overexpression	20-80	(34,39,45)
BCL6	Expression	54.5-100	(34,37,39,42,70-72)
CD3	Expression	100	(71)
CD5	No expression	100	(39)
CD10	No expression	31.6-100	(34,35,70)
CD10	Expression	26.7-100	(34,39,72)
CD19	Expression	100	(72)
CD20	Expression	100	(70-72)
CD23	Expression	86.7-100	(64,72)
CD43	No expression	100	(70)
CD79a	Expression	100	(38)
IRF8	No expression	2.6	(34)
IRF8	Expression	97	(34)
MUM1/IRF	No expression	100	(72)
TCL1A	Below normal expression	67	(35)

t(14;18)-negative FL is illustrated in Fig. 2. Furthermore, a summary of patient groups with t(14;18)-negative FL with their treatments and outcomes is illustrated in Table III.

Common treatment strategies. Unless the disease can be cured by surgery or local irradiation, FL is generally managed with radiation or chemotherapy. For those projected for treatment with radiation or chemotherapy, clinical monitoring using a 'watch and wait' approach is likely to be recommended until the patient requires treatment (1). For patients who have stage I or II low-grade FL, radiation is usually recommended as a first treatment approach. For patients with low-grade FL with a high tumor burden, chemotherapy is often followed by involved field irradiation therapy (IFRT) (22). In stage III or IV FL, patients typically receive chemotherapy regimens, such as alkylating agents for inhibition of cell growth, purine analogs and anthracycline-based agents (22). Monochemotherapy with chlorambucil or cyclophosphamide is a common approach (22). Treatment with chemotherapy plus rituximab is the accepted standard for most patients and this method is associated with increases in the overall survival of patients (2). Among anthracycline-based regimens, one of the most common treatments is R-CHOP, a combination of 5 drugs: Rituximab, cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine and prednisone (57). Another commonly used combination chemotherapy is R-CVP, which includes rituximab, cyclophosphamide, vincristine and prednisone (58). CHOP-RIT, the administration of tositumomab/iodine-131 radioimmunotherapy (targets CD20) immediately following CHOP, is also common (59). Another commonly used approach is bendamustine (an alkylating agent) plus rituximab (60). However, rituximab, a monoclonal anti-CD20 antibody, is ineffective in variants of FL that are negative for CD20 (61,62). A recently developed approach is ABT199, a BH3 mimetic investigational drug (venetoclax) that targets the BCL2 pathway (63). However, as the majority of cases of t(14;18)-negative FL lack BCL2 overexpression, this approach would be contraindicated for these patients. A better understanding of the underlying genetics of each variation on the disease may lead to more precisely targeted treatment regimens.

Major signal transduction pathways targeted in drug treatment for FL. Although the exact mechanisms of rituximab, the most common drug treatment for FL, are not yet fully known (64), it is considered that rituximab achieves its clinical effect by altering intracellular signaling pathways (64). Evidence indicates that rituximab operates by reducing activity of the p38MAPK pathway. This reduction in activity results in the inhibition of the interleukin-10 paracrine cytokine autoregulatory loop, which in turn inhibits signal transducer and activator of transcription 3 (STAT-3) activity. This inhibition of STAT-3 activity leads to a downregulation of BCL2 expression, and subsequent chemosensitization (65). Additionally, rituximab upregulates expression of Raf-1 kinase inhibitor protein (RKIP) (64). RKIP acts to reduce the activity of the extracellular signal-related kinase (ERK) 1/2 and the NF-κB pathways, which in turn inhibits transcription of AP-1 and NF-κB. The downregulation of both of these pathways leads to the subsequent reduction of BCL2 transcription and expression and susceptibility to apoptosis (64). A better understanding of the effects of drugs on molecular pathways will allow better targeted treatments.

Clinical differences between t(14;18)-positive and -negative FL. The research group of Leich *et al* (34,35,66) conducted studies examining clinical differences between patients with t(14;18)-negative and t(14;18)-positive FL. In one study comparing the 2 groups, t(14;18)-negative patients were more likely to have lower stage FL. However, no differences were observed in the other clinical variables of sex, involvement of extranodal sites, B symptoms, lactate dehydrogenase and the

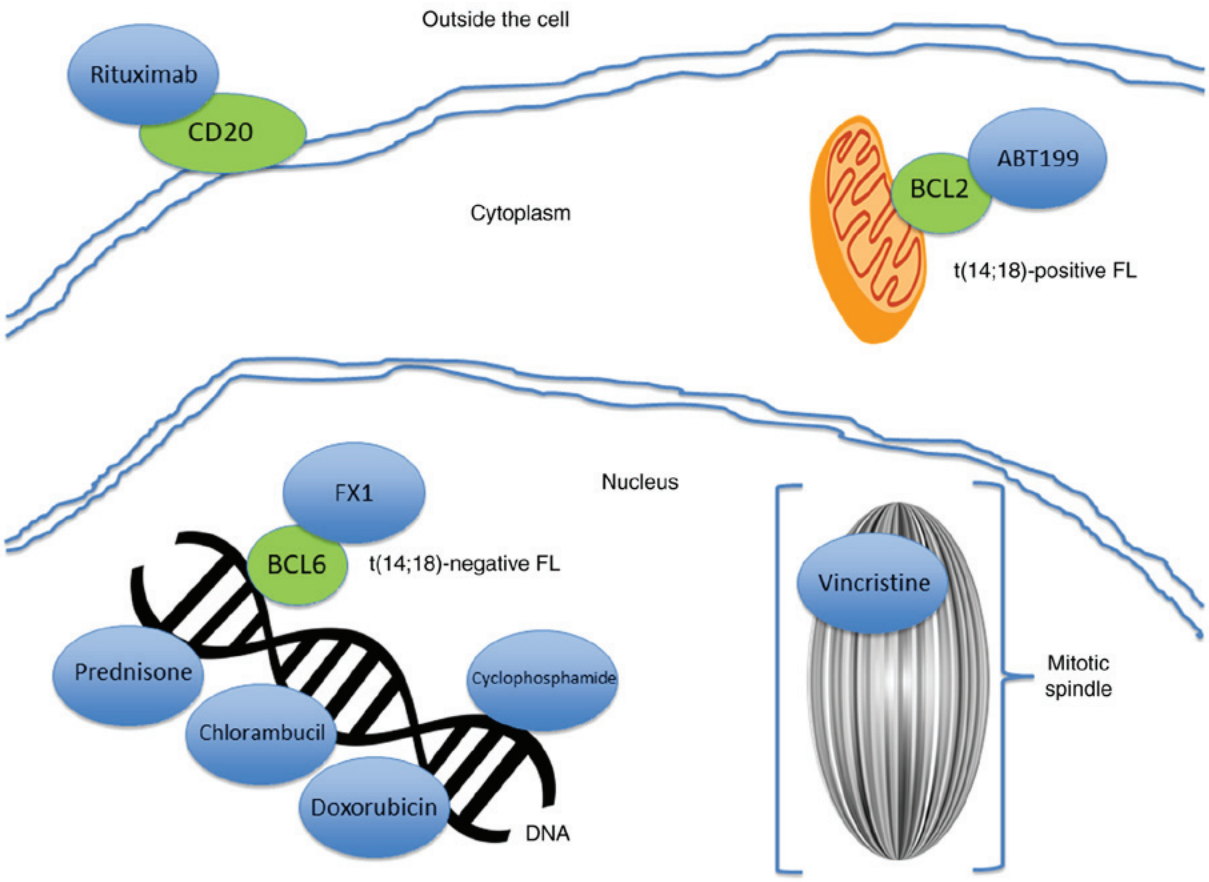

Figure 2. Major pathways relating to drug treatment intervention. In t(14;18)-positive follicular lymphoma (FL) and t(14;18)-negative FL, alkylating agents such as chlorambucil and cyclophosphamide directly bind to DNA (74). They cross-link guanine bases to cause cell death and stop tumor growth. Rituximab binds to CD20, which leads to downregulation of the B cell receptor, and induces apoptosis of CD20+ cells (74). Doxorubicin, vincristine, and prednisone are components of the CHOP regimen. Doxorubicin binds to DNA and causes breakage, leading to cell death. Vincristine binds to the mitotic spindle, causing mitotic arrest and cell death (74). Prednisone binds to the DNA and alters gene expression. For t(14;18)-positive FL, ABT199 targets the BCL2 pathway. ABT199 is a P-glycoprotein inhibitor that induces cell death (74). For t(14;18)-negative FL, FX1 binds to and inhibits BCL6, leading to cell death (73).

Eastern Cooperative Oncology Group (ECOG) performance status (34,67). In another study examining 540 advanced stage and 116 early stage patients with FL treated with chemotherapy and radiation, no differences were observed in patient characteristics between FL cases with and without t(14;18). The survival times patients of patients with advanced-stage FL also did not differ between the t(14;18)-positive and t(14;18)-negative patients (66). Larger population studies should better inform treatment strategies by identifying subtle differences between the t(14;18)-negative and t(14;18)-positive FL populations.

Relation between BCL2 and BCL6 expression and clinical variables. Studies have examined the clinical differences between patients with and without *BCL2* and *BCL6* rearrangements. Although the majority of results underscore a similarity in clinical presentation between patients with and without *BCL2* and *BCL6* rearrangements, some differences have been noted. A total of 98 patients with FL and 93 DLBCL were examined by in the study by Watanabe *et al* (68) with the aim of determining the frequencies of *BCL6* and *BCL2* translocations in the two patient groups. *BCL2* translocations were detected in 77 patients with FL and 22 patients with DLBCL. *BCL6* translocations were detected in 14 patients with FL and 14 patients with DLBCL. The patients were followed-up for 29 months after undergoing R-CHOP therapy. For patients with FL and DLBCL, the presence of *BCL2* or *BCL6* translocation was uncorrelated with clinical outcomes after treatment with R-CHOP therapy. Furthermore, neither overall survival nor progression free survival differed between the patient groups (68).

Some clinical differences between t(14;18)-negative FL patients with *BCL6* rearrangements and t(14;18)-positive FL patients have been noted (39). In one study, Jardin *et al* (39) examined a group of 15 t(14;18)-negative FL patients with *BCL6* gene rearrangements and a t(14;18)-positive comparison group. A majority of the t(14;18)-negative group had a t(3;14) translocation. There were no significant differences in age, sex, performance status, bone marrow involvement, or overall survival in comparison to a t(14;18)-positive group. However, in the t(14;18)-negative group, patients were more likely to have a stage III or IV disease. Furthermore, the lymphomas in the t(14;18)-negative group had a prominent nodal architecture, and usually had significantly larger follicles than the t(14;18)-positive FLs. The authors (39) concluded from this that BCL6 may play a role in follicular structure. These results indicated that t(14;18)-negative FL with a *BCL6* translocation may constitute a distinct subtype of FL.

Table III. Groups of patients with t(14;18)-negative FL with treatments and outcomes.

Patient group	Treatment	Outcome	(Refs.)
Five-hundred and forty patients with advanced-stage FL and 116 patients with early-stage FL. Some patients with *BCL2* translocations and others without *BCL2* translocations.	Chemotherapeutic regimens and radiation.	Patient characteristics did not differ between patients with and without *BCL2* translocations. Survival times of patients with advanced-stage FL did not differ.	(66)
Seventy-seven patients with FL and 22 patients with DLBCL with *BCL2* translocations. Fourteen patients with FL and 14 patients with DLBCL with *BCL6* translocations.	R-CHOP	Patients were evaluated at 29 months following treatment. Overall survival and progression-free survival did not differ between groups.	(68)
Fifteen patients with t(14;18)-negative FL with *BCL6* translocations. The majority of patients in the group had a t(3;14) translocation.	CHOP, radiotherapy, or chlorambucil	When compared to t(14;18)-positive controls, there was no difference in age, sex, performance status, bone marrow involvement, or overall survival.	(39)
Thirty-five cases of predominantly diffuse t(14;18)-negative FL	Radiotherapy, chemotherapy in combination with radiotherapy, or chemotherapy alone.	Therapy data were available for 19 patients. Fifteen had complete remission and one had progressive disease.	(5)
Fifty-one-year-old male with t(14;18)-negative FL who lacked BCL2 expression.	Examination of lymph node biopsy.	Diagnosis of high-grade 3A FL with DLBCL transformation.	(70)
Seven patients, including 5 females and 2 males. The cases had centroblast-predominant isolated follicles and a lack of BCL2 staining in otherwise-normal lymph nodes.	Clinical examination, including lymph node samples, bone marrow biopsies, imaging studies, and clinical evaluations.	None of the patients exhibited evidence of systematic lymphoma at the time of diagnosis or clinical follow-up visits up to 44 months after diagnosis.	(71)
One patient with t(14;18)-negative FL. The patient was a 74-year-old female with swelling in the submandibular region.	A surgery was performed and the lymph node was removed.	No recurrence of FL upon follow-up one year after surgery.	(72)

t(14;18)-negative FL with diffuse and skin-localized expression. Studies have identified uncommon forms of t(14;18)-negative FL, some with diffuse, extranodal expression, and others with expression limited to the skin. One study demonstrated that a subtype of $CD10^{-}MUM1^{+}$ FL exhibited distinctive biological and clinical features compared with the more typical $CD10^{+}MUM1^{-}$ FL (42). Twenty-two mostly t(14;18)-negative FL patients who were negative for expression of CD10 and positive for expression of MUM1 were generally older than typical FL patients (mean of 67 vs. 58.7 years old). $CD10^{-}MUM1^{+}$ FL patients also exhibited diffuse FL proliferation and were generally of a higher disease grade, either FL 3A or 3B, having a relatively poor prognosis.

In another study, a different subtype of t(14;18)-negative nodal follicular non-Hodgkin lymphoma exhibited a predominantly diffuse pattern and was characterized by deletions in the chromosomal region 1p36. These patients were more frequently diagnosed as low-grade (stage I and II) FL and generally presented with isolated large tumors (median size of 5 cm) that were frequently localized to the inguinal region. Although a complete remission could be achieved by treatment with radiotherapy alone or chemotherapy in combination with radiotherapy, disease progression generally followed an indolent course (5). This diffuse form of t(14;18)-negative FL represents a previously undocumented form of FL with distinct molecular and clinical features (5).

Moreover, a subtype of generally t(14;18)-negative FL which arises primarily in the skin has also been documented (69). Each of the evaluated 47 patients with FL was in clinical stage I. Compared with t(14;18)-positive cases, these FL cases were less likely to express BCL2 or CD10. These cases also had a higher proportion of extranodal FL sites, and had a significantly higher overall and disease specific five-year survival rate. This subtype of FL has a generally more favorable clinical outcome when compared to t(14;18)-positive FL (19,69).

Clinical reports of atypical t(14;18)-negative FL. An unusual case, difficult to diagnose, was reported by Wong *et al* (70). The authors reported a case of a 51-year-old male with t(14;18)-negative FL who lacked BCL2 expression. The patient was classified as having high-grade 3A FL with areas of large cell transformation within the same lymph node. Neoplastic cells from the patient were positive for CD20, CD79a and BCL6, and were negative for BCL2 and CD10. The clinical diagnosis was FL 3A with diffuse large B cell transformation.

Another report of atypical clinical cases with difficult diagnoses was made by Nybakken *et al* (71). These researchers reported on 7 patients (5 females ranging in age from 51 to 61 years, and 2 males aged 6 and 61 years). The patients presented with isolated atypical follicles that were composed of cytologically atypical centroblasts located within otherwise normal lymph nodes. The isolated follicles had unusual morphologic features that could be mistaken for lymphoma. The cases were generally positive for CD20 and BCL6, and were negative for BCL2 and CD3. The sites of involvement included peripheral and internal sites, such as a periaortic lymph node and rectal mucosa-associated lymphoid tissue. The authors considered a diagnosis of partial involvement by FL. The cytological characteristics of involved areas were consistent with FL grade 3B (enlarged with vesicular chromatin and prominent nucleoli, and nuclear membrane irregularity inconsistent with the morphology of the surrounding lymph node). However, the pattern of single scattered follicles was not consistent with partial FL. Furthermore, none of the patients had evidence of systematic lymphoma at the time of diagnosis or clinical follow-up visits up to 44 months after diagnosis, and the patients did not require aggressive clinical management. Nybakken *et al* (71) noted that it is of high importance to differentiate these cases from aggressive FL or a similar disease to avoid unnecessarily aggressive treatment of patients with indolent conditions.

Surgical treatment for t(14;18)-negative FL. Finally, a surgical treatment for a patient with t(14;18)-negative FL has also been reported (72). The patient was a 74-year-old Japanese female who presented with a complaint of swelling in the submandibular region. The patient was diagnosed with stage I FL. A surgery was performed and the lymph node was removed successfully. Flow cytometric analysis revealed that the lymphoma cells were positive for CD19, CD20, CD23, CD10 and BCL6. The cells were negative for BCL2 and MUM1. There was no recurrence of FL upon follow-up a year post-surgery. This case suggests a distinct type of surgical treatment for certain types of BCL2-negative FL (72).

5. Conclusions

The t(14;18) translocation is absent in approximately 10-20% of FL, a condition less common in FL grades 1 and 2 and more common in FL grades 3A and 3B. t(14;18)-negative FL is often associated with a t(3;14) translocation or the overexpression of BCL6, which is associated with morphological effects that closely resemble those associated with t(14;18). t(14;18)-negative FL patients are generally indistinguishable from t(14;18)-positive patients from a clinical perspective. However, diffuse and pediatric forms of FL, which often lack t(14;18), have a better clinical prognosis than t(14;18)-positive FL patients. In the future, the development of novel methods for targeting pathways other than the BCL2 pathway to effectively manage t(14;18)-negative FL may prove to be useful. For example, the recent study by Cardenas *et al* (73) detailed the development of specific BCL6 inhibitors, such as FX1, which could be effective in controlling t(14;18)-negative FL (Fig. 2).

Acknowledgements

Not applicable.

Funding

This study was supported in part by grants from Colleges and Universities Key Scientific Research Project Plan Basic Research Special of Henan Province (grant no. 19zx009), Science and Technology Project for Tackling Key Problems of Henan Province (grant no. 182102311172), Basic and Frontier Technology Research Program of Henan Province (grant no. 132300410448), and Science and Technology Innovation Talent Program of Henan Province (grant no. 154100510019).

Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

WR, ST, DZ and PL contributed to the conception and design of this study. WR, ST, ZuZ, TL, XZ and ZhZ were involved in the acquisition of the data and the study design. WR, ST, ZuZ, TL, XZ, ZhZ, DZ and PL were involved in the writing of the article. WR, ST critically revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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