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Advances in Diagnosis and Treatment for Nodal and Gastrointestinal Follicular Lymphomas Focused on Gene Targeted and Immune Therapeutic Agents

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1. Abstract

Globally, follicular lymphoma (FL) is the most common type of indolent B cell lymphoma (BCL). Recently, the incidence of FL has increased in Europe, the USA, and Asia, with a possible increase in gastrointestinal FL incidence. Limited knowledge of FL molecular biology and novel therapeutics among gastroenterologists has resulted in delegating the treatment to hematologists. To address this limitation, we reviewed key articles from the previous decade, particularly from the past 3 years, exploring the molecular mechanisms underlying nodal follicular lymphoma and developing innovative treatments that specifically target the responsible genetic mutations, as well as the findings of clinical trials, by particularly focusing on the treatment of primary gastrointestinal FL. Genetic abnormalities, such as t(14;18), BCL2 overexpression, factors associated with the nuclear factor NF-κB pathway, as well as histone acetylases and histone methyltransferases, are implicated in the development and proliferation of FL. . Many clinical trials have been conducted on novel therapeutics targeting these genetic abnormalities and immunomodulatory mechanisms; therefore, the treatment outcomes of FL have markedly improved recently. Finally, the emergence and progress of many new therapeutics targeting specific genetic mutations and immune mechanisms has brought great promise for curing FL; however, the situation has become challenging, with the difficult question of how to combine these numerous novel agents and what order to use for treatment. Gastroenterologists should expand their knowledge and understanding of the molecular genetic pathogenesis of advanced FL and novel therapeutics while also considering the characteristics of primary gastrointestinal FL.

2. Introduction

Follicular lymphoma (FL) is the most common type of indolent B cell lymphoma (BCL)[1], with an increasing incidence in Europe, the USA, and Asia[2]. FL is characterized by a high relapse risk and refractory nature, making it incurable with a bleak prognosis. The nuclear factor (NF)-κB pathway, triggered by B cell receptor and Toll-like receptor stimuli, plays a vital role in FL development. Abnormal histone methylation and acetylation affect gene expression, thereby affecting lymphoma development. The t(14;18) translocation, observed in most individuals with FL, leads to BCL2 overexpression, promoting cell immortalization. Genome-wide association studies (GWAS) have identified relevant loci in FL development.

Rituximab is a monoclonal antibody that targets CD20, which is present in >90% of BCL-expressing cells. Using rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) remains a standard therapy. However, in the past decade, there have been remarkable advances in the development of new FL treatment modalities that target various oncogenes. In this review, we summarize recent findings in nodal FL, with emphasis on molecular genetic analysis and diagnosis, and discuss the evolving landscape of FL therapeutics targeting

genetic abnormalities. Furthermore, we address the role of gastroenterologists in managing advanced-stage gastrointestinal FL (GI-FL).

2.1. Incidence and Epidemiology

FL is a prevalent indolent type of BCL that accounts for 10%−20% of all non-Hodgkin lymphoma cases [1]. The incidence of FL is rapidly increasing in Western and Asian countries [2], including Japan [3]. GI-FL originates from B cell lymphocytes in the lymphoid tissues of the gastrointestinal tract, particularly in the submucosal lymphoid follicles. Histologically, GI-FL exhibits a folliculocentric lymphoma cell population and is categorized as grades 1, 2, 3a, or 3b. In general, grade 3b lymphoma is treated as an aggressive medium- or high-grade lymphoma and is frequently diagnosed in patients with enlarged lymph nodes. Approximately 70%–85% of individuals with grade 3b FL are identified at an advanced stage (III/IV), frequently accompanied by significant bone marrow involvement. Although the incidence of GI-FL is lower incidence than other lymphomas, it is more common among middle-aged and older adults, without notable sex differences. Nevertheless, specific data on peak incidence in particular age groups is currently unavailable.

3. Diagnosis of GI-FL

A Combination of Methods is Used to Diagnose Gi-FL

3.1. Endoscopy

Endoscopy is an important procedure for diagnosing GI-FL. It facilitates gross diagnosis and biopsy extraction for histological examination. Gastric malignant lymphomas exhibit various endoscopic types [4]. Colorectal malignant lymphomas often present as polyp-like lesions, known as multiple lymphomatous polyposis [5], helping in diagnosis. In Japan, the widespread use of small bowel endoscopy, improved equipment, and enhanced endoscopic techniques have increased the detection rates of GI-FL [6].

3.2. Histopathological Examination

In histopathological examination, the biopsy sample is first closely examined under an endoscope. The key is to (1) identify the folliculocentric lymphoma cell population and elucidate the specific histological features associated with FL; then, (2) immunostaining is performed to provide additional diagnostic evidence.

Based on the follicular pattern of B cell aggregates, FL is classified as a grade 1–3 disease. This classification depends on a delicate balance between the formation of follicle-like structures and the characteristic atypia exhibited by lymphoma cells. In immunopathological examination, FL expresses three markers: CD20, CD10, and BCL2. Among these, BCL2 overexpression is decisive for diagnosis. At the genetic level, individuals with FL frequently exhibit the t (14;18) translocation, resulting in BCL2 overexpression. This chromosomal abnormality is not only a genetic abnormality but also a cornerstone of FL diagnosis.

3.3. Molecular Genetic Analyses

Molecular genetic analyses provide insights into FL pathogenesis and prognosis. First, detection of the t(14;18) translocation is a key element in FL diagnosis. Furthermore, FL features rearrangements in IGH and other genes, which are detectable via polymerase chain reaction. Genetic mutations in FL also affect disease progression and prognosis, which are detectable via next-generation sequencing (NGS). BCL abnormalities, as revealed via NGS, affect NF-κB pathway activation, epigenome-related enzyme dysfunction, apoptosis-related factor expression, and immune system evasion (Figure 1) [7]. Specific mutations in the NF-κB pathway (CD79B, MYD88, A20/tumor necrosis factor alpha-induced protein 3 [A20/TNFAIP3], and CARD11) occur in active B cell (ABC)-type diffuse large BCL (DLBCL), contributing to lymphoma development. NGS can help identify abnormalities in histone methyltransferases (KMT2D and EZH2) and acetylases (EP300 and CREBBP) in FL and germinal center B cell (GCB)-type DLBCL. Chromosomal t(14;18) translocations promote antiapoptotic BCL expression, which is essential for cell immortalization. Immune evasion-related gene abnormalities such as PDL1/L2 occur in various lymphomas, facilitating immune escape [7] (Figure 1).

A clinical trial has revealed the efficacy of polatuzumab vedotin, an anti-CD79B antibody–drug conjugate, in relapsed/refractory (R/R) FL and DLBCL [8]. MYD88 and CD79B mutations categorize DLBCL into two types: ABC and GCB [10], affecting prognosis [9] and treatment responses. A20/TNFAIP3 deficiencies, common in non-GCB DLBCL, affect NF-κB regulation. A20 inactivation, a key feature of lymphoma, occurs in FL [11], contributing to its pathogenesis. Furthermore, BCL10, vital for NF-κB activation, affects B cell proliferation [12].

KMT2D, a histone lysine methyltransferase, suppresses BCL; its deletion promotes B cell proliferation. Targeting KMT2D is a promising strategy for alleviating early tumorigenesis [13]. In Japan, tazemetostat, an orally administered EZH2 inhibitor, is approved for treating EZH2-mutated BCL [14,15]. Moreover, CREBBP, EZH2, MEF2B, and EP300 mutations are prevalent in FL [16,17]. Genome-wide NGS data revealed frequent mutations in histone-modifying genes (e.g., EZH2, CREBBP, and MLL2), with crucial roles in the development of lymphoma, IGH–BCL2 translocations and CREBBP mutations occur early, whereas MLL2 and TNFSFR14 mutations are observed at later stages. The 2008 WHO classification introduced three new FL variants: (1) pediatric FL, (2) primary intestinal FL, and (3) in situ FL [18].

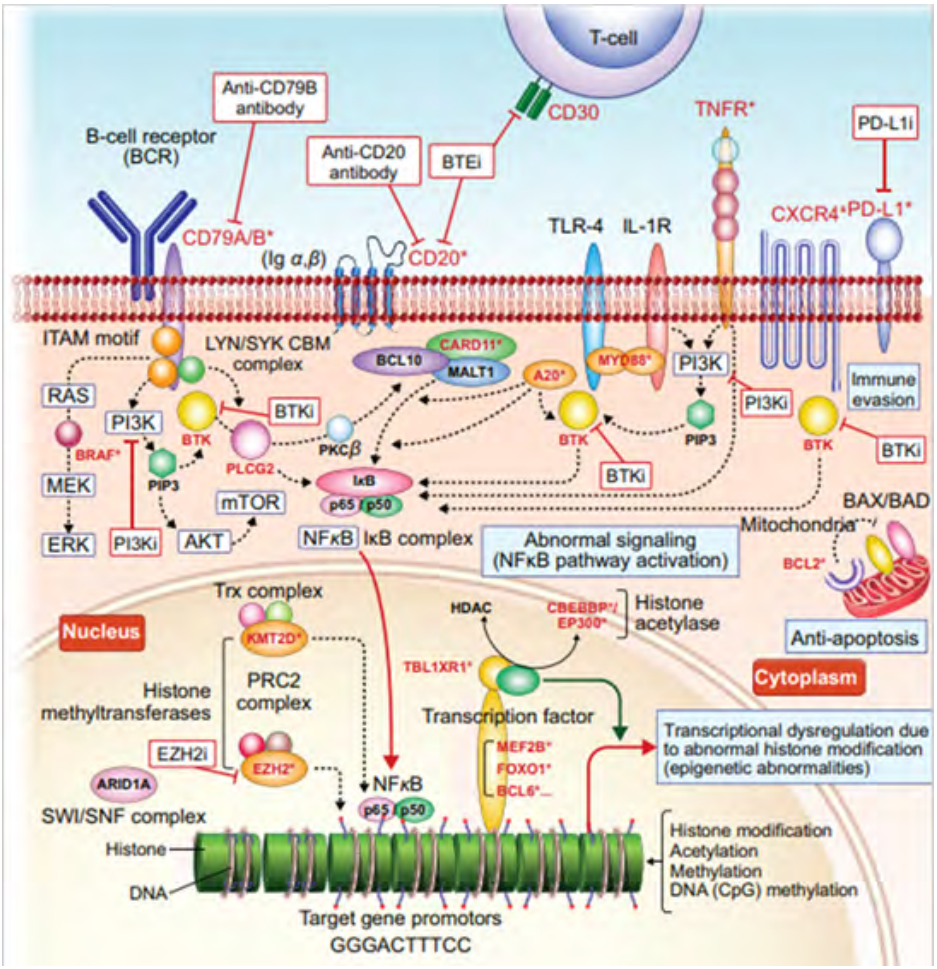

Figure 1: Follicular lymphoma (FL)-related genes involved in FL pathogenesis and proliferation, and the action of novel therapeutic agents targeting them.

3.4. GWAS

GWAS have been conducted to investigate genetic polymorphisms (single nucleotide polymorphisms [SNPs]) in relation to specific diseases. GWAS have identified genetic variants associated with FL risk. For example, Skibola et al. [19] conducted a large GWAS involving 4,523 individuals with FL and 13,344 controls of European descent. They identified non-HLA FL susceptibility loci and HLA gene mutations associated with FL risk [19]. These loci include 11q23.3 near CXCR5, 11q24.3 near ETS1 3q28 at LPP, 18q21.33 near BCL2, and 8q24.21 near PVT1. Additionally, specific HLA-DRβ1 multichain amino acids and independent signals of HLA class II rs17203612 and HLA class I rs3130437 were associated with FL risk, emphasizing the contribution of mutations at common loci outside the HLA region to FL risk [19]. Similar loci outside HLA have been identified for other non-Hodgkin lymphoma subtypes, including DLBCL, chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL), and primary central nervous system lymphoma [20]. Some loci, including the WEE1 locus, hold potential as therapeutic markers [21]. Moreover, height and coldness were examined as risk factors for different non-Hodgkin lymphoma subtypes, with a slight increase in CLL risk associated with height, but no significant coldness-related risk was observed for DLBCL, FL, or MZL [22].

Autoimmune diseases are associated with an increased risk of non-Hodgkin lymphoma, including FL, and have been explored in GWAS [23,24]. Although no association has been observed between B cell-mediated autoimmune diseases and FL or MZL risk [23], a shared genetic etiology is present between non-Hodgkin lymphoma and autoimmune diseases [24]. Furthermore, genes related to apoptosis and telomere length play a role in both autoimmune diseases and non-Hodgkin lymphoma [24]. In another study, a polygenic risk score was established using GWAS to identify the risk variants for various carcinomas, including FL, revealing a two-fold higher risk for FL associated with this score [25].

Furthermore, GWAS have been conducted to determine the association between lipid traits and non-Hodgkin lymphoma subtypes [26]. High-density lipoprotein cholesterol is positively correlated with FL, DLBCL, and MZL, whereas triglycerides exhibit a negative correlation with MZL. In another GWAS, an increased risk of developing FL was observed with a higher number of homozygous HLA class II loci, indicating the importance of HLA zygosity in individuals with non-Hodgkin lymphoma and suggesting the involvement of different immune pathways in its etiology [27].

GWAS have also been conducted to evaluate the prognostic predictors for FL. A multicenter meta-analysis identified the loci strongly associated with lymphoma-specific mortality on SNPs at 17q and 24 (rs10491178) [28]. Furthermore, high-binding SNPs in IL8 (rs4073) were associated with overall survival [28]. In addition, independent loci on the X chromosome were identified to be involved in FL etiology, with the Xq21.1 signal also observed in DLBCL [29]. Multiple loci contributing to the development of non-Hodgkin lymphoma, including FL, have been identified. Approximately 150 loci associated with non-Hodgkin lymphoma development have been identified in GWAS [30]. These loci, although fragmented, represent valuable insights, with the potential for further discovery via advanced analysis methods and more GWAS; this may ultimately contribute to the development of new therapeutic agents and potential cures for FL.

3.5. Imaging Studies

Imaging studies play a vital role in assessing disease stage, with common modalities including chest radiography, ultrasonography, computed tomography, and magnetic resonance imaging. These techniques help evaluate lymph node and visceral enlargement, detect metastases, and determine the location and size of lesions.

4. Choice of Treatments

Several key factors affect the selection of treatments for GI-FL [31,32]. First, the characteristics and progression of the lesions, including their location, size, and extent, are assessed to determine disease risk and prognosis. Second, a precise pathological diagnosis of FL is crucial, based on laboratory and histological evaluations, because it serves as the foundation for selecting the most appropriate treatment [33]. Third, accurate disease staging, determined via comprehensive diagnosis and evaluation, is essential for understanding disease progression and developing an effective treatment strategy [31].

Treatment decisions are affected by the histological subtypes and extent of the disease [34], as defined by the Lugano staging classification system [32]. While the histological grade is a valuable prognostic predictor for nodal FL, treatment selection relies on staging, which indicates the extent and spread of the disease. In individuals with primary GI-FL, personalized treatment choices are based on individual circumstances [6], changes over time, Lugano classification, and histological grade.

For advanced stages (III and IV), treatment approaches vary depending on factors such as the number of affected areas, organ involvement, spread, and distant metastases. Options may include irradiation combined with chemotherapy, with or without immunotherapy. In cases with one, two, or three lesions amenable to irradiation, radiotherapy may be considered. Additional treatment possibilities encompass chemotherapy, chemotherapy, and immunotherapy, as well as surgical resection if the patient experiences digestive tract obstruction, possibly improving symptoms and quality of life.

Treatment plans should be tailored to each patient, considering their unique requirements and constraints and the characteristics of the gastrointestinal tract. Personalized GI-FL treatment should consider the disease stage and the patient's overall health. Periodic review and adjustment of the treatment plan based on disease progression, treatment effectiveness, and patient response are essential for optimal treatment outcomes (Figure 2).

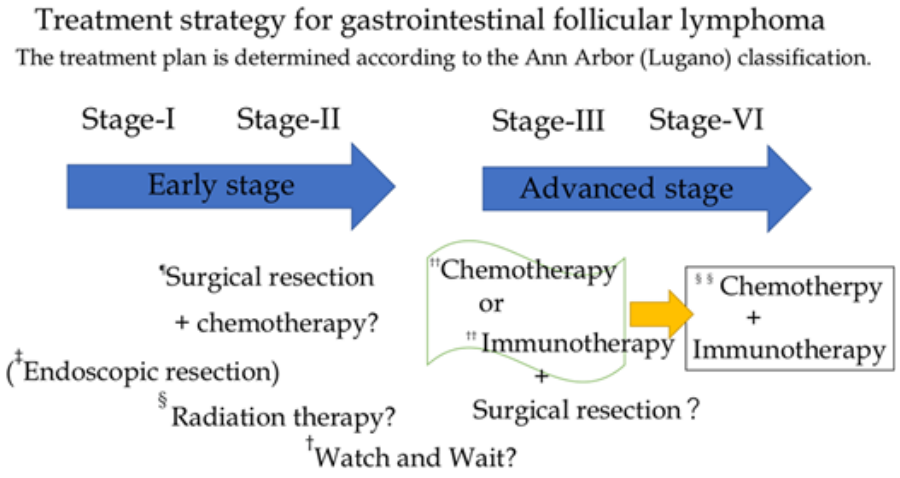

Figure 2: Treatment strategies for gastrointestinal follicular lymphoma. The treatment plan is determined based on the Ann Arbor (Lugano) classification. For example, the application of †watch-and-wait and ‡endoscopic resection is limited because of SM onset; §radiotherapy is not the mainstay depending on the number and location of the lesions; ¶surgical resection combined with chemotherapy is used as a curative treatment, even in relatively early-stage cases, and conventional chemotherapy is used in advanced stages; and †recent chemotherapy or ‡new agents as ††monotherapy or as chemotherapy in advanced stages. Diversification of treatment options, including new agents as ††single agents or in §§combination with conventional chemotherapy, and surgical resection in some cases. Increasingly individualized and tailor-made.

5. Treatment

5.1. Watch-and-Wait Approach

In early-stage GI-FL, a watch-and-wait strategy is often employed. Patients are closely monitored without immediately initiating treatment. This approach is suitable for the favorable prognosis of GI-FL subtypes and offers a good 10-year prognosis rate with surgical resection or R-CHOP therapy. Studies comparing the treated and watch-and-wait groups in stage I GI-FL revealed no significant differences in progression-free survival (PFS) or overall survival [35,36]. Recent research has indicated 5- and 10-year event-free survival rates of 91.1% and 86.9%, respectively, for patients with localized GI-FL who were managed using the watch-and-wait strategy [37]. Nevertheless, patient-specific factors, overall treatment effects, and potential side effects should be considered when choosing the watch-and-wait approach.

5.2. Radiotherapy

Radiotherapy is a treatment option for localized lesions, particularly in combination with other treatments. However, several factors limit its use in GI-FL, including potential tissue damage, dose limitations owing to radiation sensitivity, advances in chemotherapy effectiveness, and the risk of side effects and complications, particularly in the gastrointestinal tract [38,39]. Nevertheless, radiotherapy may be beneficial in specific cases to prevent FL progression.

5.3. Treatment Agents

Antibodies: Monoclonal antibodies, including rituximab, have been highly effective in treating FL. Rituximab monotherapy has a success rate of 67% for untreated FL and 46% for relapsed cases [40]. Many other antibody-based agents such as tafatasitamab[41], polatuzumab vedotin[8], loncastiximab tecilin[42], maglorimab[43], and obinutumab[44] hold promise, either alone or in combination with lenalidomide or other therapies. Furthermore, biosimilars such as CT-P10 offer comparable efficacy and safety [45]. Bispecific T cell-binding antibodies (BTEs) such as mosnetuzumab[46], glofitumab[47], epcoritamab[48,49], and odronestamab[50,51] exhibit high overall response rates and complete response rates in FL. Lastly, anti-PD-L1 antibodies such as atezolizumab[52] and pembrolizumab[53] enhance T cell function and antibody-dependent cell-mediated cytotoxicity in natural killer cells, exhibiting potential in FL treatment.

Immunomodulatory Drugs: Lenalidomide, an oral immunomodulatory drug, exhibits tumor-killing and immunomodulatory properties [54]. Combinations of lenalidomide with rituximab have demonstrated higher response rates and longer progression-free intervals compared with lenalidomide alone [55]. Other combinations and sequences are being explored in clinical trials to determine the optimal treatment regimens [56-62].

Molecular Targeted Therapies (Small-Molecule Compounds): Bruton's tyrosine kinase inhibitors (BTKis) such as ibrutinib, acalabrutinib, and piltobrutinib exhibit potential for treating FL [63-69]. BCL2 inhibitors such as venetoclax trigger the apoptosis of FL cells [70,71]. Epigenetic regulators such as tazemetostat, vorinostat[72,73] and mocetinostat[74] are being investigated. Phosphatidylinositol-3 kinase inhibitors (PI3Kis) such as idelalisib[75-77], duvelisib[78,79], umbralisib[80,81], parsaclisib[82,83], and zandelisib[84] have exhibited efficacy; however, they may be associated with adverse events. Dual inhibitors of the PI3K/Akt/mTOR signaling pathway [85] are also being explored [86,87].

Cell-Based Therapies: Chimeric antigen receptor (CAR)-T cell therapy with agents such as axicabtagene ciloleucel (axi-cell) [88,89], tisagenlecleucel (tisa-cell) [90-92], and lisocabtagene maraleucel (liso-cell) [93] exhibits high efficacy but presents hematological toxicity [94,95] and logistic challenges [96]. Nevertheless, clinical trials are being conducted to assess different cellular therapies, including CAR-T cell therapies, for R/R FL.

Response-Adapted Post-Induction Strategy: In the FOLL12 study, a standard rituximab maintenance therapy exhibited significantly better PFS than an experimental post-induction therapy for patients with FL. The standard maintenance therapy extended the PFS of patients with FL who responded positively to induction treatment [97].

These treatment options provide various choices for managing GI-FL, with ongoing research expected to further refine the treatment strategies.

6. Treatment of GI-FL

When treating GI-FL, Lugano staging and histological grade should be considered. Personalized treatment is essential, considering individual patient circumstances [6]. However, potential gastrointestinal perforation from tumor reduction should be considered. The watch-and-wait strategy is traditional; however, at present, advanced cases receive chemotherapy, immunotherapy, or both. Surgery with postoperative therapy is an option for obstruction. The approach should be tailored to GI-FL, combining surgery, chemotherapy, radiotherapy, and immunotherapy based on lesion site, stage, and patient's health. Furthermore, conservative surgical or endoscopic options may be applied depending on tumor anatomy and histology. Individualized care is key in GI-FL treatment (Figure 2).

7. Conclusion

Molecular genetic analysis of FL has revealed BCL2 gene overexpression, IGH gene rearrangement, and mutations in NF-κB pathway-related factors. Furthermore, abnormalities associated with histone methyltransferases and acetylases have been identified. Recent GWAS have identified the loci implicated in FL development. Advances in FL therapeutics include anti-CD20, CD79 monoclonal antibodies, BTEs, anti-PD-L1 antibodies, lenalidomide, BTKis, BCL2 inhibitors, EZH2i, PI3Kis, dual PI3K/Akt/mTOR pathway inhibitors, and CAR-T cell therapy. In future clin-

ical trials, elucidating the optimal combination and sequence of treatment of novel therapeutic agents aimed at curing FL is vital. Furthermore, tailor-made individual care for each patient's situation is important for selecting the treatment options for GI-FL.

8. Acknowledgment

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9. Conflict of Interest Statement

There are no conflicts of interest to declare.

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