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Treatment of indolent lymphoma

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Abstract

Treatment of indolent lymphoma has improved significantly in recent decades since the advent of rituximab (anti-CD20 monoclonal antibody). Although, some patients with limited disease can be cured with radiation therapy alone, most patients experience disease progression and recurrence during follow-up despite early initiation of treatment. Thus, watch-and-wait is still regarded the standard for asymptomatic patients. Patients with indolent lymphoma have a significant heterogeneity in terms of tumor burden, symptoms (according to anatomical sites) and the need for instant therapy. Therefore, the initiation of treatment and treatment option should be decided with a clear goal in each patient according to the need for therapy and clinical benefits with the chosen treatment. In this review, we cover the current treatment of follicular lymphoma and marginal zone lymphoma.

Key Words Indolent lymphoma, Non-Hodgkin's lymphoma, Follicular lymphoma, Marginal zone lymphoma

INTRODUCTION

Indolent lymphoma refers to a type of slowly growing non-Hodgkin's lymphoma (NHL) that has a long clinical course and is usually incurable. Indolent lymphomas include follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma and cutaneous T-cell lymphomas. Indolent lymphomas comprise 35–45% of NHL, with FL being the most frequent [1, 2]. In South Korea, MZL is the most common indolent lymphoma (21%), and the incidence of MZL and FL has been increasing in recent years [2, 3].

The majority of patients with indolent lymphoma can be observed provided they do not have symptoms due to lymphoma or rapid progression. For patients with indolent B cell lymphoma, current first-line treatments [radiotherapy (RT), anti-CD20 monoclonal antibodies, and chemo-immunotherapy] achieve a quite long progression-free interval and the expected overall survival (OS) is well beyond 20 years in rituximab era [4].

While indolent lymphomas are usually responsive to many treatment modalities, the protracted nature of the disease requires patients to be managed over a lifetime. Thus, careful judgement on the need of treatment and proper treatment modality should be made before the initiation of treatment considering the clinical situation and patient's need. In this article, we overview the current treatment of the two most common indolent lymphomas; FL and MZL.

FOLLICULAR LYMPHOMA

Follicular lymphoma comprises about 20% of all newly diagnosed non-Hodgkin's lymphomas (NHLs) [5]. BCL2 is characteristically over-expressed in about 90% of FL patients by t(14;18) translocation, leading to anti-apoptotic properties [6]. Pathologic grading based on the number of centroblasts predicts clinical outcomes. FL3B with BLC-6 translocation shows more aggressive clinical course similar to diffuse large B-cell lymphoma (DLBCL) [7]. Thus, FL3B is treated as DLBCL and the others (FL1-2 and FL3A) are treated according to the guidelines for FL. The Follicular Lymphoma International Prognostic Index (FLIPI) delineates three distinct prognostic groups and FLIPI-2 is more predictive for patients who are treated in rituximab era (Fig. 1) [8, 9]. However, these prognostic models do not guide the initiation of treatment and treatment modalities. Initiation of treatment is generally guided by GELF criteria [10] or its modified version (Table 1).

Initial treatment

Limited disease: About 10–15% of patients are diagnosed with FL are at a limited stage (stage I and II). RT is effective

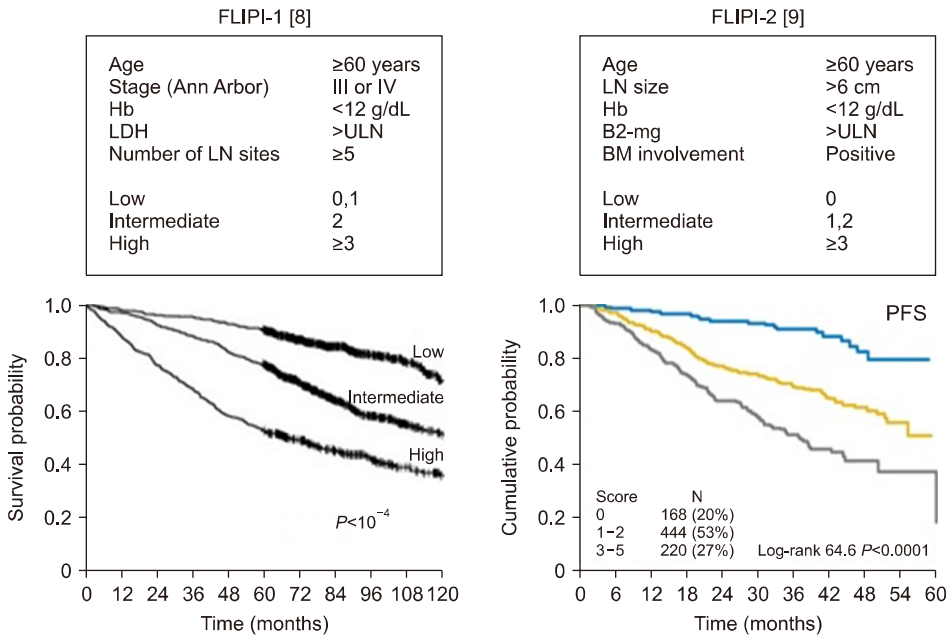

Fig. 1. Follicular lymphoma international prognostic index (FLIPI) 1,2 and survival outcomes.

Table 1. Indications for treatment in low grade lymphoma.

Indication	Detail
High tumor burden [10]	Any site >7 cm
	Three or more sites >3 cm
	Splenomegaly (>16 cm)
	Pleural or peritoneal effusion
	Circulating tumor cells >5,000/μL
	Cytopenia secondary to lymphoma
	- Absolute neutrophil count <1,000/μL
	- Platelet count <100,000/μL
Disease-related symptoms	Fever
	Night sweats
	Weight loss
	Compression
	Other lymphoma-related symptoms
Steady progression	Over at least 6 months

in the treatment of limited stage disease with long-term disease control rates of >90%. RT could be a curative treatment for limited stage FL [11]. RT dose of 24Gy is enough to control limited disease and additional dose is not beneficial [12]. Extended-field RT does not improve overall survival (OS) and also reduction of radiation field did not affect progression-free survival (PFS) [13, 14]. The addition of systemic therapy (rituximab or chemoimmunotherapy) improves PFS but not OS [15-17]. For selected patients, watch-and-wait could be a reasonable option given that there were no differences in OS outcomes between different treatment modalities [18, 19]. In a study, 67% of the patients did not require therapy at a median follow-up of 7 years [20]. Bulky and non-contiguous disease can be treated with rituximab or chemoimmunotheapy (CIT) with or without RT (Table 2).

Advanced disease: Watch-and-wait is regarded standard practice for advanced stage FL with low tumor burden even in the rituximab era, as there is no survival benefit with early treatment [21-23]. Initiation of treatment should be guided by indications for treatment (Table 1).

CIT is the most commonly used first-line therapy for patients with advanced stage FL. In a randomized phase III trial (FOLL-05), the efficacy of RCVP (rituximab, cyclophosphamide, vincristine and prednisone) and RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) was compared with RFM (rituximab, fludarabine, and mitoxantrone) as a first-line treatment in patients with advanced stage FL. With a median follow-up of 34 months, the 3-year progression-free survival (PFS) was 52%, 68% and 63%, respectively (P=0.011). RCHOP had less grade 3 or 4 neutropenia and secondary malignancies than RFM. RCVP was inferior to other combinations, thus RCVP should be avoided in patients who have high-risk features [24].

In a phase III trial (Stil NHL1) that compared BR (bendamustine and rituximab) and RCHOP as first-line treatment for patients with indolent lymphoma and mantle cell lymphoma (MCL), the overall response rate (ORR) was not different between BR and RCHOP (BR 93% vs. RCHOP 91%). However, with a median follow-up of 45 months, BR showed superior PFS than RCHOP (69 mo vs. 31 mo, P<0.001) without OS difference [25]. In a following phase III trial (BRIGHT), BR was confirmed to be at least not inferior in terms of complete response (CR) and PFS [26].

Obinutuzumab is a new type II anti-CD20 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity. In a phase III study (GALLIUM), obinutuzumab was compared with rituximab as first-line treatment in combination with chemotherapy (bendamustine, CVP or CHOP)

Table 2. Treatment of follicular lymphoma.

Disease status	Treatment	Comment
Localized disease	RT	- Potentially curative (ISRT 24–30Gy) - The addition of systemic therapy to RT improves PFS but not OS
	Rituximab	- Radiotherapy ineligible patients
	CIT	- Non-contiguous, bulky disease
	Watch and wait	- Stable, asymptomatic patients
Advanced disease	Watch and wait	- Without treatment indications (Table 1)
	CIT± antibody maintenance	- Rituximab or obinutuzumab+(CHOP, CVP, Bebdamustine) - Maintenance improves PFS but not OS
	Rituximab	- For low tumor burden
	Lenalidomide+rituximab	- As effective as chemoimmunotherapy
Relapsed disease	Watch and wait	- Stable, asymptomatic patients
	Palliative RT	- 2×2Gy
	CIT± antibody maintenance	- Long previous remission with CIT - Non-resistant regimen
	Rituximab	- For low tumor burden
	Lenalidomide+rituximab	- POD≤24 months after CIT
	PI3K inhibitors	- Double refractory disease
	EZH2 inhibitor (tazemetostat)	- EZH2 mutation-positive disease
	Radioimmunotherapy	- Not widely used
	Auto/allo-HSCT	- In selected patients
	CAR-T cell therapy	- After ≥2 lines of systemic therapy [63]

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CIT, chemoimmunotherapy; CR, complete response; EZH2, enhancer of zeste homolog 2; HSCT, hematopoietic stem cell transplantation; ISRT, involved site RT; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; POD, progression of disease; RT, radiotherapy.

in previously untreated, advanced stage FL patients [27]. Although, 3-year PFS was superior in obinutuzumab arm (80% vs. 73%, HR 0.66), serious infection, mortality and secondary malignancies were higher in Obinutuzumab arm. Thus, the benefits of obinutuzumab over rituximab as first-line therapy are not clear.

Based on promising results of a lenalidomide and rituximab combination in phase II studies [28, 29], a phase III trial (RELEVANCE) of lenalidomide and rituximab combination was conducted. Lenalidomide and rituximab combination showed similar 3-year PFS (77%) compared to rituximab-based CIT (78%) with lower grade 3 or 4 neutropenia and febrile neutropenia [30].

Rituximab monotherapy could be considered for patients who are not candidate for CIT as it showed high response rate (72–73%) with a median time to progression of 2 years for patients with low tumor burden [31, 32].

Rituximab maintenance showed PFS benefits in many studies, but not in OS improvement [33-36]

In a phase III trial (E4402 study, RESORT), rituximab maintenance and rituximab retreatment were compared in patients with low tumor burden FL who responded to rituximab induction therapy. In the study, rituximab retreatment is shown to be comparable to rituximab maintenance therapy in term of treatment failure (3.9 yr vs. 4.3 yr, P=0.54) while saving rituximab dose [37].

Rituximab maintenance following CIT (RCVP, RCHOP, or RFCM) also showed improved 3-year PFS (75% vs. 52%, P=0.001) in a phase III trial (PRIMA) [38]. Although half of the patients in maintenance group remained progression-free at 10 years, the estimated OS did not differ between the two groups (80%). Obinutuzumab maintenance following obinutuzumab-containing CIT is also available based on the GALLIUM trial [27]. For patients who achieved PR with BR treatment, rituximab maintenance improved duration of response in a retrospective analysis, but not in patients achieving CR [39].

Relapsed disease

For a relapsing disease, biopsy confirmation is strongly recommended to exclude transformation to a high-grade lymphoma. About 20% of patients with FL have transformation at disease progression [40]. FDG-PET scan is useful to guide optimal biopsy site (with highest intensity uptake).

Watch-and-wait is still valid option for relapsed FL patients with low tumor burden without transformation to high grade lymphoma. Symptomatic single lesion could be successfully relieved with low dose radiation (4Gy). For patients who need second-line therapy, there are many treatment options including rituximab monotherapy, CIT, lenalidomide-based combination, PI3K inhibitors and hematopoietic stem cell transplantation (HSCT) (Table 2). The clinical situation is different for each patient depending on disease characteristics, the first-line therapy and timing of progression. Thus, in order to select the optimal treatment, it is important to consult with the patient about the purpose of treatment before making any treatment decisions.

Rituximab monotherapy could be considered for relapsed

FL patients with low tumor burden. Rituximab monotherapy induces response in half of the patients with relapsed FL [41]. For patients who had rituximab induction therapy could retreated with rituximab if the progression of disease (POD) is long enough (>24 mo).

CIT is the most favored second-line therapy. Initial treatment could be used again in late relapse (>2 yr). However, BR is not generally recommended for patients who were treated with BR as first-line therapy because of the increased risk of infections and secondary malignancies. BR showed longer PFS (34 mo) in patients with relapsed or refractory indolent lymphoma compared with fludarabine and rituximab (12 mo) [42]. The addition of rituximab improved PFS by 12 months compared with CHOP in patients with relapsed FL [43]. However, this outcome could not be reproducible in the current practice because most of FL patients treated with rituximab or anthracycline containing regimen as first-line therapy.

Obinutuzumab-based CIT was evaluated in several studies. In a randomized phase III trial (GADOLIN), bendamustine and obinutuzumab combination improve PFS compared with bendamustine monotherapy (25 mo vs. 14 mo, $P<0.001$) in patients with rituximab-refractory indolent lymphoma [44, 45].

Rituximab or obinutuzumab maintenance could be used after achieving response [44-47]. However, for patients who progressed early after rituximab-containing treatment, obinutuzumab is preferred for its potential to overcome rituximab-resistance [48].

Single agent lenalidomide showed ORR of 23% for patients with relapsed FL with median response duration >16 months [49]. In a randomized phase II trial (CALGB 50401), the addition of rituximab to lenalidomide improved the ORR (76% vs. 53%, P=0.029) and the median time to progression (2 yr vs. 1 yr) [50]. This result was confirmed in a randomized phase III trial (AUGMENT), in which lenalidomide and rituximab combination induced the median PFS of 39 months (14 mo for lenalidomide group, $P<0.01$) for patients with previously treated FL [51]. Early relapse after CIT (POD≤24) is a validated prognostic factor for survival in patients with FL [52]. The patients with POD≤24 months could be treated with chemotherapy-free combination of rituximab and lenalidomide.

Several PI3K inhibitors (idelalisib, copanlisib, duvelisib, umbralisib) were FDA-approved for relapsed/refractory FL after 2 prior therapies with response rate of 45–61% and the median duration of response of 10–12 months [53-55]. However, the use of idelalisib is restricted by its considerable toxicities such as pneumonitis, transaminitis, and opportunistic infections. In a post hoc analysis, copanlisib is as effective in FL patients with POD≤24 months as in patients with POD >24 months (ORR 60%) and has better toxicity profiles. However, hyperglyemia and hypertension as well as relative inconvenience of frequent visits for intravenous injection are problematic. Develisib and umbralisib showed relatively favorable toxicity profiles compared to idelarisib. Many clinical trials testing PI3K inhibitors in combination with other treatments are ongoing.

Among epigenetic regulators, tazemetostat showed an ORR of 69% (CR 13%) and the median PFS of 14 months for EZH-mutant FL patients [56].

Y-ibritumomab tiuxetan showed significantly higher ORR (80% vs. 56%) and CR rate (30% vs.16%) compared to rituximab monotherapy [57]. Time to progression (15 mo vs. 10 mo) and response duration (17 mo vs. 11 mo) were longer in patients treated with Y-ibritumomab [58]. However, its use is currently limited. Auto-HSCT consolidation showed improved OS and PFS in patients with refractory or relapsed disease [59-61]. For younger patients who experienced multiple recurrence, allo-HSCT could be considered as curative treatment, although no supportive data has published yet [62].

In a phase II trial (ZUMA-5), axicabtagene ciloleucel (axi-cel) achieved 94% of ORR (CR 79%) in patients with refractory/relapsed FL who had more than two lines of previous treatment including anti-CD20 monoclonal antibodies and anthracycline containing regimen [63]. With a median follow-up of 17.5 months, 62% of the FL patients had ongoing responses. In two clinical studies evaluated different CAR-T cell therapies in NHL patients, liso-cel and tisa-cel showed promising outcomes (2-year PFS 60%) even in transformed FL patients [64-66].

MARGINAL ZONE LYMPHOMA

MZL can occur in lymph nodes (nodal MZL), spleen (splenic MZL) and extranodal sites (ENMZL). Overall, MZLs comprise about 5–15% of all NHLs in western countries. In Korea, MZL is the most common low-grade lymphoma comprising 21% of mature B cell neoplasms [2]. Chronic immune stimulation by diverse infectious agents such as Helicobacter pylori (H. pylori), chlamydia psittaci (C. psittaci), Campylobacter jejuni (C. jejuni) and Borrelia burgdorferi (B. burgdorferi), or chronic inflammation seems to play an important role in the pathogenesis of MZLs [67]. These causative agents could be targeted for the treatment lymphoma before conventional cancer treatments.

Extranodal marginal zone lymphoma

The most common site of involvement in ENMZL is the stomach followed by ocular adnexa, lung, salivary gland and intestine [68]. The MALT-IPI predicts outcomes but not guides treatments yet [69]. Currently, treatment of EMZL is guided by anatomical sites and the indications of treatments (Table 3).

Gastric ENMZL

H. pylori infection plays central role in the pathogenesis of gastric ENMZL [70, 71]. For patients with H. pylori infection, eradication of H. pylori induces regression of lymphoma in most cases (70–95%) with excellent long-term survival [72, 73]. Eradication regimens generally include a proton pump inhibitor and a combination of two different

Table 3. Treatment of marginal zone lymphoma.

Disease	Treatment	Comment
Gastric ENMZL	H. pylori eradication	- PPI+clarithromycin+(amoxicillin or metronidazole)
	RT	- H.pylori(-), or eradication failure
	Rituximab	- For radiotherapy ineligible patients
	Gastrectomy	- Major gastric bleeding
Non-gastric ENMZL	Watch and wait	- Stable asymptomatic disease
	Targeting infectious agents	- HCV treatment for HCV(+) disease
		- Doxycycline for ocular adnexal ENMZL
	RT	- Definitive or palliative
	Rituximab	- Higher response in CTx-naïve patients
	CIT	- R-chlorambucil, R-bendamustine
	Lenalidomide+Rituximab	- To avoid chemotherapy
	Surgery	- Mostly for diagnosis (thyroid, breast, intestine, etc.)
Splenic MZL	Watch and wait	- Stable asymptomatic disease
	HCV eradication	- For HCV(+) disease
	Rituximab	- Offer the most risk/benefit ratio [106]
	Splenectomy	- After rituximab failure
	CIT	- For symptomatic disseminated disease after rituximab or splenectomy failure
Nodal MZL	Treated as guidelines for FL	- Studies enrolled solely MZL are rare

Abbreviations: CIT, chemoimmunotherapy; CTx, chemotherapy; ENMZL, extranodal marginal zone lymphoma; HCV, hepatitis C virus; PPI, proton-pump inhibitor; RT, radiotherapy.

antibiotics (clarithromycin plus amoxicillin or metronidazole) [74, 75]. Predictive factors of resistance to H. pylori eradication include t(11;18), H. pylori-negativity, and submucosal invasion [76]. H. pylori eradication was more effective in gastric MALT lymphoma involving distal part [77]. When H. pylori eradication is not effective, second line eradication should be tried with alternative combinations. Microscopic persistence of lymphoma is relatively common after clinical regression of lymphoma and should be followed at least 12 months before decide another treatment [78]. H. pylori eradication could be tried in H. pylori negative patients, because some patients respond to H. pylori eradication possibly due to false negativity or infection of other Helicobacter species.

After failure with H. pylori eradication, asymptomatic patients can be observed. Involved sited radiation therapy (ISRT) is very effective inducing long-term remission in patients who experienced treatment failure with H. pylori eradication [79, 80].

Rituximab monotherapy was effective in patients with relpased/refractory to H. pylori eradication. With an ORR of 77% (CR 46%) and 54% of disease-free survival at a median follow-up of 28 months [81]. In a retrospective study, rituximab resulted in an ORR of 73% with favorable long-term survival (5-year OS and PFS, 70% and 95%, respectively) [82].

Surgical resection is also effective in the treatment of gastric ENMZL [83], However, surgical treatment should be reserved for patients who have justifiable reasons for surgery (major bleeding, perforation and obstruction) given long-term consequences of gastrectomy and effectiveness of other treatment options.

For advanced disease, treatment should be initiated when the indication of treatment is present. Treatment options are similar to advanced FL (Table 3).

Non-gastric ENMZL

Non-gastric ENMZL also have antigenic stimulus from infectious agents according to the disease sites [84]. Although the pathogenesis is not fully elucidated, a critical role for an antigenic driver has been postulated. Unlike in gastric ENMZL, treatment of underlying infectious causes does not guarantee the remission of disease in non-gastric ENMZLs. However, antibiotic therapy for C.psittaci in ENMZL involving ocular adnexa and HCV treatment in HCV infected patients could be considered if urgent treatment is not needed [85, 86].

ISRT should be considered as initial treatment for patients with localized non-gastric ENMZL involving ocular adnexa, salivary gland and thyroid. Which induced favorable 10-year relapse-free survival (74%) and OS (89%) in a retrospective analysis [87]. Recently lower dose RT is favored for its excellent local control with less radiation-related side effects [88]. Especially for ocular lymphoma, low-dose RT has definite benefit [89]. For elderly patients or frail patients who are not suitable for systemic therapy low-dose RT could be a reasonable treatment option.

Surgical resection is performed usually for the diagnosis of ENMZL involving specific anatomical sites such as thyroid, breast or colon. With completely resected lymphomas, no additional therapy is needed.

For asymptomatic patients watch-and-wait is also reasonable strategy. For patients who need therapy, single agent rituximab could be an option [90, 91]. Rituximab is more

effective in patients who were not exposed to chemotherapy (ORR 87% vs. 45%, P=0.03) [90].

Chemoimmunotherapy of chlorambucil and rituximab improved 5-year event-free survival (68%) compared with chlorambucil (51%) or rituximab monotherapy (50%) in patients with ENMZL [92]. Bendamustine and rituximab combination showed good response in patients with ENMZL including patients with t(11;18) [93].

Lenalidomide and rituximab combination showed good response (ORR 80%, CR 54%) and durable response (91% of patients are progression-free at 27 mo) in patient with ENMZL avoiding chemotherapy-related side effects in a phase II trial [94].

Other regimens such as rituximab and fludarabine combination or anthracycline-base combinations are also effective, especially for patients with aggressive clinical course [95].

Splenic MZL

Splenic MZL typically presents with splenomegaly with or without cytopenias. More than 80% of patients show bone marrow involvement. Thus, the diagnosis of splenic MZL could be suggested with bone marrow specimen in many cases before splenectomy [96, 97].

Patients who do not have lymphoma-related symptoms or progressive disease could be followed clinically without treatment for a quite long time, given that early treatment does not improve survival outcomes [98, 99]. In patients who have hepatitis C infection, treatment of HCV infection is considered first because HCV eradication could induce lymphoma regression in many cases (73–90%) [100-102]. Interferon-free treatment with direct acting antiviral (DAA) agents was also suggested in a recent study [101]. In the study, lymphoma response was observed in 73% (27/37) of patients with MZL. For a proper treatment of HCV infection, hepatology consultation is recommended.

Traditionally splenectomy was considered as first therapy for splenic MZL. However, single agent rituximab showed favorable treatment outcomes without splenectomy [103-107]. In a retrospective analysis (N=108), rituximab monotherapy (375 mg/m^2 4–8 weekly dose) induced an ORR 92% (44% CR) with a favorable 10-year PFS (64%) without significant toxicities. Furthermore, the effect of rituximab treatment lasted long duration [107, 108].

Rituximab monotherapy is also very useful for patients who have autoimmune cytopenias.

In a retrospective analysis including 226 patients, single agent rituximab offered the most risk/benefit ratio [106].

Given that splenectomy has significant side effects such as the risk of infection by encapsulated bacteria, splenectomy should be reserved for the diagnosis of histological transformation and refractory disease to rituximab therapy.

For patients who progress after rituximab therapy could be treated with rituximab re-treatment, splenectomy, combination chemotherapy or chemoimmunotherapy.

Nodal MZL

Nodal marginal zone lymphoma is treated following FL because there are scarce studies involving solely nodal MZL. However, biological characteristics of nodal MZL is increasingly revealed to be different from FL. Thus, optimal strategies in the treatment of nodal MZL should be considered.

CONCLUSION

In recent decades, treatment of indolent lymphoma has advanced significantly and now there are many more treatment options including chemotherapy-free combination, new molecular targeted agents and CAR-T cell therapy for patients with indolent lymphoma. Treatment of indolent lymphoma involves prudency and endurance in both patient and clinician, given its long-term clinical course and frequent recurrence. Treatment modality should be chosen or sequenced to maximize the treatment effect and quality of life at the same time. Finally, special attention should always be paid to each disease progression to rule out the possibility of histologic transformation.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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