J Clin Exp Hematop
Vol. 54, No. 1, June 2014

Review Article

Treatment of Follicular Lymphoma

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Follicular lymphoma (FL) is the most common subtype of indolent lymphomas. Several lines of evidence suggest that the prognosis of patients with FL has improved since the introduction of rituximab, although cure cannot be achieved. Although the treatment paradigm for FL has changed over the past decade with the introduction of rituximab and other agents, there is still no standard therapy to fit all patients. Instead, treatment decisions are made taking into consideration disease status (stage, tumor burden, and presence of symptoms) and patient factors including patient preferences. Rituximab-containing chemotherapy such as R-CHOP, R-CVP, and bendamustine plus rituximab is usually recommended for symptomatic patients. However, optimal rituximab-containing chemotherapy has not been established. Rituximab maintenance is one of the post-induction options for patients responding to first-line chemoimmunotherapy. For patients without symptoms and low-tumor burden, both expectant management (watchful waiting) and rituximab monotherapy are reasonable options. A very limited proportion of patients with FL are diagnosed at stage I with rigorous staging using bone marrow biopsy and whole-body imaging with computed tomography (CT) and/or positron emission tomography/CT. Although local radiotherapy has been the standard approach for these patients, its role is being questioned. Patients with FL who achieve remission eventually relapse and require salvage therapy. The salvage regimen should be chosen taking into account previous treatment and its response duration. Moreover, the presence of histological transformation should be assessed. 〔*J Clin Exp Hematop 54(1): 31-37, 2014*〕

Keywords: follicular lymphoma, rituximab, chemotherapy

INTRODUCTION

Follicular lymphoma (FL) is the most common subtype of indolent B-cell lymphomas. Patients with FL are usually at an advanced stage at diagnosis. Although most of them respond to initial treatment, they eventually relapse and require re-treatment. In other words, patients with advanced-stage FL cannot be cured by conventional chemotherapy at present. Therefore, patients who are diagnosed without symptoms can be observed without treatment (so-called watchful waiting) for several years. However, treatment is required when the patient presents with symptoms at diagnosis or develops symptoms during observation. Some patients are diagnosed with bulky tumor but without symptoms or lymphoma-related complications. Such patients with FL with a high tumor burden are also candidates for treatment and have been included in several clinical trials of rituximab-containing chemotherapy. In these trials, the criteria proposed by the French group [the GELF (Groupe d'Etudes des Lymphomes Folliculaires) criteria] are used to define FL with a high tumor burden.[1] In the GELF criteria, the presence of systemic symptoms, bulky mass (> 7 cm), nodal lesion of > 3 cm in 3 nodal regions or more, symptomatic splenomegaly, organ compression symptoms, and ascites/pleural effusion are defined as criteria of high-tumor burden.[1]

Treatment modalities for FL include chemotherapy, radiotherapy and immunotherapy against CD20, and stem cell transplantation, but a standard treatment approach for FL has not been established.

The introduction of rituximab, chimeric anti-CD20 monoclonal antibody, has been changing the treatment paradigm of FL. Although advanced-stage FL is still incurable, even after the introduction of rituximab, it substantially prolongs the survival of patients with FL.[2-4] In clinical practice, treatment decisions are made taking into account disease status (stage, presence of symptoms, tumor burden, previous treatment history, and progression to transformation) and patient factors (performance status, co-morbidities, and patient preferences). This review will summarize treatment approaches for FL according to disease status, especially focusing on treatment choice in previously untreated patients.

Received : September 1, 2013
Revised : September 22, 2013
Accepted : October 8, 2013
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FIRST-LINE TREATMENT FOR SYMPTOMATIC ADVANCED-STAGE FL

Rituximab-combined chemotherapy (R-chemo) is generally recommended as first-line treatment for patients with symptomatic advanced-stage FL. R-chemo regimens for FL include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone), BR (bendamustine, rituximab) and fludarabine-containing regimens. At the time of writing, bendamustine and fludarabine have not been approved for first-line treatment for FL in Japan.

Several phase 3 trials comparing R-chemo versus chemotherapy without rituximab in previously untreated FL have shown the superiority of R-chemo in terms of overall survival.[5-9] In these studies, toxicity associated with adding rituximab was mainly infusion-related and an increase of major toxicities was not observed. The survival benefit of adding rituximab to first-line chemotherapy was also confirmed with a meta-analysis of phase 3 trials.[10] A randomized study conducted by the German Low Grade Lymphoma Study Group compared R-CHOP with CHOP in patients with untreated, advanced-stage FL. Overall response rates were 96% with R-CHOP and 90% with CHOP ($P = 0.011$); complete remission (CR) rates were not statistically different (20% versus 17%). After a median follow-up of 18 months, R-CHOP significantly reduced the relative risk for treatment failure and showed longer time to treatment failure. Moreover, in spite of the short follow-up, this translated into longer overall survival (OS) in the R-CHOP arm ($P = 0.016$). Although severe neutropenia was observed more frequently with R-CHOP, the incidences of severe infection were similar with R-CHOP and CHOP (5% and 7%).[5] Another randomized study conducted in Europe compared R-CVP versus CVP. This study showed superiority of R-CVP in overall response rate (ORR) (81% versus 57%, $P < 0.0001$) and CR rate (41% versus 10%, $P < 0.0001$) without adding significant toxicity.[11] With a longer follow-up of 53 months, R-CVP showed a longer time to treatment failure (TTF) (27 months versus 7 months, $P < 0.0001$) and higher OS rate at 4 years (83% versus 77%, $P = 0.029$).[6]

In Japan, R-CHOP and R-CVP are major options for R-chemo for FL. However, the optimal chemotherapy regimen for FL remains to be determined. Intuitively, R-CHOP is associated with a higher CR rate, longer duration of response, shorter time to response, but higher rate of toxicity than R-CVP. One of the disadvantages of R-CHOP is a risk for anthracycline-related cardiotoxicity. Moreover, the impact on survival of adding anthracycline in first-line therapy is not clear. There had been no major randomized study that directly compared R-CHOP with R-CVP in patients with FL until an Italian group, Fondazione Italiana Linfomi (FIL), conducted a randomized phase III study (FOLL05) comparing R−CVP, R-CHOP, and R-FM (rituximab, fludarabine, mitoxantrone) in patients with previously untreated advanced-stage FL.[12] The three arms (R-CVP, R-CHOP, R-FM) had similar CR rates (67%, 73%, and 72%) and ORR (88%, 93%, and 91%). After a median follow-up of 34 months, 3-year TTF rates were 46%, 62%, and 59%, respectively (R-CHOP versus R-CVP, $P = 0.003$; R-FM versus R-CVP, $P = 0.006$; R-FM versus R-CHOP, $R = 0.763$). Three-year progression-free survival (PFS) rates were 52%, 68%, and 63% ($P = 0.011$), respectively, and OS was 95% for the whole series. In this study, R-CHOP and R-FM showed longer TTF and PFS compared with R-CVP. As R-FM resulted in a higher rate of severe neutropenia compared with R-CVP and R-CHOP, the investigators of this study concluded that R-CHOP had a better risk-benefit ratio compared with R-FM or R-CVP.[12] However, it would be difficult to conclude that R-CHOP is the best first-line R-chemo for FL from these results because the follow-up period is too short to evaluate the benefit on survival and long-term toxicity such as secondary malignancy and cardiotoxicity. As of now, R-chemo should be chosen taking into account both efficacy and toxicity.

The Japan Clinical Oncology Group (JCOG) conducted a randomized phase II/III study comparing standard R-CHOP (R-CHOP21) versus dose-dense R-CHOP with granulocyte colony-stimulating factor support (R-CHOP14) in patients with untreated advanced-stage indolent B-cell lymphoma (JCOG0203).[13] Patients with FL grade 1−3A represented 83% of the enrolled patients. With a median follow-up of 5.2 years, there was no significant difference in median PFS (3.7 years versus 4.7 years, $P = 0.30$) or in OS (6 year OS: 87% versus 88%, $P = 0.65$).[13] Thus, intensifying CHOP by a dose-dense approach would be of no benefit as first-line treatment for FL.

BR is an emerging option for first-line treatment for FL. A randomized phase 3 trial (StiL NHL1) conducted by a German group compared BR with R−CHOP in patients with previously untreated indolent B-cell lymphomas and mantle cell lymphoma. FL grade 1-2 represented around 50% of the enrolled patients. Although this trial was initially designed to show non-inferiority of BR in terms of PFS, median PFS was significantly longer in the BR arm (69.5 months versus 31.2 months, $P < 0.0001$). Longer PFS in the BR arm was also shown in a subset of patients with FL (not reached versus 40.9 months, $P = 0.0072$). BR was associated with lower rates of alopecia (0% versus 100%, $P < 0.0001$), infections (37% versus 50%, $P = 0.0025$), peripheral neuropathy (7% versus 29%, $P < 0.0001$), and stomatitis (6% versus 19%, $P < 0.0001$). However, skin reactions (16% versus 9%, $P = 0.024$) were more common in the BR arm. Moreover, grade 3-4 lymphocytopenia was seen in 74% in the BR arm and 43% in the R-CHOP arm (statistical significance not shown). In this study, the authors concluded that BR is more effective and less toxic than R-CHOP in those who need treatment for

indolent and mantle cell lymphoma.[14] Another study conducted in the United States (the BRIGHT study) compared BR with R−CHOP or R-CVP in patients with untreated indolent B-cell lymphomas and mantle cell lymphoma. The choice of R-CHOP or R-CVP was determined by an investigator prior to randomization. Response and toxicity data have been presented as an abstract.[15] The CR rate was numerically higher for BR than R−CHOP/R-CVP and was statistically non-inferior.[15] However, the toxicity of BR was greater than that observed in the StiL study: the incidences of nausea (all grades: 63% BR versus 58% R−CHOP/39% R-CVP), vomiting (all grades: 27% versus 13%/13%), lymphocytopenia (grade 3/4: 62% versus 33%/28%), opportunistic infections (all grades: 11% versus 7%/9%), rash (all grades: 15% versus 7%/9%), and respiratory disorders (grade 3/4: 7% versus 2%/2%) were higher in the BR arm. Although dose reductions were less common (22% versus 29%), dose delays were more common in the BR arm.[15] The results published so far indicate that BR is a reasonable option for first-line R-chemo for FL with a different toxicity profile than R-CHOP or R-CVP. However, we still need more data with long-term follow-up to conclude that BR is superior to other traditional regimens in terms of both efficacy and toxicity.

CONSOLIDATION AND MAINTENANCE THERAPY FOLLOWING FIRST-LINE THERAPY

In FL, most of the patients who achieve response with first-line treatment eventually relapse. Thus, post-remission treatment would be an attractive approach to prolong progression-free time and even survival. There are two approaches for post-induction treatment, namely, consolidation and maintenance. Consolidation therapy is a short-term intensified treatment such as high-dose chemotherapy followed by autologous hematopoietic stem cell support (HDC) and radioimmunotherapy. Several randomized controlled trials were conducted to evaluate the benefit of HDC as consolidation. Although some of these studies did show a PFS benefit of HDC, there was no improvement in OS.[1,16-18] Because of significant short- and long-term toxicity associated with HDC, it is not recommended as consolidation therapy after first-line therapy for FL.

Another approach of consolidation is radioimmunotherapy using ^{90}Y-ibritumomab tiuxetan (Zevalin™). The role of ^{90}Y-ibritumomab tiuxetan was evaluated in the FIT trial.[19] In this trial, patients with FL who achieved CR or PR after first-line chemotherapy were randomly assigned to ^{90}Y-ibritumomab tiuxetan consolidation or no further treatment. After a median follow-up period of 3.5 years, ^{90}Y-ibritumomab tiuxetan significantly prolonged median PFS (36.5 months versus 13.3 months, $P < 0.0001$), regardless of whether the response after induction was PR or CR. The most common toxicity with ^{90}Y-ibritumomab tiuxetan was hematologic and grade 3 or 4 infections were observed in 8%.[19] Moreover, PFS benefit was durable and median time to next treatment was 8.1 years for the ^{90}Y-ibritumomab tiuxetan arm versus 3.0 years for the control arm ($P < 0.001$) with a longer follow-up of 7.3 years, although estimated 8-year OS was similar.[20] However, in this study, only a few patients received induction with R-chemo (15.6% in the control arm and 13.2% in the ^{90}Y-ibritumomab tiuxetan arm).[19] Thus, the benefit of consolidation with ^{90}Y-ibritumomab tiuxetan after induction with R-chemo, common induction therapy for FL at present, is unclear. A randomized controlled trial had been initiated comparing consolidation therapy with ^{90}Y-ibritumomab tiuxetan versus rituximab maintenance in patients with FL who achieved response after first-line R-chemo. However, this trial was terminated on the basis of the sponsor's decision (NCT01662102).

Maintenance therapy is a long-term treatment that is given for a fixed period (e.g. 2 years) or indefinitely until progression. Maintenance therapy with interferon had been used for FL before the introduction of rituximab and meta-analysis showed survival benefit of interferon over observation in patients with FL.[21] Because of poor tolerability of the long-term use of high-dose interferon, however, it is no longer used as maintenance treatment for FL. Alternatively, rituximab maintenance after first-line R-chemo was introduced and was approved in many countries based on the PRIMA trial (at the time of writing, rituximab maintenance for FL has not been approved in Japan). In the PRIMA trial, patients with FL requiring therapy who achieved response after first-line R-chemo such as R-CHOP, R-CVP, or R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone) were randomly assigned to rituximab maintenance or observation.[22] Rituximab maintenance (375 mg/m^2) was started 8 weeks after the last induction treatment and repeated every 8 weeks for 12 infusions (2 years). With a median follow-up of 36 months, PFS was 74.9% in the rituximab maintenance arm and 57.6% in the observation arm ($P < 0.0001$). OS did not differ between the arms (HR 0.87, 95% CI 0.51-1.47). Grade 3/4 adverse events were observed in 24% in the rituximab maintenance group and in 17% in the observation group. Grade 2-4 infections were seen more commonly in the rituximab maintenance group (39% versus 24%, risk ratio 1.62, 95% CI 1.35-1.96; $P < 0.0001$).[22] In this study, quality of life (QOL) data were systematically collected. Although rituximab maintenance did not impair QOL, there was no improvement of QOL with rituximab maintenance.[22] Rituximab maintenance is a reasonable option to prolong PFS without severe toxicity, and longer follow-up is required to evaluate the impact on survival and QOL. Moreover, the cost-effectiveness of rituximab maintenance in terms of time and money should be considered, at least on a case-by-case basis.

MANAGEMENT OF ASYMPTOMATIC ADVANCED-STAGE FL

Asymptomatic patients can be observed without treatment until they develop symptoms. Such a policy (watchful waiting) has been one of the standard management approaches for asymptomatic advanced-stage FL.[23] A randomized controlled trial in the United Kingdom comparing observation versus immediate initiation of oral alkylating agent, chlorambucil, in asymptomatic advanced-stage low-grade lymphoma revealed that OS does not differ (6.7 versus 5.9 years, $P = 0.84$) between the arms at a median follow-up of 16 years.[24] The probability of not requiring chemotherapy at 10 years was 19% (40% in patients older than 70 years) and the median time to first systemic treatment was 2.6 years for the whole observation group.[24]

The watchful waiting policy is also relevant in the rituximab era. In a prospective observational study by an Italian group (the F2 study), 120 patients out of 1,093 previously untreated patients with FL were managed expectantly (watchful waiting). Most of these patients had advanced-stage disease with a low tumor burden according to the GELF criteria. At a median follow-up of 64 months, treatment was initiated in 50% with a median delay of 55 months for the whole cohort. The 4-year freedom from treatment failure rate of patients who were managed expectantly was not inferior to that of patients from the F2-study cohort who were initially treated with a rituximab-based regimen despite low tumor burden (79% versus 65%, $P = 0.103$).[25]

Rituximab monotherapy is another option for patients with asymptomatic, low-tumor-burden FL. In a single-arm phase 2 trial of rituximab monotherapy (375 mg/m^2, weekly, 4 doses) for patients with FL with a low tumor burden, an overall response rate of 73% was shown with a CR rate of 27% a month after treatment.[26] After a long-term follow-up of 83.9 months, the best response rate was 80% and the CR rate was 52%. Median PFS was 23.5 months and OS was 91.7%. For the patients who achieved CR, median PFS was 51.0 months.[27] In the United Kingdom, a randomized trial was undertaken to evaluate the prognostic impact of rituximab monotherapy in patients with advanced-stage, asymptomatic, non-bulky FL. In this trial, patients were randomly assigned to watchful waiting, rituximab monotherapy (375 mg/m^2, weekly, 4 doses), and rituximab for 4 weeks followed by rituximab maintenance every 2 months for 2 years. The primary endpoints were time to initiation of new therapy (TTNT) and QOL. Preliminary results of this study have been published as an abstract.[28] TTNT was not reached at 4 years and significantly longer in the rituximab arms ($P < 0.001$ for each of the rituximab arms versus the watchful waiting arm), whereas median TTNT was 33 months in the watchful waiting arm.[28] Determination of the impact of rituximab monotherapy on survival and QOL must await longer follow-up.

Although there have been several prospective trials that included patients with asymptomatic and/or low-tumor-burden FL, the role of immediate R-chemo in those patients has not been specifically addressed in clinical studies. Although the disappearance of tumor may lead to patient relief, adverse effects during R-chemo are substantial and its positive or negative impact on the disease course in the long term is uncertain.

TREATMENT OF LIMITED-STAGE FL

Around 25% of patients with FL present with stage I disease, which means that the lesion is localized to one nodal area.[29] For those patients, local radiotherapy has been recommended on the basis of several retrospective series from single centers showing that a significant proportion of patients achieve long-term disease-free survival or *de facto* cure with radiotherapy with or without systemic therapy.[30] However, the role of radiotherapy has not been addressed in a prospective clinical trial.

In the US National LymphoCare study, which is a prospective observational study on FL, 44% of patients with stage I FL were rigorously staged with bone marrow (BM) biopsy and a modern imaging study [a computed tomography (CT) scan of the whole trunk, a positron emission tomography (PET)/CT scan, or both. Rigorously staged patients had superior PFS compared with nonrigorously staged patients (HR, 0.63; 95% CI, 0.44 to 0.92), which means that only stage I cases that are diagnosed with both BM biopsy and whole-trunk imaging study are *bona fide* stage I. In stage I FL patients diagnosed with rigorous staging, diverse treatment approaches including radiotherapy, R-chemo, rituximab monotherapy, and combined modality therapy (systemic therapy + radiotherapy) resulted in similar excellent PFS, challenging the longstanding concept that radiotherapy should be recommended for stage I FL. Radiotherapy will still be a major option for stage I FL. However, other modalities without radiotherapy may be pursued if the lesion is located in an area where the probability of radiation-related toxicity is high (e.g. abdominal or submandibular lesion), especially when the lesion is bulky.

TREATMENT OF RELAPSED FL

Unfortunately, for patients with advanced-stage FL, relapse after remission is probable. Treatment options for relapsed FL include chemotherapy with or without rituximab, rituximab monotherapy, local radiotherapy, and radioimmunotherapy. Chemotherapy is followed by stem cell transplantation in selected patients. The chemotherapy regimen for relapsed FL includes CHOP, CVP, bendamustine, and purine analog-containing regimens with or without rituximab.[31-33]

Previous treatment history and its duration of response should be taken into consideration in selecting a salvage regimen. Although CHOP cannot be repeated because of the accumulation of anthracycline, one can expect a high rate of response by repeating the same regimen if the duration of response is long enough at the previous line of treatment. A purine analog-containing regimen should be avoided if autologous stem cell collection is planned because it may impair hematopoietic stem cell collection.[34] If the patient is asymptomatic and tumor burden is low, one can manage expectantly even after relapse. Moreover, rituximab monotherapy is also a reasonable option for such patients unless relapse is diagnosed during or immediately (e.g. < 6 months) after rituximab-containing therapy or loss of CD20 expression is confirmed. However, rituximab monotherapy in patients who relapse after R-chemo has not been evaluated prospectively.

Histological transformation develops in 10-70% of patients with FL. Transformation is suspected when patients with FL present with rapid nodal growth, extranodal lesion (excluding BM), new B symptoms, rapidly rising serum lactate dehydrogenase levels, or new hypercalcemia.[35] The prognosis of patients with transformation is generally poor unless it is localized at transformation.[36,37] Moreover, the efficacy of agents used for FL has not been rigorously evaluated in patients with transformation.[38,39] For patients with histological transformation, more intensive salvage regimens that are used for aggressive lymphoma may be suitable.[40] Therefore, re-biopsy should be performed when patients with FL relapse, especially if clinical signs suggest transformation. PET/CT may be useful to guide biopsy in the detection of transformation of FL,[41] as transformed FL generally shows a high standardized uptake value of 10 or more. However, in clinical practice, we sometimes face the situation where a histological specimen cannot be obtained due to either inaccessible anatomic location or the need to begin immediate therapy due to rapid progression. A retrospective study from the British Columbia Cancer Agency showed that patients with clinically diagnosed transformation have a similarly poor outcome as those with biopsy-proven transformation.[35] Therefore, when biopsy is not practical, the patient may be managed as transformation if it is clinically suspected.

CONFLICT-OF-INTEREST DISCLOSURE

The author discloses a potential conflict-of-interest that is relevant to the subject described in this article. **Honoraria**: Eisai Co., Ltd.

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