Review Article

Individualized management of follicular lymphoma

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Abstract: Follicular lymphoma (FL) is the most common indolent non-hodgkin lymphoma. Most patients with FL are diagnosed with advanced disease and are considered incurable. The classical prognostic index in FL is the FL international prognostic index (FLIPI). The management of FL is mainly determined by histologic grading, clinical stage, and tumor burden. For patients with stage I and II disease, an involved-site radiation therapy (ISRT) is recommended and may be potentially curative approach with 60% to 80% of 10-year overall survival (OS) rates, while patients with stage III and IV should be treated with systemic therapy. The watchful waiting is still an option for patients without symptoms or/and low tumor burden. Induction of immuno-chemotherapy combined with consolidation of rituximab maintenance (MR) is standard care for patients with symptomatic disease or with high tumor burden when treatment indicated. The major indication for systemic therapy is including candidate for clinical trials, threatened end organ function, cytopenia secondary to lymphoma bulky disease and steady progress etc. at present time. Routine baseline and regular hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing is strongly recommended for all patients before the initiation of immuno-chemotherapy in order to minimize the risk of hepatitis B virus (HBV) reactivation which has been observed approximately 20% to 50% of patients with positive HBsAg and 3% to 45% of patients with positive HBcAb. Prophylactic antiviral treatment in patients who are HBsAg-positive or HBcAb-positive is indicated before immuno-chemotherapy. The management for elderly patients should be carefully selected to avoid overtreatment and severe toxicities. Individualized dose adjustment for chemotherapy and an adequate supportive treatment are essential for this special population. Novel agents such as lenalidomide, ibrutinib and idelalisib are promising. In conclusion, individualized management of FL remains challenging and role of new targeted agents need to be defined.

Keywords: Follicular lymphoma (FL); rituximab; non-Hodgkin lymphomas (NHL); lymphoma and immuno-chemotherapy

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Introduction

Follicular lymphoma (FL) is considered as the most common subtype of indolent non-Hodgkin lymphomas (NHL), which describe a class of lymphomas with indolent biological behavior and usually incurable in the advanced settings. Approximately 300,000 cases of NHL are newly diagnosed worldwide each year. In China, FL accounts for 8.1% to 23.5% of newly diagnosed NHL cases, comparing with that of 22% to 35% in Western countries (1-3). The histologic grading system of FL has been standardized by Mann *et al*. (4). Grade I/II FL is considered as indolent lymphoma, while grade 3b FL is regarded as an aggressive NHL (4). The median overall survival (OS) of FL is around 8-10 years, and the OS has been improving in recent years mainly with immunochemotherapy as well as novel treatment agents or modalities. More than 70% of the patients may survive for at least 10 years (5).

The clinical manifestation and treatment option are determined by diagnosis of subtype, histologic grading, clinical staging, and tumor burden. Some patients may be asymptomatic for years, while others may present rapidly progressive disease. In the relapse/refractory settings, rebiopsy is often needed to exclude histologic transformation when clinically suspected, which is treated as relapsed aggressive NHL. The FL international prognostic index (FLIPI) is helpful for risk stratification and treatment decision (6). In addition, it is increasingly critical to design treatment strategies with limited long-term toxicities, considering the patient survival time is improving.

Early stage disease

Patients with newly diagnosed Ann Arbor stage I/II disease are rare, representing 15-25% of all patients at diagnosis (7). For these patients, an initial involved-site radiation therapy (ISRT) is recommended by most clinical practice guidelines (8). The normal dose of radiotherapy delivered to the involved region is 24-30 Gy, and some studies indicated that 24 Gy may be optimal (8,9). In select cases with bulky or slowly regressing disease, an additional 6 Gy is preferred (9). The patients with early stage disease and low tumor burden may achieve long-term disease-free survival (DFS) under ISRT. As reported by previous studies, the 10-year OS rates are 60% to 80%, with 10-year relapse-free survival rates of 45% to 60%, and median OS of 15 to 20 years (10). It is suggested that a subset of patients may be cured with this approach alone.

In addition, other systematical treatments are optional, including single agent rituximab, chemotherapy, chemotherapy combined with rituximab (R-chemo), and R-chemo combined with radiation therapy. A recent retrospective analysis from the national lympho care study (NLCS) including 471 patients with newly diagnosed stage I FL indicated that early outcomes for patients receiving radiation were similar to observation or rituximab alone (7). The best outcome was observed in patients receiving R-chemo or R-chemo combined with radiation therapy. The data suggests that systemic treatments may demonstrate similar long-term outcomes to radiation alone, and systemic treatments may deserve further evaluation in limited stage FL (7).

Another treatment strategy is to watch and wait, according to a retrospective study which showed that patients with stage I and II FL kept progression-free for prolonged periods without treatment, for a median follow-up time of 86 months (11-13). The 5, 10, and 15 years OS were 76%, 56%, and 48%, respectively. The median time to treatment was 7.8 years, with 21% transformation rate (11-13). The National Comprehensive Cancer Network (NCCN) guideline recommends observation when potential toxicity of ISRT outweighs potential clinical benefit.

However, patients with newly diagnosed stage I/II FL with high tumor burden should be treated with systemic therapy, according to the National British Lymphoma Investigation (NBLI) guidelines (14), or the Groupe d'Etude des lymphomes folliculaires (GELF) criteria (15). The NBLI criteria were designed as exclusion criteria for patients not suitable for a watch and wait strategy. The criteria were as follows: rapid disease progression, end organ damage, renal infiltration, bone lesions, and cytopenias (14). Similarly, the GELF criteria were widely accepted as eligibility criteria for patient evaluation, including: lesion >7 cm, 3 nodal sites >3 cm, substantial splenomegaly, compression (ureteral, epidural), Serous effusions, and cytopenias (15).

Moreover, chemo-radiotherapy can also be considered for patients with early-stage FL. According to a prospective study involving 102 patients with early-stage low grade lymphoma, combined-modality of COP-/cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-bleomycin chemotherapy and ISRT had obtained improved disease control rate and prolonged OS than ISRT alone (16). Notably, careful bone marrow examination (biopsies length ≥20 mm) has been reported to be correlated with increasing positivity of bone marrow involvement (35% *vs*. 20%, P=0.023) and more accurate clinical staging in diffuse large cell lymphoma (17). In a retrospective study, forty-two patients with untreated early-stage FL were enrolled. The fluorodeoxyglucose positron emission tomography (PET) findings suggested a change of upstaging to stage III-IV diseases in 31% of patients, and enlarging involved field in 14% of patients (18).

Advanced stage disease

The initial watch and wait strategy was established base on the indolent biological behavior of FL and was validated by randomized clinical trials (11-13). In general, patients who meet the criteria of NBLI or GELF are defined as "low tumor burden", and are candidates for the watch and wait approach (14,15). In a three arm study conducted by Brice *et al*., patients in the watch and wait group had a similar 5-year OS compared to the single agent prednimustine group or the interferon alpha group (11). Another prospective study demonstrated an identical 5-year OS of the watch and wait approach compared to intensive

chemotherapy with cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate with leucovorin, and prednisolone (ProMACEMOPP) (19). In a prospective study by Ardeshna *et al*. ,patients in the watch and wait group presented a longer median survival of 6.7 years compared to 5.9 years in the chlorambucil arm, moreover, 19% of these patients had not required therapy at ten years (14). According to these studies, chemotherapy could be safely delayed in these patients with low tumor burden, and the watch and wait strategy is the standard management in patients with low disease burden advance stage FL, excluded by the criteria of NBLI or GELF.

In the rituximab era, the high efficacy and low toxicity of the anti-CD20 antibody make it a potential option for initial treatment in patients with a low tumor burden. Early phase studies reported an overall response rate (ORR) of 46-48% of single agent rituximab in patients with relapsed or refractory FL, using the weekly dosing strategy (375 mg/m^2 weekly for 4 weeks) (20-22). The median time to progression (TTP) was 7-13 months. The surprising activity of rituximab prompted oncologists to explore its efficacy in the untreated indolent NHL with low tumor burden. In prior pilot studies, the ORR of single agent rituximab (375 mg/m^2 weekly doses for 4 cycles) was 47-73% in patients with low disease burden advanced stage indolent NHL (20-22). In another randomized study by Ardeshna *et al*. involving patients with low disease burden advanced stage FL without meeting GELF criteria, rituximab was administered in the standard four weekly schedule followed by maintenance rituximab given every 2 months to challenge the traditional watch and wait approach. Rituximab achieved an ORR of 85% with 39% of CR, and time to first chemotherapy has yet to be reached at 4 years. In the watch and wait arm, the median time to first chemotherapy was 33 months. Moreover, other randomized studies indicated that additional rituximab maintenance (MR) therapy appeared to prolong response duration (23). However, the ECOG E4402 study suggested the time to rituximab failure was identical in salvage rituximab treatment at disease progression as compared to maintenance therapy, and the adverse effects might outweigh the potential benefits from MR for asymptomatic patients with low tumor burden (24).

Given the above studies, it is suggested that rituximab monotherapy may be a potential choice for patients with newly diagnosed FL without meeting the GELF criteria and do not feel comfortable with a watch and wait strategy. In addition to rituximab, other approaches such as radio-immunotherapy (RIT) or immunomodulator have also been developed in patients with a low tumor burden, while none of these studies can provide high level evidence for clinical practice.

Symptomatic disease or with high tumor burden

R-chemo is the standard of care for patients with symptomatic disease or with high tumor burden after a watchful waiting period. The GELF criteria or NBLI criteria are essential for patient evaluation (14,15). Combination chemotherapy plus rituximab has been proved higher efficacy compared to chemotherapy alone. In a phase III study, rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP), significantly improved ORR (81%), CR rates (41%), and TTP (30 months) as compared to CVP (25). Furthermore, it was demonstrated that the FLIPI remained statistically significant after the intervention of rituximab, although it was designed in the pre-rituximab era (6,25). As seen with R-CVP, the superiority of rituximab, cyclophosphamide, adriamycin, vincristine, prednisone (R-CHOP) over CHOP was also confirmed by several clinical trials, in terms of ORR, PFS and OS (26,27). A meta-analysis was conducted to compare the benefit of chemotherapy and R-chemo. The analysis included 1943 patients with newly-diagnosed or relapsed indolent NHL, from different clinical trials between 1990 and 2005. It was suggested that R-chemo reduced 65% risk of death due to lymphoma. This analysis demonstrated the superiority of the rituximab-containing combination chemotherapy regimens over combination chemotherapy, in terms of ORR, PFS and OS in FL (28).

R-CHOP has been demonstrated to produce a better ORR and PFS than R-CVP, while no study has proved a better OS benefit from R-CHOP than R-CVP (29,30). However, indirect data from the PRIMA study (29) and the North American Lymphocare study suggested that R-CHOP may be associated with a prolonged survival in patients with adverse features.

Bendamustine has a novel structure combined with an alkylating compound and a purine analog. Early reports publicized the activity of bendamustine in indolent NHL (31). Single agent bendamustine produced an ORR of 73% with 11% of CR study in indolent NHL (32). The combination of bendamustine plus rituximab (BR) was reported to produce an encouraging ORR of 96% with 64% CR in patients with indolent NHL (33). Several studies compared the efficacy and toxicity of BR and R-CHOP in indolent NHL. In a phase III trial including 549 patients with mantle cell lymphoma (MCL), the ORR were similar

(BR: 93.8% *vs*. R-CHOP: 93.5%), BR was associated with better CR, PFS, and time to next treatment, while lower grade 3-4 toxicities compared to R-CHOP (34). In another phase III study from German including 279 patients with FL. BR appeared significantly less toxic than R-CHOP, with significantly better CR rate and PFS.

Fludarabine is a kind of purine with significant activity and toxicities in indolent NHL (35-42). Single agent fludarabine demonstrated a superior CR rate of 38.6% compared to a 15% in the CVP arm in newly diagnosed advanced stage NHL (43). Fludarabine-containing regimens, such as rituximab, fludarabine, cyclophosphamide and mitoxantrone (R-FCM) regimen (44) and rituximab, fludarabine, mitoxantrone (R-FM) regimen (45), demonstrated similar ORR as compared to R-CHOP regimen in patients with newly-diagnosed FL, from the PRIMA study (29) and the FOLL05 Italian study (45). In most trials, fludarabine was associated with more grade 3-4 hematologic toxicities and hematopoietic stem cell toxicities, which was unfavorable for subsequent autologous hematopoietic stem cell transplantation (AHSCT) (46). Fludarabine containing regimens, FR, R-FC, and R-FCM were attractive option for the upfront management of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), while it is not recommended in FL or marginal zone lymphoma (MZL), given its significant toxicities.

In conclusion, R-CVP, R-CHOP, and BR are recommended as initial R-chemo regimens by most clinical guidelines as initial regimen for FL. It seems that R-CHOP may be preferred over R-CVP in patients with adverse prognostic features, and BR may be preferred to R-CHOP.

Consolidation and maintenance

In general, FL has been considered as an incurable disease and most patients will progress within 3-6 years after initial treatment. In patients sensitive to initial treatment, various consolidative or maintenance strategies have been developed with the goal of delaying relapse and prolonging OS, with low risk toxicities. Several studies have therefore attempted to consolidate remission using RIT or maintenance intermittent use of immunotherapy.

The results of a randomized study indicated higher ORR and prolonged PFS observed in ^{90}Y-labeled ibritumomab (tiutexan) administration after CHOP (47). A phase III study compared upfront CHOP followed by ^{131}I tositumomab consolidation *vs*. R-CHOP in untreated patients with FL (48). No significant differences in ORR, CR rate, and 2-year PFS and toxicities. Another study compared the R-CHOP and R-CHOP followed by ^{131}I tositumomab consolidation. No significant differences were observed for PFS or OS. In the first-line indolent trial (FIT) trial, ^{90}Y ibritumomab consolidation after chemotherapy demonstrated better 8-year PFS (41% *vs*. 22%), median PFS (4.1 *vs*. 1.1 years), as compared to observation after chemotherapy, with a median follow up of 7.3 years. In most of the above studies, RIT was associated with a higher proportion of neutropenia, thrombocytopenia, myelofibrosis, or secondary hematological malignancies (49).

Maintenance strategies with rituximab have been attempted in patients treated by single agent rituximab and rituximab plus combination chemotherapy (50,51). Regardless of the regimens and different schedule, MR therapy demonstrated impressive PFS and the ability of conversion from PR to CR in several cases (29,50,51).

The PRIMA study evaluated the role of MR in patients with FL treated by a first-line induction immunochemotherapy (29). Patients responding to R-CVP, R-CHOP or R-FCM were randomized to receive either MR (375 mg/m^2, every 2 months for 2 years) or observation. At a median follow-up of 3 years, MR significantly prolonged PFS (74.9% *vs*. 57.6%), with no OS advantage over observation arm. Furthermore, a significantly higher proportion of CR (72% *vs*. 52%, P=0.0001) had been observed 2 years after completing induction in the MR arm. The best results with maintenance were also observed in the R-CHOP induction arm. MR was associated with more frequent adverse events and more frequent grade 2-4 infections. But only 4% of the patients randomized in the MR arm withdrew from study for treatment-related toxicities.

In the setting of second-line consolidation, MR demonstrated PFS improvement. In a prospective study from German Low Grade Lymphoma Study Group (GLSG), MR was evaluated in patients with recurring or refractory FL and MCL responding to FCM alone or combined with R-FCM. Compared with observation, MR significantly prolonged response duration (not being reached *vs*. 26 months, P=0.035) (52). In a phase III EORTC 20981 trial (53), 334 patients with relapsed or refractory FL were treated by CHOP or R-CHOP. After induction, MR significantly improved PFS (3.7 *vs*. 1.3 years, P<0.001) compared with observation. The 5-year OS rates were of no statistical difference.

The randomized RESORT trial investigated the role of single agent rituximab followed by observation or MR

in patients with newly diagnosed low disease burden indolent NHL. The outcomes indicated no benefit from maintenance rituximab in regards to the primary endpoint of TTP, however, maintenance rituximab did prolong the time to first chemotherapy.

The result of a meta-analysis demonstrated that MR significantly reduced the risk of death (hazard ratio 0.76; 95% CI, 0.62-0.92) in the second line setting (54). There was a trend of survival benefit for patients receiving first line MR (hazard ratio 0.86; 95 % CI, 0.60-1.25). In the 2013 American Society of Hematology (ASH) annual meeting, Chen and colleagues reported a study comparing the cost-effectiveness of MR and RIT following first-line chemo/immunochemotherapies for FL. The study involved patients from several phase III randomized trials [ECOG1496 (55), PRIMA (29), and FIT (50)]. The results suggested that RIT and MR had comparable incremental quality adjusted life-year (QALYs) before first progression, while RIT had higher incremental costs due to relatively high incidence of adverse events. Both in ASH 2013 annual meeting, Lopez-Guillermo reported a randomized phase II study in patients with FL in response after R-CHOP. The findings suggested that maintenance with rituximab was superior to consolidation with ^{90}Y ibritumomab tiuxetan in PFS (86% *vs*. 64%, P=0.01), with no differences in OS (86% *vs*. 64%, P=0.01) at 36 months of follow-up.

In conclusion, although both MR and RIT maintenance are recommended by NCCN guidelines, rituximab shows superiority in efficacy, safety, and conveniences according to several studies. If RIT is taken into consolidation, patients should be carefully evaluated and selected.

Autologous stem cell transplant

AHSCT consolidation has been demonstrated to significantly improve PFS either after induction therapy or relapsed disease in indolent NHL (56-58). Furthermore, it has been shown that AHSCT prolonged OS in patients with relapsed or refractory disease (58,59). A randomized phase III trial compared chemotherapy with CHOP for three cycles *vs*. chemotherapy followed by unpurged AHSCT *vs*. chemotherapy followed by purged AHSCT (the CUP trial) (58). The results showed that PFS was significantly prolonged in those who underwent transplantation. There was a trend towards a survival advantage favoring AHSCT (four-year OS: 75% *vs*. 46%, P=0.079), irrelevance to unpurged or purged AHSCT. Another study reported upfront AHSCT outcomes using a CHOP induction followed by four treatments of rituximab and peritransplant MR (60). While a greater CR rate (85%) and prolonged EFS was seen in patients undergoing consolidative AHSCT, they were unable to demonstrate an OS advantage. A retrospective analysis by GELA suggested that EFS and OS were superior for patients treated with rituximab-containing regimens compared to chemotherapy only-based AHSCT in relapsed or refractory FL (59). The second-line chemotherapy in combination with rituximab followed by AHSCT produced a favorable 5-year survival rate of 90%. Prior studies have indicate AHSCT is suitable for patients respond to salvage chemotherapy within fourth-line regimens, and the most appropriate time to perform AHSCT is subsequent to the second-line cytotoxic treatment, to obtain best survival benefit.

Allogeneic stem cell transplant

Studies comparing AHSCT and allogeneic hematopoietic stem cell transplantation (Allo-HSCT) were rare in FL. Allo-HSCT is associated with high treatment-related mortality (TRM) rates (about 30-40% for myeloablative and 25% for non-myeloablative Allo-HSCT) (61,62). Pre-conditioning treatment included total body irradiation (TBI), combination chemotherapy regimens, and ^{90}Y ibritumomab tiuxetan (63-65). Oncologists were interested in reduced intensity preparative regimens, hoping it was associated with better graft-versus-lymphoma (GVL) effect and decreased transplant related mortality (66-68). In a retrospective review including 904 patients with FL, the 5-year TRM of Allo-HSCT was 30% compared to 22% in the purged and unpurged AHSCT cohort. The 5-year recurrence rates were 21%, 43%, and 58% in the Allo-HSCT, purged AHSCT and unpurged AHSCT arms respectively (62). Prior studies indicated that myeloablative Allo-HSCT was associated with higher TRM but a lower recurrence rate, compared with non-myeloablative Allo-HSCT (61,62). However, a recent report revealed that both myeloablative and non-myeloablative Allo-HSCT resulted in similar TRM rates (69); moreover, non-myeloablative Allo-HSCT was associated with an increased risk of disease progression. While Allo-HSCT may have significant advances with reduced intensity treatment, further strategies are moving to attempt to decrease TRM without decreasing efficacy, especially in highly-selected patients with high-risk disease. Furthermore, more biomarkers and prognostic factors are needed to predict in relapsed indolent NHL patients who

would benefit from Allo-HSCT.

Response assessment

Imaging examinations such as CT or PET/CT are essential for diagnosis, restaging, and response assessment. Unlike in aggressive NHL or in HL, the role of PET/CT scanning in FL is still uncertain (70-73). Yet, more and more data suggests that a PET-CT scan is effective for response evaluation, with high sensitivity (94-98%) and specificity (88-100%) (70-73). A retrospective study from the database of the PRIMA study has also indicated the predictive value of PET for PFS (74). However, at present more studies are required to confirm its role for prognosis evaluation and other value for disease diagnosis, restaging, and response assessment.

Hepatitis infection

Patients with NHL are reported to have a high risk of hepatitis B virus (HBV) reactivation, especially when treated with chemotherapy with or without immunotherapy agents (75-78). The HBV reactivation may lead to deadly liver failure. Testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) are essential before anti-lymphoma treatment. HBV reactivation has been observed approximately 20% to 50% of patients with positive HBsAg and 3% to 45% of patients with positive HBcAb, when treated with chemotherapy (75,77-82). Recently, a meta-analysis was performed to examine the association between rituximab and HBV reactivation, including 971 patients with NHL from nine studies between 1997 and 2012 (80). The results showed that patients with HBcAb (+) had a high risk of HBV reactivation [relative risk (RR) =5.52, 95% CI, 2.05-14.85, P=0.0007], when administered by rituximab-containing chemotherapy. Patients with HBsAg (+) treated with R-based therapy had a high risk of HBV reactivation (RR =1.63).

The upfront antiviral prophylaxis or pre-emptive therapies are recommended strategies for HBV reactivation in patients with NHL treated with immunosuppressive therapy. The prophylactic therapy refers to prophylactic antiviral treatment in patients who are HBsAg-positive or HBcAb-positive. The pre-emptive therapy refers to close surveillance of HBV virus load and antiviral therapy upon a rising HBV DNA load (73). Lamivudine prophylaxis has been demonstrated to reduce the risks for HBV reactivation in HBsAg-positive lymphoma patients undergoing immunosuppressive cytotoxic agents (RR =0.21; 95% CI, 0.13-0.35) (78,83,84). Tenofovir, entecavir and telbivudine have demonstrated improved antiviral efficacy compared with adefovir in randomized studies in patients with chronic HBV infection (85-88).

According to the NCCN guidelines, routine HBsAg and HBcAb testing is recommended for all patients before the initiation of chemotherapy with/without anti-CD20 monoclonal antibody treatment. In patients with positive HBsAg and/or HBcAb, baseline quantitative PCR for HBV viral load should be performed. Prophylactic antiviral therapy is recommended for patients who are HBsAg and/or HBcAb positive. HBV viral load should be monitored monthly during the treatment and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antiviral treatment should be continued. If viral load fails to drop, consultation with a hepatologist is recommended. The prophylactic antivirals should be maintained for at least 6 to 12 months following the last dose of therapy. HBV vaccination should be strongly considered In HBV-naive patients.

Elderly patients

The proportion of elderly patients with FL is increasing nowadays. The treatment for this group of patients should be well discussed; however, limited studies are focused on the elderly patients. Generally, an adequate supportive treatment is essential for the reduction of toxicities and for the improvement of quality of life. The management for patients over 80-year old should be carefully selected as palliative therapy in most cases, avoiding overtreatment and severe toxicities.

According to previous data, the ORR to initial therapy is around 80% to 90%, and median OS in the elderly ranges from 5 to 7 years (89). In the pre-rituximab era, cyclophosphamide, doxorubicin, teniposide, and prednisolone (CHVP) plus interferon indicated to produce a better outcome, but less well tolerated than fludarabine (90). In the rituximab era or even "post-rituximab" era, rituximab has established its vital position. In a prior study containing rituximab induction and maintenance therapy, the median age of patients was 65 years and the ORR was 73%, with 37% CR (91). Moreover, novel treatment strategies for elderly/comorbid patients are under investigation, including single agent monoclonal antibodies (rituximab, ofatumumab, and GA-101), combination of chlorambucil with monoclonal antibodies (92), reduced-intensity fludarabine-

based regimens, reduced-intensity bendamustine, RIT, and lenalidomide with/without rituximab. High dose steroids in combination with rituximab represent a promising option for patients relapsed/refractory FL. Finally, ofatumumab monotherapy appears to be a safe and effective therapy for heavily pretreated patients with FL. Moreover, an open-label phase Ib/II trial was conducted to evaluate the safety and activity of ibrutinib, an orally administered covalent inhibitor of Bruton tyrosine kinase (BTK), in previously untreated patients aged over 65 years with symptomatic CLL/SLL (93). The result from CLL is encouraging and the efficacy of ibrutinib in patients with FL is interesting.

Histological transformation

The annual rate of histological transformation in patients with FL is around 3%. The long-term survival in patients with histological transformation to DLBCL is poor (median OS <2 years). However, patients with limited extent transformation is associated with better survival than those with advanced transformation (5-year OS: 66% *vs*. 19%, P<0.0001) (94). The recommended treatment options in NCCN guidelines include: clinical trials, RIT, chemotherapy, IFRT and best supportive care. Stem cell transplant can be considered after response to initial treatment.

Prognostic factors

The classical clinical prognostic index in FL is FLIPI, which includes: age, Ann Arbor stage, hemoglobin level, serum LDH level, and number of nodal sites (6). Other biomarkers associated with prognosis are as follows: absolute lymphocyte count (95), absolute lymphocyte count (96), the ratio of absolute lymphocyte count to absolute monocyte count (97), histological grade (98), expression of lymphoma-associated macrophage (99,100), and gene expression profiling makers (CCNB1, CDC2, CDKN3A, CKS1B, ANP32E, KIAA0101) (101-103). The detection of some gene expression is also helpful for prediction of transformation risk, including: c-myc, CXCL12, NEK2, MAPK1, CD69, DNA polymerases, WEE1, HMGA1, and RAS pathway genes (104,105).

Novel agents

Novel anti-CD20 antibodies

Rituximab is the first anti-CD20 antibody which brings anti-lymphoma treatment into a new era with significantly improved response rate and survival. Other novel anti-CD20 antibodies have been developed and studied, including ofatumomab, veltuzumab or obinutuzumab (GA101) (92). GA101 has a new type II glyco-engineered humanized anti-CD20 recognizing a distinct with increased ability to induce antibody-dependent cellular cytotoxicity (106). Several trials have suggesting a promising safety and efficacy profile of GA101 in FL patients (107). An ongoing study (GALLIUM study) has been designed to investigate the combination of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance, compared to rituximab plus chemotherapy induction followed by MR.

B-cell signaling pathway inhibitors

The B-cell receptor (BCR) signaling pathway is intricately involved in lymphomagenesis. Several downstream kinases are associated with malignant proliferation. The BTK is a specific kinase important to B-cell maturation. BTK inhibition leads to apoptosis in lymphoma models. Ibrutinib (PCI-32765) is a promising novel oral irreversible inhibitor of BTK. The single agent activity of ibrutinib has been demonstrated to produce an ORR of 42% in indolent NHL, with mild toxicities. Ibrutinib demonstrated a 44% response rate in relapsed SLL/CLL (93). As mentioned above, ibrutinib was further studied in elderly treatment-naïve patients with SLL/CLL and produce an encouraging activity without significant hematologic toxicities and non-hematology toxicities. More studies in FL or in other indolent NHL are still in development. Another important kinase from the BCR signaling pathway was the spleen tyrosine kinase (SYK). Fostamatinib, an inhibitor of SYK was active in rheumatic diseases and in CLL, where over half of the patients experienced a PR (108). More studies are needed to evaluate the efficacy of fostamatinib in FL.

Immunomodulatory (IMiD) agents

Lenalidomide is a second-generation IMiD, agent acting on the microenvironment of lymphoma. Lenalidomide is reported to be more efficient than thalidomide with less toxicity. Lenalidomide was firstly administered in myelodysplastic syndrome and multiple myeloma and then in CLL and aggressive lymphoma with encouraging results (109,110). Single agent lenalidomide (taken daily for 21-days of a 28 day cycle) resulted in an ORR of 23% with 7% of CR in indolent NHL as initial treatment (111). Lenalidomide combined with rituximab produced an ORR

of 83.3-90% with 33-65% of CR in untreated and relapsed indolent NHL, as reported by prior studies (112,113). Responses were promising regardless of FLIPI score or GELF criteria. Moreover, side effects were manageable. Neutropenia was seen in 27% of the patients. Skin rash and deep venous thrombosis the most common non-hematologic toxicities. A randomized phase II study in relapsed indolent NHL (CALGB 50401) suggested the superiority of the combination of rituximab plus lenalidomide over single agent lenalidomide, (ORR: 75% *vs*. 49%; median EFS: 2 *vs*. 1.2 years). These promising results have prompted an ongoing international phase III trial in patients with FL (the RELEVANCE trial), comparing the activity and safety of lenalidomide plus rituximab with R-chemo.

Histone deacetylase (HDAC) inhibitors

Vorinostat, an oral HDAC inhibitor, was approved by FDA in cutaneous T-cell lymphoma and in peripheral T-cell lymphoma in the relapsed setting (114,115). HDAC inhibitor has demonstrated an acceptable toxicity profile and an early efficacy signal in B-cell lymphoma. A phase II study demonstrated an ORR of 29% produced by single agent vorinostat in relapsed or refractory B-cell lymphoma (116). Further studies of vorinostat combination therapy are still under investigation.

Phosphatidylinositol 3-kinase (PI3K) inhibitors

PI3K is an important protein for cellular metabolism. PI3K has several important physiologic isoforms (α, β, δ, and γ). GS-1101 (the drug formerly known as CAL-101) is a kind of δ inhibitors and has been extensively developed in CLL undergoing phase III studies (117-119). Single agent GS-1101 has been reported to produce an ORR of 62% in relapsed FL (120,121). Further studies with GS-1101 as a single agent or with combination chemotherapy are ongoing.

Proteasome inhibitor

Bortezomib is the first extensively administered in multiple myeloma, MCL, and other relapsed indolent NHLs (122-124). In a phase II study, patients with relapsed indolent NHL were treated with rituximab plus bortezomib at either biweekly or weekly schedule. The ORRs were 49% and 43% for the biweekly and weekly regimens, respectively (122). A randomized phase III study suggested a better PFS favoring the combination arm of bortezomib plus rituximab (12.8 *vs*. 11.0 months; P=0.039), compared to single agent rituximab, in patients with rituximab-naïve or rituximab sensitive FL. However, the combination arm had more grade 3 or greater toxicities, with 20% patients experiencing peripheral neuropathy (125). Furthermore, the combination of rituximab, bortezomib and bendamustine (90 mg/m^2) has been demonstrated safe and well-tolerated (126).

In conclusion, individualized management of FL remains challenging. Treatment strategies are developed based on randomized clinical trials for the benefit of the patients. New therapeutic tools and treatment modalities will be improved in the future.

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