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## REVIEW ARTICLE

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# Rituximab in the Management of Follicular Lymphoma

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### ABSTRACT

*The incidence of follicular lymphoma, a low-grade malignant B-cell lymphoma, is increasing in most Asian populations. Follicular lymphoma is generally considered to be indolent with a life expectancy of approximately 10 to 14 years. However, it is characterised by repeated relapse, and disease progression typically occurs 3 to 5 years after initial treatment. Rituximab, a monoclonal antibody, demonstrates consistent survival benefits when administered as part of a first- and second-line immunochemotherapy. Consequently, rituximab is now considered the standard of care for follicular lymphoma, and is recommended as the first-line therapy for early-stage asymptomatic disease. Available evidence also demonstrates survival benefits for rituximab as maintenance therapy in patients who have responded to induction therapy with either frontline rituximab or chemotherapy. Improved survivals in patients receiving rituximab-based first-line induction and maintenance therapies suggest that this treatment strategy may be preferable to adopting a watch-and-wait policy in patients with asymptomatic follicular lymphoma. While rituximab has improved treatment outcomes in follicular lymphoma patients, the appropriate timing, dosing and duration of therapy remain to be clarified in future clinical trials. Given the indolent nature of follicular lymphoma and the relatively long life expectancy associated with this disease, prognostic tools have an important role in guiding clinical decisions based on individual patient risk.*

**Key Words:** *Lymphoma, follicular; Rituximab*

## 中文摘要

### Rituximab治療濾泡性淋巴瘤

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本濾泡性淋巴瘤是一種惡性度較低的B細胞腫瘤，其病發率在大多數亞洲國家中不斷上升。濾泡性淋巴瘤病情緩慢，患者生存期約為10至14年。可是患病期間會不斷復發，患者一般會在首次治療後3至5年出現病情惡化。Rituximab是一種單克隆抗體，作為一線及二線的免疫化療可改善病人存活期，所以它被用作濾泡性淋巴瘤的標準治療，亦被推介為治療早期無症狀的濾泡性淋巴瘤的一線藥物。現有的證據顯示患者對rituximab或化療的引導治療出現療效後，再接受rituximab作為維持治療也可以改善病人存活期。這情況亦顯示此治療策略對於無症狀的濾泡性淋巴瘤患者來說，比採取觀望措施較為可取。雖然rituximab可改善濾泡性淋巴瘤患者的病情，可是對於施予的時間、使用劑量的多少，以及療程的長短，都須要日後作進一步的探討與臨床研究。由於濾泡性淋巴瘤的病情較為緩慢，患者的生存期相對較長，預後工具對根據患者個人風險而做的臨床決策有重要作用。

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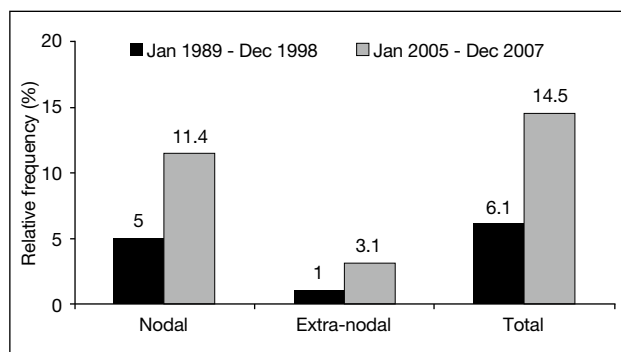
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## INTRODUCTION

Follicular lymphoma (FL) is a low-grade, malignant B-cell lymphoma.<sup>1</sup> It is the second most frequently occurring lymphoma in the western world constituting approximately 25% of all lymphomas.<sup>1,2</sup> FL is generally considered to be indolent, and is associated with a life expectancy of approximately 10 to 14 years.<sup>1,3</sup> The prognosis of patients with FL may be determined based on the Follicular Lymphoma International Prognostic Index (FLIPI), which evaluates clinical and biological parameters.<sup>4</sup>

Although FL is generally considered to be uncommon in Asian patients, recent epidemiological evidence indicates that it is becoming more common in most Asian populations.<sup>5,6</sup> In Hong Kong, it is the second most common lymphoma, accounting for 15 to 20% of mature B-cell lymphomas and 40 to 50% of low-grade lymphomas.<sup>5</sup> A survey among lymphoma patients in a single institution in Southern Taiwan noted an increasing frequency of FL, from 6.1% between 1989 and 1998 to 14.5% between 2005 and 2007 (Figure;  $p=0.007$ ).<sup>6</sup>

There is also a trend for FL to occur in younger individuals. Data from Taiwanese patients demonstrated that the median age at diagnosis had decreased from 69 years (January 1989 to December 1998) to 55 years (January 2005 to December 2007;  $p=0.036$ ).<sup>6</sup> In the



**Figure.** Relative frequency of follicular lymphomas in a single institution in Taiwan (adapted from Chuang).<sup>6</sup>

**Table 1.** Ann Arbour classification.<sup>11</sup>

Stage	Area of involvement
I	One lymph node region or extralymphatic site
II	Two or more lymph node regions or $\geq 1$ lymph node region plus a single localised extralymphatic site on the same side of the diaphragm
III	Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (IIIE) or spleen (IIIS)
IV	Diffuse or disseminated extralymphatic organ involvement

majority of patients, FL is diagnosed at an advanced stage (III or IV), with disseminated disease and at least one extranodal location, most often involving the bone marrow.<sup>1,7</sup> This patient profile highlights the need for earlier diagnosis and intervention with effective therapies to improve patient survival.

## MANAGEMENT OF FOLLICULAR LYMPHOMA

FL is characterised by slow growth and a high initial response rate.<sup>8</sup> However, it has a continuous pattern of relapse, and disease progression typically occurs three to five years after initial treatment.<sup>5</sup> The treatment approach should take into consideration the patient's symptoms, prognosis, and priorities regarding desired outcome (prolongation of life or improved quality of life [QoL]).<sup>4</sup> Traditionally, treatment of FL has been palliative rather than curative,<sup>2,9</sup> and management of asymptomatic patients involves either a watch-and-wait approach or the use of monotherapy with a view to maintaining QoL over a prolonged period of time.<sup>4,7</sup> The view that deferred therapies did not appear to influence survival outcomes was based on data collected when effective treatment for FL was not available. However, emerging targeted therapies may lead to a change in this treatment paradigm.<sup>10</sup>

Staging of FL is essential for making appropriate therapeutic decisions. FL is usually staged according to the Ann Arbour classification (Table 1): only 5 to 10% of patients present with stage I or II disease.<sup>11</sup>

### Early-stage Follicular Lymphoma

In patients with early-stage FL (stage I / II) treatment may potentially be curative.<sup>3</sup> Locoregional radiotherapy is indicated in such patients.<sup>5</sup> Supplementation with rituximab monotherapy appears to be a logical option, although formal data supporting this approach are lacking.

### Advanced Disease

In patients with advanced disease, the treatment involves regimens containing an alkylating agent,

such as the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, vincristine and prednisolone (CVP).<sup>5</sup> In patients with advanced stage FL, the German Low-Grade Lymphoma Study reported overall response rates and two-year survival rates of 90% with a frontline CHOP regimen.<sup>12</sup> Emerging evidence from several ongoing studies indicates that CVP may be less potent than other regimens (e.g. CHOP, fludarabine, mitoxantrone and dexamethasone [FND]), although a definitive conclusion cannot be made until these studies are completed.

At present, there is a lack of data on the comparative effectiveness of various chemotherapeutic regimens in Chinese patients with indolent FL. In patients with advanced stage FL (grade III / IV), rituximab plus FND is the standard treatment at Queen Mary Hospital. In one study, a first-line fludarabine-based chemotherapeutic regimen was used in the treatment of 95 Chinese patients with low-grade B-cell lymphoid malignancies.<sup>13</sup> FND was more effective in patients with primary than relapsed / refractory disease (two-year overall survival rates, 92 vs 58%, respectively;  $p < 0.001$ ). Overall response rates in this study were comparable to those previously reported in western patients.<sup>13</sup> The most common FND-related toxicities in Chinese patients, namely neutropenia and pneumonia, were observed in 7% of the 509 treatment cycles. These rates were also comparable to those reported in trials in western patients.<sup>13</sup>

The chimeric monoclonal antibody rituximab has revolutionised the treatment of FL, and over the past decade clinical trials investigating its effectiveness as an immunochemotherapy option for this condition have demonstrated improvements in overall survival outcomes. As a result, rituximab is now considered to be the standard of care in the first-line treatment of FL.<sup>14</sup>

## RITUXIMAB

The monoclonal antibody rituximab targets the CD20 protein expressed on the surface of all mature B cells, and is therefore active in many B-cell lymphomas that express this molecule.<sup>8</sup> Rituximab has demonstrated efficacy as a single agent. Furthermore, there is a synergistic effect between rituximab and chemotherapeutic agents, because their mechanisms of action are not prone to cross-resistance. As rituximab does not have overlapping toxicities with other chemotherapeutic drugs, reduction in the dose intensity of chemotherapy is not needed with concomitant

immunochemotherapy. Thus, rituximab is used effectively as monotherapy as well as in combination with other chemotherapeutic agents.<sup>1</sup>

National Comprehensive Cancer Network guidelines advocate the addition of rituximab to a chemotherapeutic regimen for first- and second-line treatment of FL. Rituximab maintenance treatment has also been recommended for up to two years.<sup>14</sup> These guidelines also note that rituximab monotherapy is an acceptable treatment option in patients who are elderly or have an unsatisfactory performance status.

It is now standard to combine rituximab with chemotherapy as induction treatment in FL. The usual immunochemotherapeutic regimen involves eight cycles of rituximab and six to eight cycles of chemotherapy. The serum concentration of rituximab is lower in men, suggesting that men might require a higher dose (500 mg/m<sup>2</sup>) as compared to women (375 mg/m<sup>2</sup>). However, further clinical trials are needed to confirm this proposition.

In patients with symptomatic advanced FL, the addition of rituximab to frontline therapy with CHOP significantly improves outcomes, without an increase in clinically relevant toxicities.<sup>12</sup> In a study among treatment-naïve patients with advanced FL ( $n = 428$ ), the combination of rituximab and CHOP (R-CHOP) reduced the risk of treatment failure by 60% ( $p < 0.001$ ) and produced a significantly higher overall response rate (96 vs 90%;  $p = 0.011$ ), longer duration of remission ( $p = 0.001$ ) and improved overall survival compared to CHOP alone (6 vs 17 deaths at three years;  $p = 0.016$ ).<sup>12</sup> Granulocytopenia occurred more frequently in patients receiving R-CHOP than CHOP (63 vs 53%;  $p = 0.01$ ), although severe infections were rare and occurred with a similar frequency with both regimens (5 vs 7%).<sup>12</sup> Favourable outcomes have also been reported with the addition of rituximab to frontline CVP (R-CVP) in patients with advanced FL.<sup>15</sup> After a median follow-up of 30 months, time-to-progression (median, 32 vs 15 months;  $p < 0.0001$ ) and time-to-treatment failure (median, 27 vs 7 months;  $p < 0.0001$ ) were significantly longer with R-CVP than with CVP alone.<sup>15</sup>

Given the generally long life expectancy of FL patients, drugs that have a favourable long-term toxicity profile are preferable.<sup>9</sup> As rituximab has an acceptable toxicity profile, it can be safely used as maintenance therapy for FL patients who have responded to

immunochemotherapy induction treatment. Increasing evidence suggests beneficial effects for rituximab maintenance therapy compared with observation alone, both in first complete remission, and in second or more advanced remissions after relapses.<sup>8,16</sup>

A meta-analysis of randomised trials that included 1143 adult patients with FL showed that the addition of rituximab maintenance therapy (as four weekly infusions every six months or as a single infusion every two to three months, for up to two years) to a standard chemotherapy regimen was associated with significantly better overall survival than observation or treatment only at relapse (hazard ratio [HR] for death = 0.60; 95% confidence interval [CI], 0.45-0.79).<sup>8</sup> Survival benefits were observed in both treatment-naïve (HR = 0.68; 95% CI, 0.37-1.25) and relapsed / refractory FL (HR = 0.58; 95% CI, 0.42-0.79). These results indicate that initiation of rituximab maintenance may confer greater survival advantages than commencement of treatment after relapses have occurred. However, the higher rate of infection-related adverse events reported with rituximab maintenance therapy (HR = 1.99; 95% CI, 1.21-3.27) should be considered when formulating treatment decisions.<sup>8</sup>

The Primary Rituximab and Maintenance (PRIMA) study evaluated the efficacy of rituximab as maintenance therapy every two months for two years in FL patients with a high tumour burden (n = 1018) treated with first-line rituximab-based chemotherapy.<sup>16</sup> Rituximab maintenance therapy significantly improved the progression-free survival (PFS) versus observation (75 vs 58%; p <0.0001) with a median follow-up of 36 months.<sup>16</sup> Rituximab conferred a survival advantage

across all levels of risk (FLIPI). Rituximab maintenance therapy also delayed the time to next anti-lymphoma treatment and next chemotherapy apart from improving patient QoL.<sup>16</sup> Rituximab was generally well-tolerated. However, grades 3 and 4 adverse events occurred with a higher frequency in the rituximab than observation arm (24 vs 17%; p = 0.026). Nevertheless, few patients withdrew from treatment due to rituximab-related toxicities (4% vs 2% in the observation arm; p = 0.029).<sup>16</sup>

While rituximab has improved survival outcomes in FL patients, the appropriate timing, dosing, and duration of rituximab therapy need to be clarified in future clinical trials.

### PREDICTING PATIENT OUTCOMES

The quality of response achieved following first-line therapy should be evaluated to ensure that patients receive optimal management for FL. A number of prognostic tools have been shown to facilitate this aim by means of predicting patient outcomes.<sup>17-19</sup>

A subanalysis of data from the PRIMA study demonstrated that the positron emission tomography-computed tomography (PET-CT) status after induction chemotherapy is an independent predictor for FL progression.<sup>17</sup> Patients who remained PET-positive after induction immunochemotherapy had a significantly worse PFS at 42 months compared with PET-negative patients (33 vs 71%; p <0.001).<sup>17</sup> Therefore, it is important to perform a PET-CT after completion of therapy. Patients who remain PET-positive after treatment with six cycles of a standard rituximab-containing regimen have a worse prognosis and additional treatment may be necessary.

**Table 2.** FLIPI and FLIPI 2 prognostic indexes for follicular lymphoma.<sup>18,19</sup>

FLIPI				FLIPI-2			
5 Factors	Age (years)	<60	vs ≥60	5 Factors	Age (years)	<60	vs ≥60
	Haemoglobin (g/L)	≥120	vs <120		Haemoglobin (g/L)	≥120	vs <120
	Serum LDH	≤ULN	vs >ULN		Serum β-2 microglobulin	≤ULN	vs >ULN
	Ann Arbour stage	I-II	vs III-IV		Bone marrow involvement	Absent	Present
	No. of nodal sites	≤4	vs >4		Longest diameter of largest lymph node (cm)	≤6	>6

Abbreviations: FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactate dehydrogenase; ULN = upper limit normal.

**Table 3.** Levels of risk for follicular lymphoma adapted from Hitz et al.<sup>19</sup>

FLIPI					FLIPI-2				
Risk group	No. of factors	5-Year OS	10-Year OS	Relative risk	Risk group	No. of factors	3-Year PFS	3-Year OS	5-Year PFS
Low	0-1	91%	71%	1	Low	0-1	91%	99%	79%
Intermediate	2	78%	51%	2.3	Intermediate	2	69%	96%	51%
High	≥3	53%	36%	4.3	High	≥3	51%	84%	20%

Abbreviations: FLIPI = Follicular Lymphoma International Prognostic Index; OS = overall survival; PFS = progression-free survival.

The FLIPI is a simple, widely used prognostic index that uses simple clinical data to classify patients according to their risk of progression.<sup>18,19</sup> It uses five adverse prognostic factors to rank patients according to their level of risk as: low, intermediate, or high (Tables 2 and 3).<sup>18,19</sup> However, FLIPI was developed prior to the advent of chemoimmunotherapy and consequently might be not representative of the present course of the disease. The modified FLIPI-2 that evaluates prospective data is easily applied and more accurately predicts the likelihood of disease progression.<sup>19</sup> Independent risk factors for PFS include: beta2-microglobulin levels higher than the upper limit of normal, largest lymph node >6 cm, bone marrow involvement, haemoglobin <120 g/L, and age ≥60 years (Table 2). The respective three-year PFS rates were 91%, 69%, and 51% for patients with FL at low, intermediate, and high risk, respectively (p<0.00001). Across these levels of risk, the three-year survival rates were 99%, 96%, and 84%, respectively (p<0.0001).

Given the indolent nature of FL and the relatively long life expectancy associated with this disease, prognostic tools have an important role in guiding clinical decisions according to individual patient risk.

## CONCLUSIONS

Recent advances in the treatment options for FL have improved outcomes for many patients. However, patients continue to experience relapses and treatment strategies are needed that extend remissions and prolong survival, whilst minimising toxicity. Rituximab is the first-line treatment for FL to demonstrate consistent survival benefits. Consequently, it is now considered to be the standard of care for FL, and first-line rituximab is recommended for early-stage asymptomatic disease. Data suggest that rituximab can be effectively and safely used as maintenance therapy for up to 2 years in patients with FL who have responded to induction therapy. Improved survival outcomes in patients receiving treatment with rituximab as induction and maintenance therapy indicate that this treatment strategy may be preferable to adopting a watch-and-wait policy in those who are asymptomatic at diagnosis.

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