



REVIEW

Front-line management of non-Hodgkin lymphoma in Australia. Part 1: follicular lymphoma

Judith Trotman ^{1,2} Chan Y. Cheah,^{3,4,5} Paula Marlton ^{6,7} and Stephen Opat^{8,9}

¹Department of Haematology, Concord Hospital, and ²Department of Medicine, University of Sydney, Sydney, New South Wales, ³Department of Haematology, Sir Charles Gairdner Hospital, ⁴Department of Haematology, Pathwest Laboratory Medicine, and ⁵School of Medicine, University of Western Australia, Perth, Western Australia, ⁶Division of Cancer Services, Clinical Haematology, Princess Alexandra Hospital, and ⁷University of Queensland School of Medicine, Brisbane, Queensland, ⁸Clinical Haematology and School of Clinical Sciences, Monash Health, and ⁹Department of Medicine, Monash University, Melbourne, Victoria, Australia

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Correspondence

Judith Trotman, Department of Haematology, Concord Hospital, University of Sydney, Hospital Road, Concord, Sydney, NSW 2139, Australia.
Email: judith.trotman@health.nsw.gov.au

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Abstract

Outcomes with follicular lymphoma (FL) have improved in the modern era and median survival is now beyond 15 years. Therapeutic decisions need to consider this increased survival as well as recent clinical trial data and emerging treatments. In this context, we present here current approaches to front-line management of FL in Australia. Treatment choices depend on the disease stage, tumour burden, the patient's age, symptoms, comorbidities and preferences. Only about 10–15% of patients with FL are diagnosed with early stage disease. For patients with low-grade, early stage disease, radiotherapy (RT) is recommended. The addition of chemotherapy has been shown to increase progression-free survival (PFS) but without demonstrated overall survival advantage. For patients with low-tumour-burden, advanced-stage FL, immediate treatment may not be required and we recommend considering active monitoring. For stage III/IV disease that is symptomatic and/or with high tumour burden, established first-line treatment is chemotherapy in combination with rituximab, often followed by rituximab maintenance. The listing of bendamustine and now obinutuzumab on the Pharmaceutical Benefits Scheme has expanded the first-line treatment options in Australia to include bendamustine in combination with rituximab (without rituximab maintenance permitted) or with obinutuzumab plus 2 years obintuzumab maintenance. In the FL subgroup of the Study group indolent Lymphomas (StiL) trial, therapy with bendamustine plus rituximab significantly increased PFS compared with rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone, without rituximab maintenance. Initial tolerability may be more favourable with bendamustine in combination with anti-CD20 antibody therapy than other therapies overall, but clinical vigilance is still required because of concerns of late infectious toxicities associated with prolonged T-cell depletion.

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Introduction

While the incidence of non-Hodgkin lymphoma in Australia has increased over the past three decades,¹ 5-year survival rates for the disease have improved.¹ Across the nation, the incidence of non-Hodgkin lymphoma is about 20 per 100 000 person-years, with almost 5000 new cases diagnosed in 2013.¹ Of the slow-growing indolent subtypes, follicular lymphoma (FL) is the most common, making up 20–30% of all non-Hodgkin lymphoma cases in Australia.² Potential risk factors and reasons for differences in incidence within the Australian environment are currently being examined in the Lymphoma, Lifestyle, Environment and Family (LEAF) study.³ There are few studies providing survival follow up of more than 5 years; however, registry data suggest that median survival is beyond 15 years in the modern era.⁴ This long-term survival needs to be taken into consideration in therapeutic decision-making, such as on long-term toxicities. The median age at diagnosis is the mid-60s and thus many patients will die with, but not from, their FL or its complications.

Diagnosis and staging

The diagnosis of FL is based on excisional lymph node biopsy, with core biopsy performed only in situations where an excision is not possible.⁵ Histopathological grading, in accordance with the World Health Organisation classification, is determined by the number of centroblasts per high-powered field. Grades 1–3A are considered histologically low-grade FL. However, patients with grade 3A disease were excluded from several low-grade FL trials. Grade 3B (characterised by sheets of centroblasts) is treated as an aggressive lymphoma.⁵ FL is staged according to the area of involvement, from stage I (single lymph node group) to stage IV (multiple extranodal sites or lymph nodes and extranodal disease). To that end, an adequate bone marrow aspirate and trephine biopsy are essential components of a complete staging assessment (Table 1).⁵ Staging work-up usually includes contrast-enhanced computed tomography (CT); positron emission tomography (PET) imaging (funded for indolent lymphoma in Australia from November 2017) is recommended for more accurate disease staging. The FL-specific International Prognostic Index (FLIPI) is a prognostic score originally developed in the pre-rituximab era based on retrospective data analysis.⁶ The more recent FLIPI2 was developed prospectively in newly diagnosed patients commencing systemic therapy in the rituximab era and is thus a more relevant prognostic tool in such patients, with added parameters (Table 2).⁶ The FLIPI remains

Table 1 Initial work-up

Physical examination
Peripheral lymph nodes, liver, spleen
Routine bloods
Full blood count, renal and liver function tests, protein electrophoresis, β microglobulin
Serology
Hepatitis B and C, and HIV
Radiological investigations
CT scan of neck, chest, abdomen, pelvis; PET-CT scan
Bone marrow aspirate and trephine (when indicated)
Histology (with a comprehensive panel of immunohistochemical markers [†]); cytology

[†]Immunohistochemistry markers could include CD3, CD5, CD10, CD20, CD21, CD23, BCL2, BCL6 and Ki67. CT, computed tomography; PET-CT, positron emission tomography–computed tomography. Table adapted from Dreyling *et al.* 2016⁵.

prognostic, however, in the rituximab era, with 5 and 10-year follow-up data⁷ and is widely used in clinical practice. There have been no direct comparisons between the two but, as has been noted in a pooled analysis, only FLIPI2 remained prognostic in the context of end-of-induction PET-CT status.⁸ While both indices can be taken into account for an individual patient, neither is sufficiently robust or predictive enough to define or alter indication for treatment, which is guided by the Groupe d'Etude des Lymphomes Folliculaires (GELF) and British National Lymphoma Investigation (BNLI) criteria.

Current treatment approaches

Overview

A flow chart of current treatment approaches is shown in Figure 1. Treatment choices for FL depend on the

Table 2 Follicular Lymphoma-specific International Prognostic Index (FLIPI) risk factors

Parameter	Definition of risk factors	
	FLIPI1	FLIPI2
Serum marker	Elevated LDH	Elevated β 2 microglobulin
Nodal sites	>4 lymph node regions	Longest diameter of largest involved node >6 cm
Stage	Advanced [†]	Bone marrow involvement
Haemoglobin	<12 g/dL	<12 g/dL
Age	>60 years	>60 years

[†]III–IV as per Ann Arbor classification. Score: 0–1 risk factors, low risk; 2 risk factors, intermediate risk; 3–5 risk factors, high risk. LDH, lactate dehydrogenase. Table adapted from Dreyling *et al.* 2016⁵.

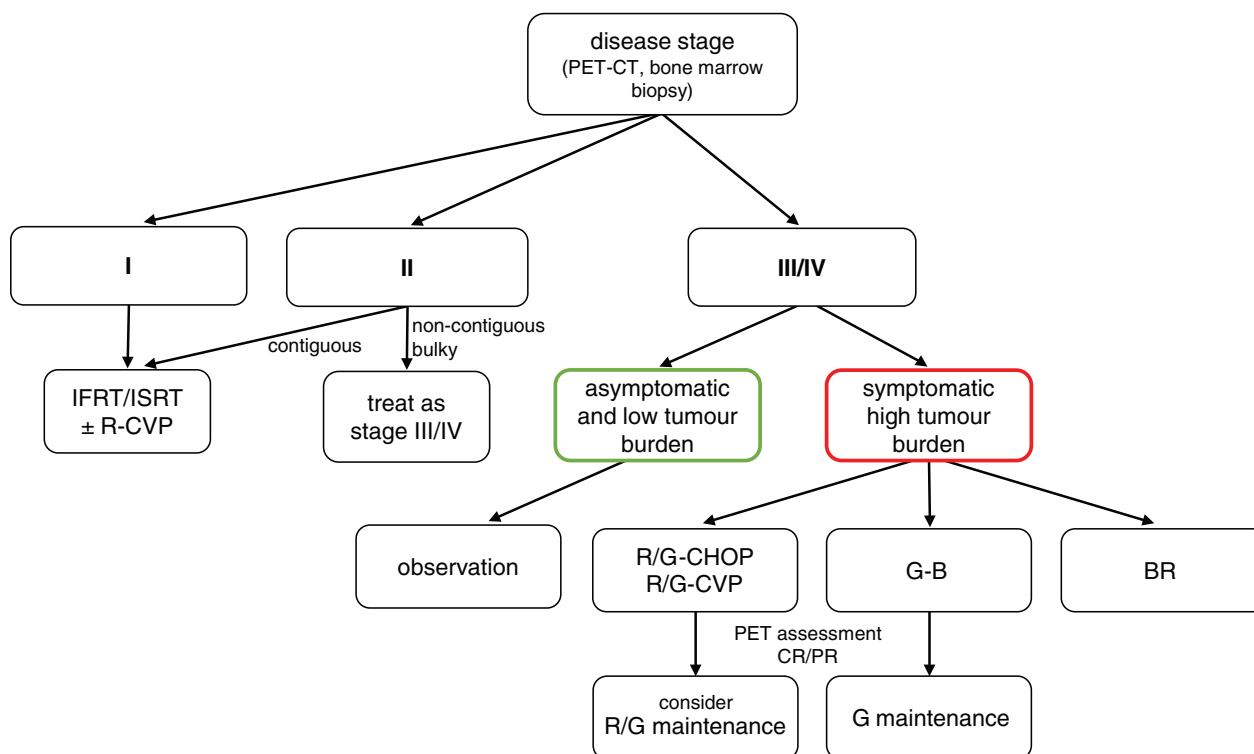


Figure 1 Flow chart of current front-line treatment approaches for follicular non-Hodgkin lymphoma in Australia. B, bendamustine; CHOP, chemotherapy with cyclophosphamide, vincristine, doxorubicin and prednisone; CR, complete response; CVP, cyclophosphamide, vincristine and prednisone; G, obinutuzumab (Gavyza); IFRT, involved field radiation therapy; ISRT, involved site radiotherapy; PET, positron emission tomography; PR, partial response; R, rituximab.

stage of the disease, tumour burden, the patient's age, symptoms, comorbidities and preferences.^{5,9} The central goals of therapy are to restore health and prolong life. Subject to availability and patient eligibility, clinical trials should be the first consideration. The international PETReA study will assess the potential of PET-adapted therapy to triage patients after induction rituximab–chemotherapy in previously untreated patients (grades 1–3a) with high tumour burden.¹⁰ For early stage disease (stages I and II), when the disease is potentially curable, treatment with RT, given either with or without chemotherapy combined with the anti-CD20 monoclonal antibody rituximab (chemoimmunotherapy), is recommended. For advanced-stage disease (III and IV), the decision to treat is based on the absence or presence of symptoms and tumour burden. There are several well established chemoimmunotherapy regimens in use and the recent listing of both bendamustine and obinutuzumab on the Pharmaceutical Benefits Scheme (PBS) has expanded the first-line treatment options in Australian clinical practice for patients with stage III–IV disease. Table 3

summarises the treatment options available in Australia for the different stages of FL.

Early stage disease

Diagnosis of early stage disease is relatively uncommon (10–15% of patients with FL), and careful staging with a PET–CT is required for confirmation.⁵ The European Society for Medical Oncology (ESMO) recommends RT with curative intent for low-grade, early stage disease.⁵ Patients with non-contiguous, multifocal or bulky stage II disease may more appropriately be considered and managed as advanced-stage disease.⁵ Challenging the traditional emphasis on RT alone are the recent, preliminary results from the only randomised study on early-stage FL, conducted by the Trans-Tasman Radiation Oncology Group/Australasian Leukaemia and Lymphoma Group, comparing RT alone with RT plus cyclophosphamide, vincristine and prednisolone (CVP) or rituximab-CVP (R-CVP). The addition of R-CVP to RT improved progression-free survival (PFS); however, there was no impact on overall survival (OS), and

Table 3 Summary of FL treatment regimens available in Australia

Stage	Treatment	PBS listed	Source/trial
Early stage			
Stage I	RT ± R-CVP	Yes	<ul style="list-style-type: none"> • ESMO: RT with curative intent⁵ • Trans-Tasman Radiation Oncology Group/Australasian Leukaemia and Lymphoma Group: RT + R-CVP improved PFS (but not OS) versus RT alone¹¹ • LymphoCare study: R-chemo or RT + systemic therapy improved PFS (but not OS) versus RT alone¹²
Stage II, contiguous	Treat as Stage I	—	
Stage II non-contiguous, multifocal or bulky	Treat as advanced stage	—	
Advanced stage			
Asymptomatic, low tumour burden	Active monitoring for symptoms and signs of disease progression; consider imaging for abdominal disease	—	<ul style="list-style-type: none"> • Multicentre clinical trial: no difference in OS with active monitoring versus systematic therapy (median follow up: 16 years)¹³ • GELF criteria⁵¹ • BNLI criteria¹³ • NCCN criteria⁴⁶
Symptomatic and/or high tumour burden	R-CHOP or R-CVP, then R-maintenance	Yes	<ul style="list-style-type: none"> • R-CHOP improved overall response versus CHOP alone²⁴ • R-CVP improved OS versus CVP alone¹⁸ • FOLL05: R-CHOP improved PFS and time to treatment failure versus R-CVP¹⁵
	BR	Yes	<ul style="list-style-type: none"> • STiL: BR improved PFS versus R-CHOP in FL subgroup and less toxicity^{21,29} • BRIGHT: BR improved PFS versus R-CHOP/R-CVP^{16,17}
	Obinutuzumab-chemo	Yes	<ul style="list-style-type: none"> • GALLIUM: obinutuzumab-chemo improved PFS versus R-chemo¹⁹

BNLI, British National Lymphoma Investigation; BR, bendamustine and rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; ESMO, European Society for Medical Oncology; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; NCCN, National Comprehensive Cancer Network; OS, overall survival; PBS, Australian Pharmaceutical Benefits Scheme; PFS, progression-free survival; R, rituximab; RT, radiotherapy; RCT, randomised comparative trial; STiL, Study group indolent Lymphomas.

whether the exposure of patients to the potential toxicity of R-CVP is justified remains uncertain.¹¹ In the LymphoCare population-based study, for patients with stage I FL, treatment with either chemotherapy in combination with rituximab or systemic therapy in combination with RT significantly improved PFS compared with RT alone. There were no differences in OS between treatment groups.¹² While the ESMO guidelines support either watchful waiting or rituximab monotherapy to avoid the side effects of radiation,⁵ we consider such situations uncommon and note that rituximab monotherapy

is not funded in Australia or New Zealand for either early or advanced-stage disease.

Advanced stages: asymptomatic, low tumour burden

For low-tumour-burden advanced-stage disease, active monitoring ('watch and wait') may be considered without adversely affecting long-term outcomes. The GELF criteria (Table 4) can help identify those patients with FL in whom immediate therapy, rather than a watch-and-wait

Table 4 Criteria for initiation of therapy: GELF, NCCN and BNLI†

Criteria
GELF‡
Bulky disease: nodal/extranodal tumour mass >7 cm diameter or ≥3 nodal sites, each >3 cm diameter
Symptomatic splenomegaly
Organ compression; pleural effusion or peritoneal ascites
Elevated lactate dehydrogenase or elevated serum β2 microglobulin levels
B symptoms: unexplained fever >38°C; drenching night sweats; or loss of >10% body weight within 6 months
Lymphocyte count >5.0 × 10 ⁹ /L
Cytopenias (granulocytes <1.0 × 10 ⁹ /L; platelets <100 × 10 ⁹ /L)
NCCN§
Candidate for clinical trial
Symptoms
Threatened end-organ function
Cytopenia secondary to lymphoma
Bulky disease (as per GELF criteria)
Steady progression
BNLI¶
Presence of pruritis or B symptoms
Rapid, generalised disease progression in the preceding 3 months
Life-endangering organ involvement
Significant bone marrow infiltration (haemoglobin <10 g/dL, white cell count <3.0 × 10 ⁹ /L or platelets <100 × 10 ⁹ /L)
Bone lesions
Renal infiltration
Macroscopic liver involvement

†Some of the parameters in this table should be considered in context and not taken as definite indication to commence treatment (e.g. isolated elevated lactate dehydrogenase or serum β2 microglobulin).

‡From Brice *et al.* 1997.⁵¹ §From NCCN clinical practice guidelines 2017.⁴⁶ ¶From Ardeshta *et al.* 2003.¹³ BNLI, British National Lymphoma Investigation; GELF, Groupe d'Etude des Lymphomes Folliculaires; NCCN, National Comprehensive Cancer Network.

approach, is more appropriate. Patients should be monitored for symptoms and signs of disease progression, and consideration should be given to additional imaging for abdominal disease in particular. Outside of clinical trials, we generally do not recommend treating asymptomatic, indolent, low-volume disease not meeting GELF criteria for the initiation of therapy. Even in the presence of one or more of the GELF criteria, immediate treatment may not be required for all patients, and clinical judgement should be used. Close monitoring for symptoms or other features of disease progression may, for example, be appropriate for patients with slightly elevated serum lactate dehydrogenase levels but with otherwise low tumour burden. In addition to GELF criteria, parameters for initiation of therapy have also been published by the National Comprehensive Cancer Network (NCCN) and the BNLI (Table 4).

Patients with low-grade non-Hodgkin lymphoma who were randomised to either systemic therapy or watchful waiting in a multicentre clinical trial did not differ in OS

during a median follow up of 16 years.¹³ However, another study reported that patients who received rituximab monotherapy had an improved quality of life, with a better illness-coping style, compared with patients assigned to watchful waiting.¹⁴ Rituximab monotherapy is not currently subsidised for induction therapy in Australia or New Zealand.

Advanced-stage disease: symptomatic and/or high tumour burden

Established first-line treatment for stages III and IV disease that is symptomatic and/or with high tumour burden is chemoimmunotherapy. This is frequently followed by anti-CD20 antibody maintenance therapy (see 'Antibody maintenance' section) because of the PFS advantage. Key clinical studies in advanced stage FL are summarised in Table 5.^{15–22}

Chemoimmunotherapy

The addition of rituximab to conventional chemotherapy represented an important advance in the therapy of advanced-stage FL.^{18,23–25} It has improved all measures of outcome, including response rates, PFS, time to treatment failure and OS. The benefits of rituximab were observed when added to the anthracycline-based cyclophosphamide, doxorubicin, vincristine and prednisolone combination (R-CHOP) (overall response: 96% for R-CHOP vs 90% for CHOP; $P = 0.011$),²⁴ as well as when added to the alkylator-based CVP regimen (Table 5).¹⁸ Outcomes with fludarabine-based treatment were also improved.²⁶ The question of which chemotherapy backbone provides the best outcomes was the subject of the FOLL05 trial, which demonstrated that R-CHOP was superior to R-CVP in terms of PFS and time to treatment failure (median follow up: 34 months) and was less toxic than therapy with rituximab in combination with fludarabine and mitoxantrone¹⁵; recently reported data from long-term follow up (median 84 months) confirm these results.²⁷ The risk of cardiac toxicity with R-CHOP,²⁸ particularly in older patients with cardiac risk factors and other comorbidities, needs to be carefully considered when choosing the most appropriate regimen for individual patients.

The utility of first-line therapy with bendamustine and rituximab (BR), recently listed on the PBS in Australia, has been examined in two randomised studies. In the Study group indolent Lymphomas (StiL) trial, BR was compared with R-CHOP in 514 patients with untreated low-grade lymphoma or mantle cell lymphoma. BR was better tolerated than R-CHOP, with no alopecia and lower rates of haematological toxicity, infections, peripheral neuropathy, stomatitis and cardiac toxicity. The

Table 5 Key phase III clinical trials in patients with advanced-stage follicular lymphoma

Study	Treatment (n)	Median follow up (months)	PFS	OS	Potentially treatment-related deaths
Federico <i>et al.</i> 2013 (FOLL05) ¹⁵	R-CVP (n = 178); R-CHOP (n = 178); R-FM (n = 178)	34	At 3 years, R-CVP: 52%, R-CHOP: 68%, R-FM: 63% (overall $P = 0.011$)	At 3 years for all patients combined: 95%; NR separately per treatment arm	None
Flinn <i>et al.</i> 2014, 2017 (BRIGHT) ^{16,17}	BR (n = 224); R-CVP (n = 119); R-CHOP (n = 104)†	BR: 65; R-CVP/R-CHOP: 64	At 5 years: BR: 66%, R-CVP/R-CHOP: 56%; HR: 0.61 ($P = 0.0025$)	At 5 years: BR: 82%, R-CVP/R-CHOP: 85%; HR: 1.15 ($P = 0.5461$)	n = 3, in the BR arm (at interim analysis) ¹⁶
Marcus <i>et al.</i> 2008 ¹⁸	R-CVP (n = 159); CVP alone (n = 162)	53	Not assessed	Kaplan–Meier estimates at 48 months, R-CVP: 83%, CVP: 77% ($P = 0.029$)	None
Marcus <i>et al.</i> 2017; Hiddemann <i>et al.</i> 2017 (GALLIUM) ^{19,20}	BR, R-CHOP or R-CVP followed by R maintenance (n = 601); G-B, G-CHOP, G-CVP followed by G maintenance (n = 601)‡	41	At 3 years, INVa, R-chemo: 75%, G-chemo: 82%, HR: 0.68 ($P = 0.0016$). IRCa, R-chemo: 79%, G-chemo: 83%; HR: 0.72 ($P = 0.0118$)	At median 35 months follow up, R-chemo: 92%, G-chemo: 94%; HR: 0.75 ($P = 0.210$)	At median 41 months of follow up, R-chemo: 3.5%, G-chemo: 4.0%
Rummel <i>et al.</i> 2013 (STiL) ²¹	BR (n = 139 analysed); R-CHOP (n = 140 analysed)§	45	BR: not reached, R-CHOP: 41 months; HR: 0.61 ($P = 0.0072$)	Did not differ between groups (actual data NR)	NR
Salles <i>et al.</i> 2011 (PRIMA) ²²	R-CHOP, R-CVP or R-FM followed by R maintenance (n = 505); R-chemo followed by observation (n = 513)¶	36	R: 75%, observation: 58%; HR: 0.55 ($P < 0.0001$)	R: 95%, observation: 94%; HR: 0.87 ($P = 0.60$)	n = 1, in the rituximab arm

†The BRIGHT study enrolled patients with indolent non-Hodgkin lymphoma or mantle cell lymphoma, 31% of whom had follicular lymphoma (but data for these patients are not presented separately). ‡Data are presented here for patients with follicular lymphoma. GALLIUM also included 195 patients with marginal zone lymphoma. §Data are presented here for patients with follicular lymphoma. STiL also included 235 patients with other types of lymphomas. ¶All included patients received one of three non-randomised chemoimmunotherapy induction regimens (CHOP, CVP or FCM), with each participating centre choosing its preferred induction regimen. Regimens: B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CVP, cyclophosphamide, vincristine, prednisolone; FCM, fludarabine, cyclophosphamide, mitoxantrone; FM, fludarabine, mitoxantrone; G-chemo, obinutuzumab, chemotherapy (CHOP, CVP or B); R, rituximab; R-chemo, rituximab, chemotherapy (CHOP, CVP or B). HR, hazard ratio; INVa, investigator-assessed; IRCa, independent review committee-assessed; NR, not reported; OS, overall survival; PFS, progression-free survival; STiL, Study group indolent Lymphomas.

investigators reported increased PFS in the FL subgroup (n = 279; median PFS not reached in BR arm vs 40.9 months in R-CHOP arm; hazard ratio (HR): 0.61; $P = 0.0072$), as well as in the mantle cell lymphoma and Waldenström, macroglobulinaemia subgroups, but there was no PFS advantage in the marginal zone lymphoma subgroup.^{21,29} Results after a median follow up of 87 months confirmed the PFS benefit for the entire group of patients (data not reported separately for FL); however, a significant improvement in OS was not seen.²⁹ An even more recently updated analysis, with a median follow up of 113 months, showed a significantly increased time to next treatment (TTNT) with BR versus R-CHOP in patients with indolent lymphomas (median TTNT not reached vs 56 months respectively).³⁰ In the BRIGHT study, BR was shown to be non-inferior to R-CHOP/R-CVP in terms of clinical response, with more

vomiting and drug hypersensitivity reactions but less peripheral neuropathy and alopecia relative to R-CHOP/R-CVP.¹⁶ Longer follow up of BRIGHT confirmed the PFS advantage of BR over R-CHOP/R-CVP, with 5-year PFS rates of 65.5 and 55.8% respectively (HR: 0.61; $P = 0.0025$).¹⁷ Most of the difference in PFS was seen in patients with mantle cell lymphoma (HR: 0.40; $P = 0.0035$) rather than the other indolent histological subtypes (HR: 0.70; $P = 0.0582$).

Additional data on chemoimmunotherapy with bendamustine in FL came from the GALLIUM study, in which patients were randomly assigned to induction treatment with obinutuzumab-chemotherapy (with three doses of obinutuzumab in the first cycle) or rituximab-chemotherapy, with responding patients receiving maintenance treatment for up to 2 years with the same antibody.¹⁹ The chemotherapy backbone (bendamustine, CHOP or CVP)

was pre-selected by each site, with all patients at that location receiving the same regimen. Bendamustine was administered to 57% of patients, CHOP to 33% and CVP to 10%. Obinutuzumab-chemo demonstrated superiority to rituximab-chemo in terms of estimated 3-year rates of investigator-assessed PFS (80.0 vs 73.3%, respectively), the primary end-point, with a HR for progression, relapse or death of 0.66 ($P = 0.001$) after a median follow up of 34.5 months.¹⁹ Three-year investigator-assessed PFS data in the group receiving bendamustine induction (BR: 76.4%; bendamustine plus obinutuzumab (G-B): 84.1%; HR: 0.63; $P = 0.0062$) were consistent with overall results²⁰; however, comparison between chemotherapy backbones was neither randomised nor a pre-specified end-point, and patients receiving bendamustine tended to be older with more comorbidities, while more patients receiving CHOP had high-risk FLIPI and bulky disease. The rate of fatal adverse events during the 41-month median follow up was 5.3% (36/676) in patients who received bendamustine as part of induction and 1.8% (9/513) in those who received CHOP or CVP as part of induction.³¹

Infections

It is challenging to compare the infectious complications of BR and R-CHOP. Rates of infection were lower in patients treated with BR than in those treated with R-CHOP during the main observation period of the StiL trial, despite the lower rate of granulocyte colony-stimulating factor use in the BR group (4%, vs 20% in the R-CHOP group).²¹ Rates of infection were similar between treatment groups in the BRIGHT study.¹⁶ Information on infections during long-term follow up was not meticulously collected in the StiL trial, and no adverse event data were collected during the 5-year follow-up period in the BRIGHT study.¹⁷

In the GALLIUM study, in which all responding patients continued antibody maintenance for 2 years (median follow up: 35 months), the rates of infection of grades 3–5 in patients who received bendamustine as part of induction was 7.8% (53/676) in the induction phase, 14.7% (91/617) during the maintenance and observation phase and 5.8% (31/533) during follow up.¹⁹ In patients who received CHOP or CVP as part of induction, the rate of grades 3–5 infection events was 6.6% (34/513) in the induction phase, 5.2% (24/466) during the maintenance and observation phase and 1.9% (7/360) during follow up.¹⁹ Significant T-lymphopenia was observed in patients who received bendamustine induction, with prolonged recovery both during and after maintenance, whereas patients receiving CHOP and CVP experienced minimal changes in T-cell counts.³¹ An analysis by chemotherapy regimen with a longer median follow up of 41 months showed an overall rate of grades 3–5 infections of 22.9%

(155/676) in patients who received bendamustine as part of induction and 12.1% (62/513) in those who received CHOP or CVP as part of induction.²⁰ More patients aged ≥ 70 years who were treated with bendamustine experienced fatal events before new anticancer treatment, compared to either CHOP or CVP (13% vs 2% vs 4%, respectively); however, in patients aged < 70 years the incidence was similar (3% vs 2% vs 1%, respectively).³¹

In the phase Ib GAUDI study ($N = 81$), the rate of infection during induction was 54% in patients receiving obinutuzumab plus bendamustine and 63% in those receiving obinutuzumab plus CHOP and was 72 and 58%, respectively, in the two groups during subsequent obinutuzumab maintenance.³² Post-marketing data from patients treated with bendamustine show a risk of opportunistic infections, including *Pneumocystis jirovecii* pneumonia, cytomegalovirus infection and varicella zoster virus.³³

Secondary neoplasms

The rate of secondary neoplasms in the GALLIUM study during the 41.1-month median follow up was 8.9% (60/676) in patients who received bendamustine as part of induction and 4.5% (23/513) in those who received CHOP or CVP as part of induction,²⁰ and rates of grades 3–5 non-melanoma skin cancer were 1.5% (10/676) and 0.2% (1/513), respectively, in the two groups.³⁴ Meticulous annual skin checks for cutaneous cancers are thus important in patients treated with bendamustine, particularly in the Australian and New Zealand setting.

Other special precautions that are recommended when using bendamustine are presented in the Box 1 below. In addition, all patients with lymphoma should adhere to current immunisation recommendations.

Box 1 Special precautions in using bendamustine

- Because BR can depress both cellular and humoral immunity, live vaccines, such as the herpes zoster vaccine, should be avoided, and patients with hepatitis B should be given antiviral prophylaxis.³⁵
- Patients should be monitored and/or receive prophylaxis for unusual infections (i.e. *pneumocystis jirovecii*) and related complications.³⁶
- Patients with recurrent infection should be tested for hypogammaglobulinaemia.
- Patients may also benefit from tetanus re-vaccination and pneumococcal vaccination if antibody titres are non-protective.

Lenalidomide and rituximab

Following a phase II study demonstrating encouraging activity and safety in untreated patients,³⁷ an international

phase III study (RELEVANCE) was performed in which patients with treatment-naïve high-tumour-burden FL were randomised to either the immunomodulatory drug lenalidomide and rituximab or chemoimmunotherapy (investigators choice of R-CHOP, BR or R-CVP) followed by rituximab maintenance.³⁸ The co-primary end-points were complete remission (CR) or CR unconfirmed (CRu) at 120 weeks and PFS, and the study was designed to show superiority for the experimental arm; 1030 patients were randomised and after a median follow up of 37.9 months, superiority was not established for either end-point (CR/CRu rate 48 vs 53%; 3-year PFS 77 vs 78%; $P = 0.13$ and 0.48 respectively). Given the results of this study, chemoimmunotherapy remains the standard of care, and this combination is not listed in the PBS in Australia.

Antibody maintenance

Patients with FL who achieve a partial or complete response following induction therapy with either R-CVP or R-CHOP are eligible for PBS-subsidised rituximab maintenance therapy (up to 12 doses or 2-year treatment duration, whichever comes first). The pivotal study supporting the use of rituximab maintenance following rituximab-containing induction therapy was PRIMA, in which 1217 patients with FL fulfilling GELF criteria for treatment received one of three chemoimmunotherapy regimens (R-CVP, R-CHOP or R-FCM) as induction, and patients who achieved partial response or better ($n = 1019$) were randomised to either rituximab maintenance (375 mg/m² intravenously every 2 months for 2 years) or observation.²² After a median follow up of 36 months, patients randomised to rituximab maintenance experienced substantial benefit in PFS (the primary end-point) relative to those who were observed (3-year PFS: 74.9 vs 57.6%; HR: 0.55, $P < 0.001$).²² The benefit in PFS was seen irrespective of baseline factors, including gender, age, FLIPI, induction chemotherapy (with the exception of F-CM due to low patient numbers) and response to induction. There was no apparent difference in patient-reported global health status or quality of life between the arms, nor was there a significant difference in serum immunoglobulins. However, patients who received rituximab maintenance did experience an increased rate of grades 3–4 adverse events (24 vs 17%; risk ratio: 1.46; $P = 0.002$) and grades 2–4 infections (39 vs 24%; risk ratio: 1.62; $P < 0.001$). The majority of these were sinopulmonary in nature. The long-term outcomes from this study were presented in abstract form, and after a median duration since randomisation of 6.1 years³⁹ and 9.7 years (in patients agreeing to long-term follow up),⁴⁰ the PFS advantage for patients allocated to rituximab maintenance persisted (6-year PFS: 59.2 vs 42.7%, HR: 0.58, $P < 0.001$ ³⁹; 10-year estimated PFS: 51 vs

35%, HR: 0.60⁴⁰). No unanticipated late toxicity signals were observed, and there was no difference in the response rates to second-line therapy. OS was excellent in both arms and not significantly different for those who receive rituximab maintenance (6-year OS: 87.4 vs 88.7%³⁹; 10-year OS estimates: 80% in each treatment arm⁴⁰).

Vidal *et al.* performed a meta-analysis of seven trials that included 2317 patients in which individuals were randomised to rituximab maintenance or observation after induction, with a primary end-point of OS.⁴¹ There was substantial heterogeneity in terms of treatment population (treatment-naïve and relapsed/refractory) and induction regimens (rituximab, chemotherapy or chemoimmunotherapy). A benefit of OS was seen only in those patients who did not receive rituximab as part of their first induction therapy. The median OS for patients randomised to rituximab maintenance was 12 years, compared with 11.5 years for those observed (HR: 0.79; 95% confidence interval (CI): 0.66–0.96), but there was no statistically significant difference in the subgroup that received rituximab as part of induction (HR: 0.85; 95% CI: 0.67–1.07).⁴¹

A further important caveat is that, at the time of writing, there are limited data supporting rituximab maintenance after bendamustine induction. In a recent retrospective analysis of patients with FL treated at MD Anderson Cancer Center in the United States, among the 33 patients treated with BR followed by rituximab maintenance, the 3-year PFS was an encouraging 97%.⁴²

Rummel *et al.* recently reported initial results from the StiL NHL7-2008 trial (MAINTAIN, NCT00877214) in which patients with treatment-naïve follicular, indolent or mantle cell lymphoma receive six cycles of bendamustine followed by either 2 or 4 years of maintenance rituximab.⁴³ Although the median PFS and OS are not yet reached, the preliminary data after median observation time of 36 months from randomisation suggest only a trend toward improvement in PFS with 4 years versus 2 years of maintenance (HR: 0.63; 95% CI: 0.36–1.11), with no difference in OS.⁴³ After 75 months of follow up, 17 patients (2.8%) had died from infection.⁴⁴ However, the study compares different durations of rituximab maintenance, rather than maintenance with observation alone. In a *post hoc*, retrospective analysis of the BRIGHT data, patients responding to BR who received maintenance rituximab had superior PFS (HR: 0.50; 95% CI: 0.26–0.94; $P = 0.0295$) and trended towards superior overall OS (HR: 0.39; 95% CI: 0.14–1.05; $P = 0.0537$) relative to no maintenance.⁴⁵ In patients responding to R-CHOP/R-CVP, rituximab maintenance was associated with similar PFS (HR: 0.66; 95% CI: 0.38–1.16; $P = 0.1443$) but superior OS (HR 0.32; 95% CI: 0.10–1.05; $P = 0.0481$), compared with no maintenance.⁴⁵

Interestingly, recent ESMO guidelines recommend rituximab maintenance irrespective of induction chemotherapy regimen.⁵ In contrast, the authors of the NCCN guidelines consider rituximab maintenance ‘optional’ and highlight the lack of data following bendamustine induction.⁴⁶ In a contemporary Australian setting, patients who receive rituximab-containing induction regimens should be considered for rituximab maintenance based on substantial PFS benefit for those patients treated with R-CHOP or R-CVP. Given the paucity of randomised data supporting a clear benefit for rituximab maintenance after BR (and as it is not reimbursed in Australia), we cannot routinely recommend it at this time. Notwithstanding this, all patients in the GALLIUM trial received either rituximab or obinutuzumab maintenance after induction chemoimmunotherapy, with a significant PFS advantage in patients receiving obinutuzumab. Therefore, paradoxically, maintenance obinutuzumab is PBS listed when used after induction with G-B. For younger, fit patients at low risk of infectious complications, the use of G-B should be considered over BR; however, it must be noted that follow up of the GALLIUM study remains relatively short for a patient population with such a prolonged median OS.

Response assessment and monitoring

PET status at the end of induction therapy in FL has been demonstrated to be more highly predictive of PFS and OS than CT-based response assessment and assists clinicians to differentiate those patients at the highest risk of relapse from those likely to experience many years in remission.⁸ This predictive power of achieving complete metabolic remission (CMR) has been confirmed in the GALLIUM study.⁴⁷ The currently recruiting PETReA study aims to quantitate the benefit of rituximab maintenance in patients who achieve CMR following induction chemoimmunotherapy and identify any benefit of addition of lenalidomide to rituximab maintenance in patients who fail to do so.¹⁰

In the longer term, patients should be observed with careful history-taking and physical examination every 3–6 months depending on their pretreatment risk factors and

PET response.^{5,48} A full blood count, renal and liver function tests and serum lactate dehydrogenase are recommended. For patients with neck irradiation, ongoing thyroid function surveillance is indicated. On the basis of published studies, routine surveillance CT scans are discouraged and follow-up imaging should be prompted by clinical indication,⁴⁸ although the judicious use of scanning in patients with residual abdominal masses is appropriate.

Refractory relapsed setting

Patients with primary refractory disease have poor outcomes and should be considered for aggressive therapy, including transplantation or novel agents. A similar approach should be taken in patients relapsing within 2 years.⁴⁹ Histological transformation to high-grade lymphoma is a risk that needs to be considered in the event of disease refractoriness or recurrence in the first year (in PRIMA, 58% of all histological transformations occurred in the first year after treatment) and may require intensive salvage with autologous stem cell transplantation.⁵⁰ A detailed discussion of relapsed/refractory FL is beyond the scope of this article.

Conclusion

Outcomes for most patients with newly diagnosed FL are favourable, with median OS exceeding 15 years. For patients with high-tumour-burden advanced-stage disease, chemoimmunotherapy is the current standard of care, with two anti-CD20 antibody choices and several options of chemotherapy backbone. Goals of care, patient fitness and patient wishes should be central to treatment decisions. Bendamustine is highly active, with less alopecia, peripheral neuropathy and cardiotoxicity than R-CHOP, and trial results have suggested a PFS advantage for BR; however, some studies have shown higher serious infection rates, particularly when followed by maintenance anti-CD20 antibody. Beyond the new chemoimmunotherapy options discussed, it is hoped that emerging molecularly targeted therapies may further change the landscape for induction therapy in FL in the near future.

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