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

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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 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 on the Pharmaceutical Benefits Scheme has expanded the first-line treatment options in Australia to include bendamustine in combination with rituximab for patients with Grade 1–2 disease. In the FL subgroup of the StiL trial, therapy with bendamustine plus rituximab significantly increased PFS compared with rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), without rituximab maintenance. Initial tolerability may be more favourable with bendamustine than other therapies overall, but clinical vigilance is still required

because of concerns of late infectious toxicities associated with prolonged T-cell depletion.

Keywords: follicular lymphoma; disease management; bendamustine; rituximab; induction chemotherapy.

Introduction

While the incidence of non-Hodgkin lymphoma in Australia has increased over the last three decades,[1] 5-year survival rates for the disease have improved.[1] Nationwide, 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 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 around 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 (WHO) classification, is determined by the number of centroblasts per high-powered field. Grades 1 to 3A are considered histologically low grade FL. However, patients with Grade 3A disease were excluded from a number of 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 revised version (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 prognostic, however, in the rituximab era with 5 and 10 year follow-up data[7] and is widely used in clinical practice. There have been no direct comparison 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 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 radiotherapy (RT), given either with or without chemotherapy combined with the anti-CD20 monoclonal antibody rituximab (chemoimmunotherapy), is recommended. For advanced-stage III and IV disease, 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 bendamustine on the Pharmaceutical Benefits Scheme (PBS) has

expanded the first-line treatment options in Australian clinical practice to include bendamustine in combination with rituximab (BR) 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 in 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 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 as 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 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 judgment 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 stage III and IV disease that is symptomatic and/or with high tumour burden is chemoimmunotherapy. This is frequently followed by rituximab maintenance therapy (see 'Rituximab maintenance' section below) 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 mitoxantrone (R-FM);[15] 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 in choosing the most appropriate regimen for individual patients.

The utility of first-line therapy with BR, recently listed on the PBS in Australia, has been examined in two randomised studies. In the 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 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 Waldenströms 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 recent 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 (hazard ratio [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 histologic 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 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 showed superiority to rituximab-chemo in terms of estimated 3-year rate of investigator-assessed PFS (80.0% vs 73.3%, respectively), the primary endpoint, 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: 84.1%; HR: 0.63; P = 0.0062) were consistent with overall results;[20] however, comparison between chemotherapy backbones was neither randomised, nor a pre-specified endpoint 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 41 months 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, but there was arguably a lower than usual rate of granulocyte-colony stimulating factor use than in the R-CHOP group (20%, vs 4% in the BR 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 grade 3–5 infection 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 grade 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 grade 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]

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 41.1 months 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 grade 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 text box below. In addition, all patients with lymphoma should adhere to current immunisation recommendations.

Text box. 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 jiroveci*) 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 follicular lymphoma were randomised to either the immunomodulatory drug lenalidomide and rituximab or chemo-immunotherapy (investigators choice of R-CHOP, BR or R-CVP) followed by rituximab maintenance.[38] The co-primary endpoints 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 endpoint (CR/CRu rate 48 vs 53%; 3 year PFS 77 v 78%; *P*=0.13 and 0.48 respectively). Given the results of this study, chemo-immunotherapy remains standard of care and this combination is not PBS-listed in Australia.

Rituximab 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 years 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 (375mg/m^2 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 endpoint) 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 sex, 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 grade 3–4 adverse events (24% vs 17%; risk ratio: 1.46; $P = 0.002$) and grade 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 since randomisation of 6.1 years[39] 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: 0.60[40]). 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 arm[40]).

Vidal *et al.* performed a meta-analysis of seven trials including 2317 patients in which individuals were randomised to rituximab maintenance or observation after induction, with a primary endpoint 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 in 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: 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 USA, 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 a trend toward improvement in PFS with 4 years versus 2 years 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 trend toward 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, virtually all patients receive rituximab-containing induction regimens and thus rituximab maintenance should be considered, 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.

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 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 pre-treatment risk factors

and PET-response.[5, 48] A complete 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 judicial 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.

Summary

Outcomes for most patients with newly diagnosed with FL are favourable, with median OS exceeding 15 years. For patients with high tumour burden advanced stage disease, chemo-immunotherapy is the current standard of care, with several options of chemotherapy backbone. Goals of care, patient fitness and 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. Improved anti-CD20 antibodies such as obinutuzumab and emerging molecularly targeted therapies may further change the landscape for induction therapy in FL in the near future.

References

1. Australian Institute of Health and Welfare. Cancer in Australia 2017. Cancer series no. 101. Cat. no. CAN 100. Canberra: AIHW. 2017.

2. Leukaemia Foundation Australia. Follicular lymphoma. Available at: http://www.leukaemia.org.au/blood-cancers/lymphomas/non-hodgkin-lymphoma-nhl/follicular-lymphoma/follicular-lymphoma. Accessed 12 February 2018.

3. Cancer Council Victoria. Lymphoma, Lifestyle, Environment and Family (LEAF) study (https://www.cancervic.org.au/).

4. Tan D, Horning SJ, Hoppe RT, Levy R, Rosenberg SA, Sigal BM, et al. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. Blood. 2013;122(6):981–7.

5. Dreyling M, Ghielmini M, Rule S, Salles G, Vitolo U, Ladetto M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v83–90.

6. Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol. 2009;27(27):4555–62.

7. Provencio M, Sabin P, Gomez-Codina J, Torrente M, Calvo V, Llanos M, et al. Impact of treatment in long-term survival patients with follicular lymphoma: A Spanish Lymphoma Oncology Group registry. PLoS One. 2017;12(5):e0177204.

8. Trotman J, Luminari S, Boussetta S, Versari A, Dupuis J, Tychyj C, et al. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. The Lancet Haematology. 2014;1(1):e17-e27.

9. Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood. 2016;127(17):2055–63.

10. EU Clinical Trials Register [Internet]. European Medicines Agency, London 1995. EudraCT Number: 2016-004010-10. PETReA: Phase 3 evaluation of PET-guided, Response-Adapted therapy in patients with previously untreated, high tumour burden follicular lymphoma [Internet]. 2018 [cited 27/06/18]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004010-10

11. MacManus MP, Fisher R, Roos D, O'Brien P, Macann AMJ, Christie D, et al. Treatment with 6 cycles of CVP or R-CVP after involved field radiation therapy (IFRT) significantly improves progression-free survival compared with IFRT alone in stage I–II low grade follicular lymphoma: results of an international randomized trial. Int J Radiat Oncol. 2016;96(5):938 (abstract).

12. Friedberg JW, Byrtek M, Link BK, Flowers C, Taylor M, Hainsworth J, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol. 2012;30(27):3368–75.

13. Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003;362(9383):516–22.

14. Ardeshna KM, Qian W, Smith P, Braganca N, Lowry L, Patrick P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol. 2014;15(4):424–35.

15. Federico M, Luminari S, Dondi A, Tucci A, Vitolo U, Rigacci L, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013;31(12):1506–13.

16. Flinn IW, van der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944–52.

17. Flinn IW, van der Jagt R, Chang JE, Wood P, Hawkins TE, Macdonald D, et al. First-line treatment of iNHL or MCL patients with BR or R-CHOP/R-CVP: results of the BRIGHT 5-year follow-up study. J Clin Oncol. 2017;35:7500 (abstract).

18. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol. 2008;26(28):4579–86.

19. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med. 2017;377(14):1331–44.

20. Hiddemann W, Barbui AM, Canales Albendea MA, Cannell PK, Collins GP, Durig J, et al. Immunochemotherapy with obinutuzumab or rituximab in previously untreated follicular lymphoma (FL) in the randomized phase III GALLIUM study: analysis by chemotherapy regimen. Hematol Oncol. 2017;35(Suppl S2):117–9.

21. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grunhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.

22. Salles G, Seymour JF, Offner F, Lopez-Guillermo A, Belada D, Xerri L, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet. 2011;377(9759):42–51.

23. Herold M, Dolken G, Fiedler F, Franke A, Freund M, Helbig W, et al. Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: chemotherapy versus chemotherapy plus rituximab. Ann Hematol. 2003;82(2):77–9.

24. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106(12):3725–32.

25. Bachy E, Houot R, Morschhauser F, Sonet A, Brice P, Belhadj K, et al. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. Haematologica. 2013;98(7):1107–14.

26. Hiddemann W, Dreyling M, Unterhalt M. Rituximab plus chemotherapy in follicular and mantle cell lymphomas. Semin Oncol. 2003;30(1 Suppl 2):16–20.

27. Luminari S, Ferrari A, Manni M, Dondi A, Chiarenza A, Merli F. Long-term results of the FOLL05 trial comparing R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage symptomatic follicular lymphoma J Clin Oncol. 2017;[Epub ahead of print].

28. Limat S, Daguindau E, Cahn JY, Nerich V, Brion A, Perrin S, et al. Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma. J Clin Pharm Ther. 2014;39(2):168–74.

29. Rummel MJ, Maschmeyer G, Ganser A, Heider A, von Grunhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas – 7 year updated results from the StiL NHL1 study. Blood. 2014;124:4407 (abstract).

30. Rummel MJ, Maschmeyer G, Ganser A, Heider A, von Grunhagen U, Losem C, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: nine-year updated results from the StiL NHL1 study. J Clin Oncol. 2017;35:7501 (abstract).

31. Hiddemann W, Barbui AM, Canales MA, Cannell PK, Collins GP, Dürig J, et al. Immunochemotherapy With Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety. Journal of Clinical Oncology. 2018;0(0):JCO.2017.76.8960.

32. Grigg A, Dyer MJ, Diaz MG, Dreyling M, Rule S, Lei G, et al. Safety and efficacy of obinutuzumab with CHOP or bendamustine in previously untreated follicular lymphoma. Haematologica. 2017;102(4):765–72.

33. Medicines and Healthcare products Regulatory Agency UK. Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatitis B reactivation. Drug Safety Update. 2017;10(11):Available at: https://www.gov.uk/drug-safety-update/bendamustine-levact-increased-mortality-observed-in-recent-clinical-studies-in-off-label-use-monitor-for-opportunistic-infections-hepatitis-b-reactivation#post-marketing-data.

34. Hiddemann W, Barbui AM, Canales Albendea MA, Cannell PK, Collins GP, Durig J, et al. Immunochemotherapy with obinutuzumab or rituximab in previously untreated follicular lymphoma (FL) in the randomized phase III GALLIUM study: analysis by chemotherapy regimen. Slides presented at the 14th International Conference on Malignant Lymphoma, Lugano, Switzerland, 14–17 June 2017. Available at: http://lugano.post-ash.co.uk/wp-content/uploads/2017/07/WendyOsbourne.pdf. Accessed 13 November 2017. 2017.

35. Cheson BD, Brugger W, Damaj G, Dreyling M, Kahl B, Kimby E, et al. Optimal use of bendamustine in hematologic disorders: treatment recommendations

from an international consensus panel - an update. Leuk Lymphoma. 2016;57(4):766–82.

36. Burchardt A, Barth J, Rummel J, Sandherr M. Immunotherapy with bendamustine–rituximab as induction therapy for indolent lymphomas results in a severe lymphopenia with low CD4+ and CD8+ counts without an increase in atypical infections. First results of the Infectious Disease (ID) project of a prospective, randomized, multicentre study (StiL NHL 7-2008, MAINTAIN; NCT00877214). Hematol Oncol. 2013:32 (abstract).

37. Fowler NH, Davis RE, Rawal S, Nastoupil L, Hagemeister FB, McLaughlin P, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol. 2014;15(12):1311-8.

38. Fowler NH, Morschhauser F, Feugier P, Bouabdallah R, Tilly H, Palomba ML, et al. RELEVANCE: Phase III randomized study of lenalidomide plus rituximab (R2) versus chemotherapy plus rituximab, followed by rituximab maintenance, in patients with previously untreated follicular lymphoma. J Clin Oncol 2018;36((suppl; abstr 7500)).

39. Salles G, Seymour JF, Feugier P, Offner F, Lopez-Guillermo A, Belada D, et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy. Blood. 2013;122(21):509 (abstract).

40. Salles GA, Seymour JF, Feugier P, Offner F, Lopez-Guillermo A, Belada D, et al. Long term follow-up of the PRIMA study: half of patients receiving rituximab maintenance remain progression free at 10 years Blood. 2017;130:486 (abstract).

41. Vidal L, Gafter-Gvili A, Salles G, Bousseta S, Oberman B, Rubin C, et al. Rituximab maintenance improves overall survival of patients with follicular lymphoma – individual patient data meta-analysis. Eur J Cancer. 2017;76:216–25.

42. Cheah CY, Chihara D, Ahmed M, Davis RE, Nastoupil LJ, Phansalkar K, et al. Factors influencing outcome in advanced stage, low-grade follicular lymphoma treated at MD Anderson Cancer Center in the rituximab era. Ann Oncol. 2016;27(5):895–901.

43. Rummel MJ, Viardot A, Greil R, Hertenstein B, Lerchenmuller C, Ganser A, et al. Bendamustine plus rituximab followed by rituximab maintenance for patients with untreated advanced follicular lymphomas. Results from the StiL NHL 7-2008

Trial (MAINTAIN trial) (ClinicalTrials.gov Identifier: NCT00877214). Blood. 2014;124:3052 (congress abstract).

44. Rummel MJ, Buske C, Hertenstein B, Lerchenmüller C, Koenigsmann M, Lange E, et al. Four versus two years of rituximab maintenance (R-maintenance) following bendamustine plus rituximab (B-R): initial results of a prospective, randomized multicenter phase 3 study in first-line follicular lymphoma (the StiL NHL7-2008 MAINTAIN study). Blood. 2017;130:483 (ASH meeting slides).

45. Kahl BS, Burke JM, van der Jagt R, Chang J, Wood P, Hawkins T, et al. Assessment of maintenance rituximab after first-line bendamustine-rituximab in patients with follicular lymphoma: an analysis from the BRIGHT trial. Blood. 2017;130:484 (abstract).

46. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: B-cell lymphomas Version 22017. 2017.

47. Trotman J, Barrington S, Belada D, Meignan M, MacEwan R, Owen C, et al. PROGNOSTIC VALUE OF PET-CT AFTER FIRST-LINE IMMUNOCHEMOTHERAPY FOR FOLLICULAR LYMPHOMA IN THE PHASE III GALLIUM STUDY. Hematological Oncology. 2017;35(S2):38-40.

48. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–68.

49. Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the national LymphoCare study. J Clin Oncol. 2015;33(23):2516–22.

50. Sarkozy C, Trneny M, Xerri L, Wickham N, Feugier P, Leppa S, et al. Risk factors and outcomes for patients with follicular lymphoma who had histologic transformation after response to first-line immunochemotherapy in the PRIMA trial. J Clin Oncol. 2016;34(22):2575–82.

51. Brice P, Bastion Y, Lepage E, Brousse N, Haioun C, Moreau P, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 1997;15(3):1110–7.

Table 1. Initial workup

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

*Immunohistochemistry markers could include CD3, CD5, CD10, CD20, CD21, CD23, BCL2, BCL26 and Ki67

CT, computed tomography; PET-CT, positron emission tomography-computed tomography

Table adapted from Dreyling et al. 2016[5].

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

Parameter	**Definition of risk factors**	
	FLIPI 1	**FLIPI2**
Serum marker	Elevated LDH	Elevated β2 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

Score: 0–1 risk factors, low risk; 2 risk factors, intermediate risk; 3–5 risk factors, high risk.

*III-IV as per Ann Arbor classification

LDH, lactate dehydrogenase

Table adapted from Dreyling et al. 2016[5].

Table 3. Summary of FL treatment regimens available in Australia

Stage	Treatment	PBS listed	Source/trial	
Early stage				
Stage I	RT ± R-CVP	Yes	• ESMO: RT with curative intent[5]	RCT (non-inferiority; 614 sites; 26-month median follow-up)
			• Trans-Tasman Radiation Oncology Group/Australasian Leukaemia and Lymphoma Group: RT + R-CVP improved PFS (but not OS) vs RT alone[11]	RCT (n=150; 10yr follow-up)
			• LymphoCare study: R-chemo or RT + systemic therapy improved PFS (but not OS) vs RT alone[12]	Prospective registry data with 5yr follow-up
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	-	• Multicentre clinical trial: no difference in OS with active monitoring vs systematic therapy (median follow-up: 16 years)[13]	RCT (n=309; 16yr follow-up)
			• GELF criteria[51] • BNLI criteria[13] • NCCN criteria[46]	
Symptomatic and/or high tumour burden	R-CHOP or R-CVP , then R-maintenance	Yes	• R-CHOP improved overall response vs CHOP alone[24]	RCT (n=428; 3yr follow-up)
			• R-CVP improved OS vs CVP alone[18]	RCT (n=321; median 53 month follow-up)
			• FOLL05: R-CHOP improved PFS and time to treatment failure vs R-CVP[15]	RCT (n=501; 3yr follow-up)
	BR	Yes	• STiL: BR improved PFS vs R-CHOP in FL subgroup, and less toxicity[21, 29]	RCT (n= 514; 7yr follow-up; non-inferiority)
			• BRIGHT: BR improved PFS vs R-CHOP/R-CVP[16, 17]	RCT (n=419; 5yr follow-up; non-inferiority)
	Obinutuzumab-chemo	*	• GALLIUM: obinutuzumab-chemo improved PFS vs R-chemo[19]	RCT (n=1202; 34.5 months interim analysis)

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.
*currently under consideration for PBS listing

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

Criteria
GELF[a]
– 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 >38ºC; drenching night sweats; or loss of >10% body weight within 6 months
– Lymphocyte count >5.0 x 10^9/L
– Cytopenias (granulocytes <1.0 x 10^9/L; platelets <100 x 10^9/L)
NCCN[b]
– Candidate for clinical trial
– Symptoms
– Threatened end-organ function
– Cytopenia secondary to lymphoma
– Bulky disease (as per GELF criteria)
– Steady progression
BNLI[c]
– 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 x 10^9/L or platelets <100 x 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 (for example, isolated elevated lactate dehydrogenase or serum β2 microglobulin)

BNLI, British National Lymphoma Investigation; GELF, Groupe d'Etude des Lymphomes Folliculaires; NCCN, National Comprehensive Cancer Network.

[a]From Brice et al. 1997[51].

[b]From NCCN clinical practice guidelines 2017.[46]

[c]From Ardeshna et al. 2003.[13]

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 *et al*. 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 *et al*. 2014, 2017 (BRIGHT)[16, 17]	BR (n = 224); R-CVP (n = 119); R-CHOP (n = 104)[c]	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 *et al*. 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 *et al*. 2017; Hiddemann *et al*. 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)[d]	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 follow-up, R-chemo: 3.5%, G-chemo: 4.0%
Rummel et al. 2013 (STiL)[21]	BR (n = 139 analysed); R-CHOP (n = 140 analysed)[b]	45	BR: not reached, R-CHOP: 41months; HR: 0.61 ($P = 0.0072$)	Did not differ between groups (actual data NR)	NR
Salles *et al*. 2011 (PRIMA)[22]	R-CHOP, R-CVP or R-FM followed by R maintenance (n = 505); R-chemo followed by observation (n = 513)[a]	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

[a]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.
[b]Data are presented here for patients with follicular lymphoma. STiL also included 235 patients with other types of lymphomas.

[c]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).
[d]Data are presented here for patients with follicular lymphoma. GALLIUM also included 195 patients with marginal zone lymphoma.
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.

Figure legend

Figure 1. Flow chart of current front-line treatment approaches for follicular non-Hodgkin lymphoma in Australia.

CHOP, chemotherapy with cyclophosphamide, vincristine, doxorubicin and prednisone; IFRT, involved field radiation therapy; ISRT, involved site radiotherapy; PET, positron emission tomography; R-CHOP, CHOP in combination with rituximab; R-CVP, chemotherapy with cyclophosphamide, vincristine and prednisone in combination with rituximab.