Management of patients with follicular lymphoma treated first line with obinutuzumab

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Abstract (200 words unstructured)

Recently, obinutuzumab was included in the Australian Pharmaceutical Benefits Scheme (PBS) for use in first line, advanced or bulky stage 2, follicular lymphoma, providing more immunochemotherapy treatment options available than ever before. Rituximab with chemotherapy has been the standard of care since reimbursement in the late 90s; however, obinutuzumab-based regimens have shown superior progression free survival (PFS) in comparison to rituximab-based options, albeit at an increased risk of grade ≥3 adverse events. As median overall survival approaches 20 years or more, the long-term effects and sequencing of any strategy should be considered. Here we discuss the considerations for selection of front-line therapy, based on evidence and local Australian clinician experience, in the management of first line follicular lymphoma.

Key words (5 in alphabetical order): chemoimmunotherapy, follicular lymphoma, obinutuzumab, rituximab

Introduction

Now that there are more treatment combinations available for first line follicular lymphoma, we are faced with a potential challenge to the long-standing standard of care. Is it just as simple as switching from rituximab to obinutuzumab? Can we base our decision purely on the efficacy and safety of the phase 3 study? The existing follicular lymphoma literature has several limitations that may impact on its real world application including the biases with selection into clinical trials, limited duration of follow-up and lack of patient reported outcome data.

Translation of clinical studies requires consideration of "real-world" factors including patient and disease characteristics such as age, comorbidities, disease stage, histological subtype and importantly, patient preference. We believe that clinicians should adopt a patient-centered

approach that considers both efficacy and toxicity within each individual's context. In general, it is recommended to use the most efficacious and well-tolerated option first line so that the patient has the longest freedom from symptomatic disease and the burden of treatment, while minimizing risk of morbidity.

Current options for first line follicular lymphoma in Australia

The options for first line treatment of follicular lymphoma, subsidized under the Australian Pharmaceutical Benefits Scheme (PBS), are rituximab or obinutuzumab with a chemotherapy backbone (bendamustine, CHOP [cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), prednisone/prednisolone] or CVP [cyclophosphamide, vincristine, prednisolone]) plus the same antibody (rituximab or obinutuzumab) as maintenance therapy (excluding maintenance following rituximab-bendamustine therapy).[1]

Rituximab chemotherapy has been the standard of care for follicular lymphoma based on its efficacy in combination with chemotherapy. It has been studied in several large phase 3 trials in previously untreated follicular lymphoma, including the trial by Marcus *et al.* comparing rituximab plus CVP (R-CVP) with CVP, which demonstrated an improvement in both PFS and overall survival (OS),[2] the non-inferiority StiL NHL1 study of rituximab and bendamustine compared to rituximab and CHOP (R-CHOP),[3] and the BRIGHT study comparing rituximab-bendamustine with rituximab plus standard chemotherapy.[4]

In addition, the value of rituximab maintenance following rituximab chemotherapy (CHOP or CVP) has been demonstrated in the PRIMA trial. This study showed that two years of rituximab maintenance therapy significantly improves PFS, albeit with increased infections.[5] PRIMA led to adoption of rituximab maintenance following R-CVP or R-CHOP induction. However, questions about the use of maintenance after bendamustine remained, because it has not been studied exclusively. This means that evidence-based treatment decisions cannot always be made as

there are data gaps in the design and sequence of consecutive studies, particularly with regard to chemotherapy and maintenance.

Obinutuzumab, like rituximab, is an anti-CD20 IgG1 monoclonal antibody. However, in contrast to rituximab, obinutuzumab is fully humanized, recognizes a unique epitope of CD20, and has a modified hinge region, resulting in spatial alterations to the CD20-mAb assembly complex on B-cells. In addition the Fc region has been defucosylated enhancing FcγRIII receptor binding.[6, 7] The net effect of these changes is to augment antibody-dependent cellular cytotoxicity and phagocytosis, direct non-apoptotic cell death and diminish complement-dependent cytotoxicity.[8]

Treatment with obinutuzumab- and rituximab-based chemotherapy were compared in the phase 3 GALLIUM study in patients with previously untreated follicular lymphoma.[9] Treatment with obinutuzumab plus chemotherapy (CHOP, bendamustine or CVP), followed by obinutuzumab maintenance, significantly improved PFS and time to next anti-lymphoma treatment compared to rituximab plus chemotherapy followed by rituximab maintenance after a median follow up of 57.3 months.[10] The PFS rate was 78.1% for obinutuzumab-based chemotherapy vs 67.2% for rituximab-based chemotherapy (HR 0.73 (0.59 to 0.90); p=0.003).[10]

No difference in OS was observed between the treatment arms; however, based on the 80% 10-year OS identified in the PRIMA study, several more years of follow up would be required for enough events to occur to detect a difference in survival in the GALLIUM study (i.e. with 10 years of follow up, there is an 80% chance of detecting a 6% improvement in OS at a significance of 0.05%). Furthermore, OS differences may not be observed with relapsing patients successfully salvaged with other therapies.

Patients who received obinutuzumab in the GALLIUM study were more likely than those who received rituximab to experience grade ≥3 adverse events (79.2% vs 71.2%) and serious adverse events (48.7% vs 42.2%), although the rate of adverse events resulting in death was the

same (4.0%).[10] The most common adverse events in both arms included infusion-related reactions (IRRs), nausea and neutropenia.

This study led to obinutuzumab plus chemotherapy (with CHOP, bendamustine or CVP) and obinutuzumab maintenance (for all combinations) being subsidized by the Australian government in patients with CD20+ advanced follicular lymphoma.

Obinutuzumab dosing was based on pharmacokinetic studies and selected to achieve saturation of CD20 binding sites within the first treatment cycle.[11, 12] This is in contrast to rituximab, where no formal dose finding studies were performed. The 1000 mg dose of obinutuzumab was shown to rapidly saturate CD20 binding sites on the lymphoma cells, regardless of body surface area or body weight.[13] Furthermore, obinutuzumab has a very wide therapeutic index.

In follicular lymphoma, a dose of 1000 mg obinutuzumab is given on days 1, 8 and 15 of the first treatment cycle, and then on day 1 only for subsequent cycles of induction therapy (Table 1).[14] In the GALLIUM study, obinutuzumab was administered for six 28-day cycles when combined with bendamustine and for eight 21-day cycles when combined with CHOP and CVP.[9] As patients received CHOP for six 21-day cycles only, patients receiving obinutuzumab-CHOP received obinutuzumab alone in cycles 7 and 8. Note that the dosing schedule for follicular lymphoma is different from that for chronic lymphocytic leukemia (CLL), where obinutuzumab-related infusion reactions are more common (Table 1).

Considerations for choice of treatment in the management of first line follicular lymphoma

There is no standard approach to the first line treatment of follicular lymphoma. The choice of monoclonal antibody and chemotherapy backbone combination is based on a number of factors including patient age, comorbidities, disease stage, histological features, symptoms, toxicities, plans for maintenance therapy and patient preference. It is important to appreciate that some older patients with advanced disease will have a near normal life expectancy,[15, 16] and therefore treatment that can result in long-term morbidity are best avoided. Of course, the availability of subsidized treatment also guides the treatment approach in Australia. We have highlighted in

Table 2 a number of considerations when making the choice of induction therapies in advanced follicular lymphoma.

Choice of monoclonal antibody

As the pre-planned sub analysis of the Gallium study failed to identify a single patient population that would be more suitable for either monoclonal antibody, the choice of antibody should be based on efficacy and safety.[17] Important considerations when selecting a monoclonal antibody include judgement regarding the benefit of a prolonged treatment free interval (4 year time to next treatment 84% vs 76.7%) versus the small increased risk of febrile neutropenia (7.4% vs 4.7%) and infusion reactions (12.3% vs 7.4%).

Choice of chemotherapy backbone

The choice of chemotherapy should be based on the patient's specific comorbidity profile and preference. Considerations include alopecia, neuropathy and cardiotoxicity with CHOP and increased nausea and rash, protracted lymphopenia, and prolonged overall duration of treatment with bendamustine. It is worth noting that fatal adverse events were higher among patients receiving bendamustine in the GALLIUM trial regardless of whether the patient was randomized to rituximab- or obinutuzumab-based chemotherapy (5% and 6% respectively vs 2% with CHOP or CVP).[18] Also, clinicians may choose not to treat grade 3A disease with bendamustine due to limited prospective data. The median OS in follicular lymphoma is now over 20 years,[19] therefore the late effects of chemotherapy (including therapy related myelodysplasia and acute myeloid leukaemia, acquired immune deficiency, infertility and stem cell toxicity) are very important considerations.

Considerations for later lines of therapy

Generally, a different chemotherapy backbone from that used in first line therapy is used in the second line. Repeated cycles of purine analogues (including bendamustine) are generally not recommended, due to concerns about lymphodepletion, action and risk of myelodysplasia and

other secondary neoplasms.[9, 18] For patients who receive primary therapy with bendamustine, R-CHOP may be preferred if the duration of the first remission was less than 3 years. R-CHOP may also be the preferred option if there was progression during or shortly after completion of maintenance and in the case of suspected histologic transformation to large B-cell lymphoma. Patients who are fit and are ≤70 years who progress within two years of induction (POD24 - see below) should be considered for salvage therapy and autologous stem cell transplant.[15] This higher risk population is also frequently included in clinical trials of novel agents, so such opportunities should be explored in every case.

Obinutuzumab-bendamustine is also PBS subsidized for "rituximab-refractory" patients (defined as no response or relapse during or within 6 months of the last dose of rituximab).[1] The GADOLIN study demonstrated that obinutuzumab-bendamustine plus obinutuzumab maintenance, in patients with refractory disease following R-CHOP or R-CVP as first line therapy, prolonged PFS and OS compared to second line bendamustine therapy alone.20 After 31.8 months median follow-up the median investigator-assessed PFS was 25.8 months (R-bendamustine arm) vs 14.1 months (bendamustine alone arm); HR 0.57 (95% CI 0.44 to 0.73; $p<0.0001$). The HR for OS was 0.67 (95% CI 0.47 to 0.96; $p<0.0269$, risk reduction 33%).

Surrogate measures and their role in guiding the management of follicular lymphoma

As the median time to progression is now 10 years, and median OS is over 20 years, there is a need for surrogate endpoints to evaluate therapeutic strategies in follicular lymphoma in a reasonable timeframe. POD24 (Progression of disease by 24 months post induction), complete response at 30 months after initiation of treatment (CR30), and end of induction (EOI) PET scanning have been suggested. However, only CR30 has been formally validated as a surrogate for PFS.[21-23] These surrogate endpoints, and others, provide us with additional information to assist in the decision-making process for treatment and management of follicular lymphoma.

TTNT

The majority of patients with stage III/IV follicular lymphoma are still expected to relapse at some point and given that some of the novel/targeted agents require continuous dosing, treatment-free interval with good quality of life is a meaningful goal for patients. TTNT is considered more relevant to patients than PFS as low volume asymptomatic relapse does not require immediate treatment and patients can continue to live life normally.[24] A long TTNT enables patients to plan work, study, holidays, life events and finances. The TTNT in the GALLIUM study was 84.2 months in the obinutuzumab-chemotherapy arm and 76.7 months in the rituximab-chemotherapy arm (HR 0.70 (0.54 to 0.90), p=0.0046). A similar TTNT of approximately 78 months with rituximab was also reported in recent update of the PRIMA study[25]

In clinical trials, frequent computerized tomography (CT) scans mean that progressive disease is detected earlier than in clinical practice. However, follow up is rarely performed beyond 5 years, therefore accurate determination of PFS is often not possible. In retrospective studies, where serial scans are not performed, TTNT is a more objective measure of progression. However, TTNT definition can vary, therefore a close reading of definitions in maintenance studies is required to understand the impact.

POD24

Progression of Disease within 24 months (POD24) from initiation of chemotherapy has been identified as a marker of extremely poor outcome with only half of those progressing at this time being alive at 5 years. In the original POD24 study 20.8% of patients receiving R-CHOP had progressed within 2 years.[15]

In the GALLIUM study, POD24 had been experienced by 18.9% (95% CI: 15.9% to 22.4%) in the rituximab-chemotherapy arm, and 12.5% (95% CI: 10.1% to 15.6%) in the obinutuzumab-chemotherapy arm, a relative risk reduction for early progression or death for any reason of

33.9% (95% CI: 12.8 to 49.8).[26] Patients who do not experience progression of disease within 24 months may essentially have a normal life expectancy.[15, 16]

PET

PET is now the standard of care imaging modality for accurate staging and assessing disease characteristics at baseline. While baseline PET may be used to select sites to biopsy to identify transformed disease in patients with a clinical suspicion of such, baseline maximum standardized uptake value did not predict future histological transformation from follicular lymphoma to aggressive lymphoma in 595 patients in the GALLIUM study.[27] Multiple studies have confirmed that a positive PET scan at EOI chemotherapy defines a group who fail to obtain complete metabolic response (CMR) with a five-fold risk of early progression and five-fold risk of death, and who may derive the greatest benefit from maintenance or consolidation *therapies.22, 28-31 Radiotherapy may be considered where there are isolated sites that remain* PET positive. EOI PET is useful in assisting patients to make life decisions based on the probability of relapse.

PET-response adapted therapy in now being incorporated in clinical trials designed to maximize efficacy while minimizing toxicity of first-line therapy for follicular lymphoma. A randomized comparison of standard maintenance rituximab and response adapted post-induction therapy based on MRD and PET analysis is scheduled in the FOLL12 study (EUDRACT 2012-003170-60), which has completed recruitment of 810 patients. Patients with no evidence of residual disease following induction therapy undergo observation, while those with a positive PET scan have radioimmunotherapy added to their rituximab maintenance therapy. Similarly, the recently commenced PETReA study (EudraCT 2016-004010-10) is examining the role of end of induction PET in two separate randomized groups to optimize therapy after induction with rituximab-chemotherapy in patients with previously untreated high tumor burden follicular lymphoma Stage I to IIIA. The study will quantitate the PFS benefit as well as the rate of infections from antibody maintenance in patients who achieve CMR, compared to those who do

not receive maintenance. Patients who fail to achieve complete metabolic response will be randomized to antibody maintenance alone compared to maintenance with the addition of lenalidomide.

MRD

MRD is proposed as another surrogate measure of response, albeit limited by sensitivity. More sensitive MRD assays are currently under development and will likely be better predictors of clinical progression. In the GALLIUM study, 815/1101 (74%) patients with MRD evaluable samples had an MRD marker meeting the predefined quality criteria. 92% of MRD evaluable patients receiving G-chemotherapy achieved MRD negativity vs 85% of those receiving R-chemotherapy.[32] Patients who achieved MRD negativity experienced longer PFS. Of 298 patients with both MRD and EOI PET analysis, 250 patients achieved both complete metabolic response (CMR) and MRD negativity. Risk of progression or death in patients achieving only CMR or MRD negativity was 2.1-fold greater than that in patients who achieved both, suggesting that EOI PET and MRD responses could provide complementary information.[33] Further data are required to understand the interaction between MRD status and EOI PET-CT results. PET-CT scans provide a more immediately applicable and measurable tool for prognostication at the end of induction.

Best practice guidance for managing patients receiving obinutuzumab in follicular lymphoma

Obinutuzumab maintenance therapy

The benefit of rituximab maintenance (mainly following R-CHOP and R-CVP-based induction) was first demonstrated in the PRIMA study.[34] which lead to regulatory approval. However, reimbursement of rituximab maintenance following bendamustine-based induction was not approved in Australia based on a lack of safety and efficacy data in this setting.

In contrast, the GALLIUM study used maintenance in all arms and PBS subsidy is available for obinutuzumab maintenance following obinutuzumab-bendamustine therapy. However, it should be noted that there are no studies quantifying the additional benefit derived from maintenance therapy with obinutuzumab following obinutuzumab versus observation after first line induction.

There are long-term safety and efficacy data supporting the use of rituximab from the follow up of the PRIMA, BRIGHT, FOLL05 and StiL NHL1 studies. The distinction between safety in induction and safety in maintenance is important, and there is an interaction between chemotherapy backbone and the safety of the antibody partner, in induction and likely also in maintenance .[34-37] Consequently, tolerability of maintenance, choice of chemotherapy and the patient preference are key considerations when deciding whether maintenance therapy should be used. Some patients do not like the idea of returning to the hospital every 2-3 months for maintenance therapy, while other patients prioritize the prolonged period without second line chemotherapy.

Patients with a tendency to chest and sinus infections prior to induction are generally considered unsuitable for maintenance therapy, and such patients (13%) were excluded from enrollment in the MAINTAIN study of 2- vs 4-year maintenance rituximab after R-bendamustine therapy. In GALLIUM, the incidence of adverse events, after Bendamustine chemotherapy, such as the risk of grade 3-5 infection, whether they received rituximab or obinutuzumab (induction and maintenance) was concerning (obinutuzumab-bendamustine 26%, R-bendamustine 20%, compared to obinutuzumab -CHOP and R-CHOP both 12% and obinutuzumab -CVP and R-CVP both 13%).[18] There were eight patients (2.4%) who received obinutuzumab -bendamustine who had fatal adverse events classified as “infections and infestations” compared with 2 patients (0.6%) in the R-bendamustine arm, 1 patient (0.5%) in the obinutuzumab -CHOP arm and no patients in the R-CHOP and obinutuzumab -CVP and R-CVP arms.[17] Four of the eight fatal infections in the obinutuzumab-bendamustine group occurred after the initiation of new anti-

cancer therapy. Fatal events occurring before new anticancer treatment were more common with bendamustine (16 of 119, 13%) than CHOP (one of 55, 2%) and CVP (one of 25, 4%).

The MAINTAIN study[38] and post-hoc analysis of the BRIGHT study where patients were randomized to R-bendamustine or standard therapy did not raise the same concerns, but data collection for infectious complications was not prolonged in BRIGHT and these observations provide little information about the safety of maintenance. Also, prophylaxis against infection was not mandated in the GALLIUM and MAINTAIN studies and was used less often in the bendamustine arm.[9]

Obinutuzumab-bendamustine followed by obinutuzumab maintenance is a reasonable option, however the clinician should be aware of the increased number of fatal events observed in this arm in the GALLIUM study, (mainly occurring during the maintenance phase) and consider prophylaxis and/or heightened awareness for opportunistic infections to facilitate early treatment withdrawal.

Does receiving first line obinutuzumab impact on options at relapse?

The choice of second line therapy will depend on factors such as whether progression of disease was within 24 months, whether the patient is a candidate for autologous stem cell transplant, whether histological transformation has occurred, which chemotherapy backbone was used in first line therapy, clinical trial availability and patient fitness. There are no data suggesting that patients who have progressive disease after obinutuzumab-chemotherapy will be any less responsive to second line therapy than after rituximab-chemotherapy. The survival of both the obinutuzumab and rituximab arms after a POD24 event was similar.[26]

The approach to salvage therapy depends on the durability of response and tolerability of the first line regimen. Often CHOP is used as a backbone in those who received first line bendamustine. Currently in Australia bendamustine is only subsidized for use in combination with obinutuzumab (not rituximab) as second line therapy in the rituximab refractory

population. Re-treatment options after obinutuzumab -CHOP include R-CVP. Readers are encouraged to explore clinical trial options in all patients with relapsed disease.

Infusion related reactions (IRRs): incidence, prevention, and treatment, when using obinutuzumab

In the GALLIUM study, the incidence of IRRs higher with obinutuzumab (59.3%; 95% CI 55.3% to 63.2%) and rituximab (48.9%; 95% CI 44.9% to 52.9%, p<0.001) with the majority of reactions occurring during induction.[9] Grade 3 or higher reactions occurred in 6.7% of patients receiving obinutuzumab and in 3.7% of those receiving rituximab.[17] Rates of Grade 3 or higher reactions were low during maintenance treatment. As in CLL, patients with follicular lymphoma with high tumor burden and/or high circulating white cell count may be at increased risk of severe IRRs.

IRRs occur mainly during the infusion of the first 1000 mg of obinutuzumab. At cycle 1 day 1 patients with very high tumor burden and/or high circulating white cell count may need to be admitted to hospital overnight. Dosing strategies to reduce IRRs are outlined in Table 1. In contrast to patients with CLL, a split starting dose is usually not required in follicular lymphoma, but this may be considered in patients with a large circulating burden of lymphoma cells. Pre-medications with intravenous corticosteroid at least 60 minutes prior, as well as paracetamol and antihistamine can reduce the risk of IRRs. From the CLL11 study,[39] it was found that hydrocortisone was suboptimal, premedication should occur with either methylprednisolone 80 mg intravenously, or dexamethasone 20 mg intravenously. Hypotension may occur during obinutuzumab infusions, therefore consider withholding antihypertensive treatments for 12 hours prior to and throughout each infusion, and for the first hour after administration.

It is also important to prepare the patient for the possibility of an infusion reaction. Medical and nursing staff should be aware of the possibility of IRRs and there should be a plan in place for their management. Other recommendations are that the patient is well hydrated; has a second intravenous cannula inserted if at high risk of IRRs, and resuscitation facilities are close at hand.

The treatment strategy depends on the severity of the IRR.[14] Generally, the infusion should be stopped, steroids and antihistamines given and once symptoms have resolved the infusion

recommenced at a slower rate. For patients with Grade 1 or 2 reactions, it may be sufficient to reduce the infusion rate, treat the symptoms and continue the infusion upon resolution of the symptoms. Patients with Grade 3 reactions require temporary interruption of the infusion and treatment of symptoms. Upon resolution of the symptoms, the infusion may be restarted at no more than half the rate used at the time the IRR occurred. If the patient does not experience any further IRR symptoms, the infusion rate may be escalated at increments and intervals as appropriate for the treatment dose. If a patient experiences a second occurrence of a Grade 3 IRR or a Grade 4 IRR, the infusion should be permanently discontinued.

Neutropenia: incidence, monitoring and treatment when using obinutuzumab

Neutropenia occurred more frequently with obinutuzumab than rituximab in the GALLIUM study (50.6% vs 45.1%, all grades; 43.9% vs 37.9%, Grade 3 to 5).[9, 17] Neutropenia has been observed both during induction in combination with chemotherapy and late onset, occurring more than 28 days after administration. Monitoring for neutropenia should occur with blood counts performed at least weekly, particularly during the first cycle of treatment, and then prior to dosing throughout the treatment course. If neutropenia occurs, therapy should be withheld until the neutropenia resolves to less than grade 2. In this setting, granulocyte-colony stimulating factor (G-CSF) may be used, and secondary prophylaxis provided to those patients who had treatment delays because of neutropenia. It may not always be possible to distinguish chemotherapy-induced neutropenia from obinutuzumab-induced neutropenia, but isolated neutropenia is more likely to be due to obinutuzumab treatment. Prophylactic antibiotics could be considered if the patient is considered high risk for prolonged neutropenia based on age or comorbidity (such as renal impairment). Patients with neutropenia should be carefully monitored for the presence of infection. Late onset infection can also be severe, although rate of infection (febrile neutropenia) is low. If neutrophils are less than 0.5 to 1 x 10^9/L, consider using G-CSF. Monitor neutrophil count closely in patients administered G-CSF. Occasionally

patients with severe neutropenia may need to withdraw from obinutuzumab maintenance therapy.

Infections: incidence, considerations and prophylaxis when using obinutuzumab

In the GALLIUM study, there was a higher incidence of infection in the obinutuzumab arm than the rituximab arm (77.3% vs 70.0%), including higher rates of Grade 3 or higher infection (19.8% vs 15.6%).[9, 17] There was no particular type of infection that was more common in the obinutuzumab arm. Patients should be screened for prior hepatitis B exposure and monitored for reactivation and receive prophylaxis (such as entecavir, lamivudine) from when they start obinutuzumab until 12 months (perhaps until 24 months) after completion of anti-CD20 therapy. Hepatitis B viral DNA levels should be monitored periodically. Check for tuberculosis (TB) exposure and offer prophylaxis to those with serological evidence of exposure who have not been treated previously.

John Cunningham (JC) virus infection has been described with anti-CD20 monoclonal antibodies. Any patient who develops new neurological symptoms should be investigated for JC virus infection, due to risk of progressive multifocal leukoencephalopathy.

Anti-infective prophylaxis should be individualised based on patient age, comorbidities, prior history of infection and nature of cytotoxic therapy administered. Hepatitis B virus-DNA monitoring or anti-viral prophylaxis should also be monitored in patients who are anti-Hepatitis B core antibody positive. Practice varies between institutions and may vary according to specific risks in any given location of practice. All patients should be immunized against influenza and *Pneumococcus* preferably prior to starting treatment. Conjugated pneumococcal vaccine should be considered in those with suspected acquired immunodeficiency. If baseline immunoglobulin levels are <4g/L (or >4g/L and less than the local upper limit of normal with one life threatening infection) consider intravenous immunoglobulin prophylaxis. Older patients often

need G-CSF support to prevent neutropenic sepsis (except for those receiving CVP based therapy).

Some clinicians/institutions provide routine prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) in all patients on chemotherapy-antibody combinations. In GALLIUM there were three cases of PJP in total (one in obinutuzumab-bendamustine, one in R-bendamustine and one in obinutuzumab-CHOP), of which none had received prophylaxis and all recovered.[9] For patients receiving bendamustine, the need for prophylaxis against PJP (with cotrimoxazole) and varicella zoster virus (VZV; with valaciclovir), herpes simplex virus (HSV; with valaciclovir), could be considered particularly in elderly or frail patients. Data describing the rates of infection is scarce. Four cases of PJP were described in one Irish institution in patients following R-bendamustine treatment in patients who were elderly, heavily pre-treated or who received doses of bendamustine in excess of the standard 90 mg/m^2 typically used.[19] A multicenter retrospective analysis of a cohort of patients in Israel treated with any bendamustine containing regimen over five years found that viral infections occurred in 11.3% of patients, of which 2.1% experienced HSV and 3.0% VZV infections.[40, 41] In addition, fluconazole can be prescribed in the small subset of patients, generally only older patients administered steroid containing regimens, who develop clinical thrush.

Tumor lysis syndrome: incidence, prevention and management when using obinutuzumab

The rates of tumor lysis syndrome (TLS) in the GALLIUM study were 1% and 0.5% (all grades) for obinutuzumab and rituximab respectively.[9] In general, the risk of TLS is low in follicular lymphoma; however, patients with a high tumor burden and/or a high circulating lymphocyte count (>25 x 10^9/L) and/or renal impairment (creatinine clearance <70 mL/min) are at higher risk of TLS and should be admitted for cycle 1 for monitoring and receive prophylaxis. Strategies include hydration and administration of allopurinol or rasburicase if allergic to allopurinol or considered very high risk. Patients should have urea and electrolytes, phosphate, lactate dehydrogenase, calcium and urate monitored up to twice daily (if high risk) and those

found to have biochemical evidence of TLS managed with intravenous fluids, consideration of rasburicase, and close inpatient monitoring of fluid balance and biochemistry.

Thrombocytopenia and bleeding: incidence, prevention and management when using obinutuzumab

Grade 3 to 5 thrombocytopenia was reported in 6.1% of patients receiving obinutuzumab-chemotherapy in the GALLIUM study and no major bleeding signal was observed.[9] However, severe and life-threatening thrombocytopenia was noted in a small number of patients receiving obinutuzumab in the CLL11 study. While there was no increase in fatal bleeding over rituximab, in CLL11, all 13 obinutuzumab-related events (four grade 4 and one serious) occurred in cycle 1.

To prevent serious bleeding, patients with moderate thrombocytopenia (platelet count less than 50 x 10^9/L) or receiving anti-platelet therapy should have a specific bleeding management plan that may include cessation of anti-platelet agents prior to day 1 obinutuzumab. These patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves (weekly monitoring during cycle 1, and for later cycles pre-cycle blood test, and possibly a mid-cycle blood test depending on prior therapies), and dose delays should be considered in case of severe or life-threatening thrombocytopenia.

Summary of experience/peer-peer guidance

Despite many advances in the care of patients with follicular lymphoma there are several gaps in our knowledge including the biological effect of specific genetic lesions, outcomes using obinutuzumab-bendamustine without maintenance, geographical variation in infectious risk, long-term risk of hypogammaglobulinaemia, infections and secondary cancers, the role of MRD and PET scan in routine clinical care, and the impact of various treatment strategies on quality of life. As follicular lymphoma is currently incurable, the majority of patients will require more

than one line of therapy. Data on 'whole of life' strategies derived from population based registries may be useful to inform decisions regarding sequencing of therapies.

We understand that in Australia the approach to first line therapies varies between institutions and individual clinicians and is very much centered around patient risks and priorities. Importantly, no contemporary trial in which patients were randomized to compare rituximab-chemotherapy regimens (Stil-NHL1, BRIGHT, FOLL05) has demonstrated an OS benefit for one chemotherapy regimen over another. Prior to the availability of obinutuzumab, established approaches to first line treatment of follicular lymphoma included R-CHOP with rituximab maintenance in 'fitter' patients, or R-bendamustine for 6 cycles with no maintenance or R-CVP plus rituximab maintenance if patients are less 'fit'.

With obinutuzumab available, the first line treatment options now include obinutuzumab-CHOP and obinutuzumab maintenance if fit or obinutuzumab-bendamustine with maintenance in those, particularly younger patients, willing to trade off the increased risk of infections to avoid alopecia and peripheral neuropathy, and to optimize PFS. Obinutuzumab -CVP and obinutuzumab maintenance is a very reasonable option in the elderly and less fit.

In contrast to CLL, obinutuzumab IRRs in follicular lymphoma are easily anticipated and managed. Patient education and support during the infusion is very important. Slightly higher rates of Grade 2 or higher thrombocytopenia are expected with obinutuzumab therapy, particularly in older patients.

Unusual opportunistic infections have been noticed during maintenance following bendamustine induction. While the post-hoc analysis of the BRIGHT study did not reveal any survival disadvantage for bendamustine, CHOP is favored as the chemotherapy backbone if maintenance is planned and infectious risk is high.

Conclusion

The efficacy of obinutuzumab in comparison to rituximab makes it a useful addition to the treatment choices for patients with previously untreated follicular lymphoma. In clinical trials, obinutuzumab has been associated with an improved PFS, albeit with a higher frequency of Grade 3 and 4 adverse events, particularly IRRs, neutropenia and infections. However, our experience is that the majority of these events can be effectively managed, and it is uncommon that patients would need to withdraw from obinutuzumab treatment.

While recent studies have demonstrated substantial improvement in progression free survival and time to next treatment, they have failed to demonstrate a difference in overall survival. As the majority of patients have excellent outcomes with contemporary therapy, a very large study with extended follow up would be required to detect any difference in overall survival, if present.

Financial considerations may impact the ability of developing countries to deliver contemporary therapies such as obinutuzumab.

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Table 1 Dose and infusion rate of obinutuzimab for patients with follicular lymphoma and chronic lymphocytic leukaemia[14]

Day of treatment cycle		**Dose of obinutuzumab**	**Rate of infusion**
Follicular lymphoma			
Cycle 1	Day 1	1000 mg	Administer at 50 mg/h. The rate of infusion can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.
	Day 8	1000 mg	If no IRR or a Grade 1 IRR occurred during the previous infusion, where the final infusion rate was ≥ 100 mg/h, infusions can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h. If the patient experienced a Grade 2 IRR or higher during the previous infusion administer at 50 mg/h. The rate of infusion can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.
	Day 15	1000 mg	
Cycles 2 to 6 or 2 to 8	Day 1	1000 mg	
Maintenance for patients with follicular lymphoma	Every 2 months until progression or up to 2 years	1000 mg	
Chronic lymphocytic leukemia			
Cycle 1	Day 1	100 mg	Administer at 25 mg/h over 4 h. Do not increase the infusion rate.
	Day 2 or Day 1 (continued)	900 mg	If no IRR occurred during the previous infusion, administer at 50 mg/h. The rate of infusion can be escalated in increments of 50 mg/h every 30 minutes to a maximum rate of 400 mg/h. If the patient experienced an IRR during the previous infusion, start administration at 25 mg/h. The rate of infusion can be escalated in increments of up to 50 mg/h every 30 minutes to a maximum rate of 400 mg/h.
	Day 8	1000 mg	If no IRR occurred during the previous infusion where the final infusion rate was ≥ 100 mg/h, infusions can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a
	Day 15	1000 mg	
Cycle 2 to 6	Day 1	1000 mg	

			maximum of 400 mg/h. If the patient experienced an IRR during the previous infusion administer at 50 mg/h. The rate of infusion can be escalated in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h.

IRR: infusion-related reaction

Table 2 Considerations when selecting induction therapies in advanced follicular lymphoma

Monoclonal antibody	**Advantages**	**Disadvantages**
- Rituximab	Fewer infusions required Less infusion reactions	Shorter PFS and TTNT. Increased proportion with a POD24 event. Increased MRD positivity
- Obinutuzumab	Improved PFS and TTNT Reduced risk of POD24 compared to rituximab Increased MRD negativity Maintenance subsidized after bendamustine induction	Mild increase in neutropenia and infection
Chemotherapy	**Advantages**	**Disadvantages**
- CHOP	Utility in Grade 3a and 3b established. Effective in suspected histological transformation. Lower risk of long term stem cell toxicity Lower risk of persistent immunodeficiency	Alopecia. Risk of vincristine-related peripheral neuropathy and anthracycline-related cardiomyopathy. Increased risk of febrile neutropenia. Corticosteroids not well tolerated in elderly Corticosteroids can induce/destabilize diabetes.
- CVP	Well tolerated in older patients. Increased depth of response with obinutuzumab	Risk of peripheral neuropathy Corticosteroids not well tolerated in elderly Corticosteroids can induce/destabilize diabetes.
- Bendamustine	No Alopecia. Less febrile neutropenia. No cardiomyopathy or neuropathy risk. Improved PFS of R-B over R-CHOP	Most data for R-B is in patients with Grade 1 or 2 FL; some clinicians avoid Bendamustinebendamustine in Grade 3A. Potential small increased risk of stem cell toxicity, second cancers and opportunistic infections in combination with maintenance. Increased mortality in those receiving

	without maintenance	bendamustine induction (post hoc analysis, GALLIUM study) Not recommended in patients with severe renal impairment

AE: adverse event; B: bendamustine; FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; OS: overall survival; PFS: progression-free survival; POD24: progression of disease within 24 months; QoL: quality of life; R: rituximab; R-B: rituximab-bendamustine; TTNT: time to next treatment.