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SPEAKER SERIES

Immunochemotherapy for follicular lymphoma

Making Education Easy 2019

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Abbreviations used in this review

ANC = absolute neutrophil count
BR = bendamustine-rituximab
CCI = Charlson Comorbidity Index
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
CMR = complete metabolic response
CR = complete response
CVP = cyclophosphamide, vincristine, prednisone
ECOG = Eastern Cooperative Oncology Group
FDG = fluorodeoxyglucose
FL = follicular lymphoma
G-CSF = granulocyte colony-stimulating factor
GI = gastrointestinal
Hb= haemoglobin
MCL = mantle-cell lymphoma
MRD = minimal residual disease
NHL = non-Hodgkin's lymphoma
OS = overall survival
PR = partial response
PET-CT = positron emission tomography-computed tomography
PFS = progression-free survival
POD24 = progression of disease within 24 months
QoL = quality of life
TTNT = time to next treatment

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This review is a summary of a presentation on immunochemotherapy for the treatment of follicular lymphoma by Australian Haematologist Professor Mark Hertzberg, who spoke in Auckland in March at the 2019 Annual Scientific Meeting of the NZ branch of the Haematology Society of Australia and New Zealand.

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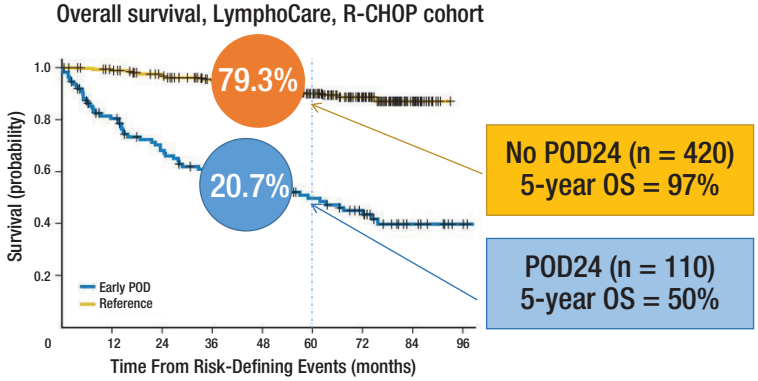
Can we predict FL patients destined to do poorly?

Professor Hertzberg explained that the outcomes for most patients with follicular lymphoma (FL) are generally good (median OS 14-20 years), however, a subgroup (approx. 20% of patients) are early progressors and tend to do poorly, especially those who are rituximab-refractory.[1] It is important to try to identify these patients at diagnosis. Over the years, a number of prognostic indices have been developed with an aim to improve the prognostic assessment and treatment of patients with FL, but unfortunately there is currently no perfect risk score for predicting at diagnosis how a patient with FL will fare.

The Follicular Lymphoma International Prognostic Index (FLIPI) is often used to stratify FL patients for treatment in prospective trials.[2] Professor Hertzberg, however, does not find that the FLIPI or its updated version, FLIPI-2, has a substantial impact on everyday clinical practice.[3] The more recent M7-FLIPI, a clinico-genetic risk model incorporating the mutation status of seven genes, the FLIPI, and the Eastern Cooperative Oncology Group (ECOG) performance status, defines a high-risk group of patients (accounting for approx. 22% of the FL cohort) with a 5-year failure-free survival of 25.0% (those identified as low-risk exhibited a 5-year failure-free survival rate of 68.24%, $p < 0.0001$).[4] The M7-FLIPI reclassifies approximately half of the patients identified as high-risk by the FLIPI, into the low-risk group, however, genetic testing for calculation of the prognostic score is not available in routine practice.

Progression of disease within 24 months of diagnosis (POD24) has been identified as a predictor of OS, with 5-year OS in those with and without POD24 estimated to be 50% and 97%, respectively (**Figure 1**).[1] In a recent study, a majority of patients with POD24 exhibited transformation of disease, particularly those receiving bendamustine-rituximab (BR), and the choice of second-line therapy must take this into consideration.[5] Of all the prognostic indices, the M7-FLIPI has been found to have the highest specificity to predict POD24, albeit with lower sensitivity.[6] This risk model prospectively identifies the smallest subgroup of patients at highest risk of early failure of first-line immunochemotherapy and death, including those not fulfilling the POD24 criteria.[6]



OS = overall survival; POD = progression of disease; POD24 = progression of disease within 24 months; R-CHOP = rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone

Figure 1. Survival in FL patients with (79.3% of the cohort) and without (20.7%) progression of disease within 24 months (POD24) in the US National LymphoCare Study [Adapted from Casulo C et al., 2015].[1]

Recently, a simplified scoring system, the PRIMA-Prognostic Index for de novo FL patients treated initially with immunochemotherapy was developed.[7] This index, which relies upon only two parameters, enables stratification of patients into low-, intermediate-, and high-risk groups according to serum lactate dehydrogenase (LDH) and β_2-microglobulin.

Another marker that may help guide response-adapted therapy in FL in clinical practice is FDG-PET-CT scanning.[8] In a pooled analysis of three multicentre prospective studies of first-line rituximab chemotherapy for patients with high-tumour-burden FL, only 23% of patients with a positive end of treatment (EOT) PET scan (who represented 16.7% of all patients) were progression-free at 4 years compared with 63% of those who had a negative PET scan ($p < 0.0001$), with 4-year OS rates of 87% and 97%, respectively ($p < 0.0001$). In Australia, PET-CT scanning is frequently utilised in this patient group and Professor Hertzberg believes that such imaging has a useful role at the end of induction therapy, but should not be used routinely for surveillance imaging in patients after induction or maintenance therapy.

Which induction therapy?

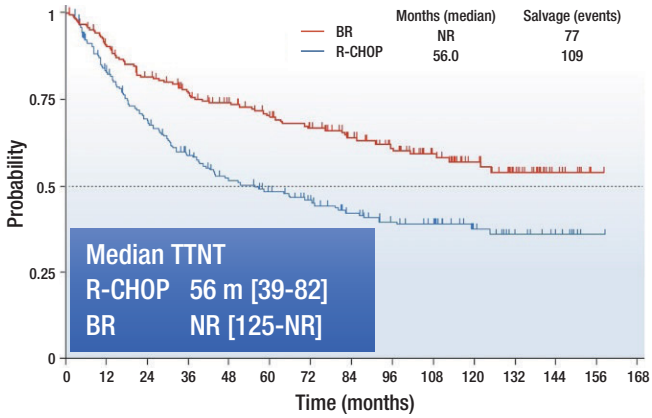
For patients with low tumour burden advanced stage disease, a watch and wait approach is still appropriate. The GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria may be applied in clinical practice to determine if a patient is suitable for induction chemoimmunotherapy. According to the GELF criteria, a person has high tumour burden if they have ≥1 of the following:[9-11]

- Bulky disease: any nodal or extranodal tumour mass ≥7 cm in diameter
- Involvement of ≥3 lymph nodes, each ≥3 cm in diameter
- Presence of systemic or B symptoms
- Symptomatic splenomegaly
- Symptomatic extranodal disease (pleural effusions, ascites)
- Compression syndrome compromising organ function (ureteral, orbital, gastrointestinal)
- Cytopaenia due to underlying lymphoma (ANC <1.0, Hb <100, platelets <100)
- Leukaemia (>5.0 x 10^9/L circulating malignant cells).

In recent years, a number of studies have investigated various induction chemoimmunotherapy regimens in FL patients exhibiting high tumour burden.

The StiL NHL study

The phase III StiL NHL study, investigating first-line BR (every 4 weeks for up to 6 cycles) versus a standard rituximab-chemotherapy regimen comprising rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP), every 3 weeks for up to 6 cycles, for indolent (53% FL grades 1-2) and mantle-cell lymphomas (MCL), reaffirmed the value of bendamustine in this patient group.[12] After a median follow-up of 113 months, time to next treatment (TTNT) was significantly prolonged with BR compared with R-CHOP (HR 0.52; 95% CI 0.38-0.69, $p < 0.001$); median TTNT was not yet reached in the BR group versus 56 months in the R-CHOP group (**Figure 2**).[13] Secondary neoplasms were observed in similar numbers in each treatment group.



BR = bendamustine-rituximab; NR = not reached; R-CHOP = rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone; TTNT = time to next treatment

Figure 2. Time to next treatment in indolent FL patients treated with BR or R-CHOP as first-line treatment [Adapted from Rummel MJ et al. 2017].[13]

The BRIGHT study

The BRIGHT study, a randomised trial of BR versus R-CHOP or rituximab + cyclophosphamide, vincristine, prednisone (R-CVP) for 6 cycles (with 2 additional cycles by investigator discretion), designed for FDA approval of bendamustine as first-line therapy for indolent NHL or MCL, investigated the comparative efficacy and safety of these regimens.[14] In this study, BR was non-inferior to R-CHOP/R-CVP as assessed by complete response (CR); 31% vs 25%, respectively, CR-rate ratio 1.26, $p = 0.0225$ for non-inferiority. Safety findings revealed significantly increased incidences of vomiting, drug-hypersensitivity and lymphopenia in BR recipients; R-CHOP/R-CVP recipients experienced higher rates of peripheral neuropathy, alopecia, and neutropenia. QoL across a number of domains showed greater improvements in recipients of BR compared with R-CHOP/R-CVP.[15] A 5-year follow-up of the BRIGHT study (median follow-up 65 months) revealed an almost 40% reduction in the risk of progression with BR; progression-free survival (PFS) 65.5% with BR versus 55.8% with R-CHOP/R-CVP (HR 0.61; 95% CI 0.0.45-0.85, $p = 0.0025$).[16] Not surprisingly, there was no difference in overall survival (OS) between the two groups, because patients could be readily rescued.

The GALLIUM study

In the international, open label, phase III GALLIUM study, 1202 previously untreated CD20-positive indolent NHL patients (including those with grade 1-3a FL) were randomised to chemotherapy (CHOP, CVP or bendamustine) and either rituximab 375 mg/m^2 on day 1 of each cycle or obinutuzumab 1000 mg on days 1, 8 and 15 of cycle 1 and day 1 of cycles 2-8, for 6 or 8 cycles depending on chemotherapy choice.[17] Australian sites contributed about 10% of patients to the study and all sites chose bendamustine as the chemotherapy backbone. Patients with a CR or partial response (PR) at the end of induction continued to receive rituximab or obinutuzumab every 2 months for 2 years or until disease progression. At 3-year follow-up (median 41.1 months), there was a 32% reduction in the risk of investigator-assessed PFS with obinutuzumab-chemotherapy compared with rituximab-chemotherapy; HR 0.68 (95% CI 0.54-0.87), $p = 0.0016$ and absolute difference of 6.5% (**Figure 3**). At this time point, a 28% reduction in the risk of progression was seen upon Independent Review Committee assessment; HR 0.72 (95% CI 0.56-0.93), $p = 0.012$.[18] The benefit of obinutuzumab-chemotherapy was maintained at 4-year follow-up

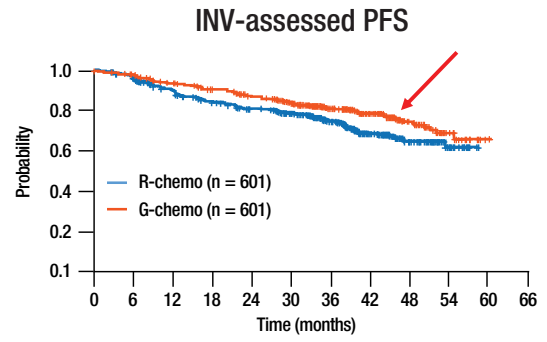
(median 57.3 months), with a 27% reduction in risk of progression compared with rituximab-chemotherapy as determined by investigator assessment; HR 0.73 (95% CI 0.59-0.90), p = 0.0034 and absolute difference of 11%.[19] At this time point, a substantial benefit in favour of obinutuzumab-chemotherapy was seen in TTNT, with a 30% reduction in the need for subsequent therapy; HR 0.70 (95% CI 0.54-0.90), p = 0.0046. The benefit of obinutuzumab over rituximab was seen with all chemotherapy backbones. While the study was not designed or powered to compare differences between rituximab-chemotherapy and obinutuzumab-chemotherapy within chemotherapy groups, there appeared to be a greater advantage for those patients receiving obinutuzumab-bendamustine versus rituximab-bendamustine; investigator-assessed PFS HR 0.63 (95% CI 0.46-0.88).

In an exploratory analysis of the GALLIUM study, relative to rituximab-chemotherapy, obinutuzumab-chemotherapy reduced the risk of a POD24 event by 46% and a PFS event by 34%.[20] Professor Hertzberg explained that this is a particularly important result, as POD24 is associated with poorer outcomes. Landmark analysis, undertaken to estimate 2-year OS rates according to POD status revealed that the relative risk of mortality at 2 years post-landmark was 12-fold higher in the POD24 group than in the group who had not progressed within 24 months of randomisation (OS at 2 years post-landmark 82.4% vs 98.2%), with the earlier the occurrence of progression, the higher the subsequent mortality risk.[20] Furthermore, the cumulative incidence of transformation in the first 24 months was found to be substantially higher in patients with POD24 versus those not experiencing POD24.[21]

A second exploratory analysis in the GALLIUM study found that a greater proportion of patients in the obinutuzumab-chemotherapy arm of the trial achieved minimal residual disease (MRD)-negative status at mid induction and end of induction (as determined by t(14;18) and/or immunoglobulin variable domain allele-specific RQ-PCR) than those in the rituximab-chemotherapy arm; mid induction 94.3% versus 88.9% (p = 0.013), end of induction 92.0% versus 84.9% (p = 0.0041).[22] Among patients who had achieved a CR or PR at end of induction, those who had an MRD-negative response continued to have a longer PFS than those who had an MRD-positive response (HR 0.38; 95% CI 0.26-0.56, p < 0.0001) and this was irrespective of treatment arm (obinutuzumab-chemotherapy or rituximab-chemotherapy).[23] This exploratory analysis supported the potential prognostic value of MRD assessment at end of induction in FL patients treated with immunochemotherapy.

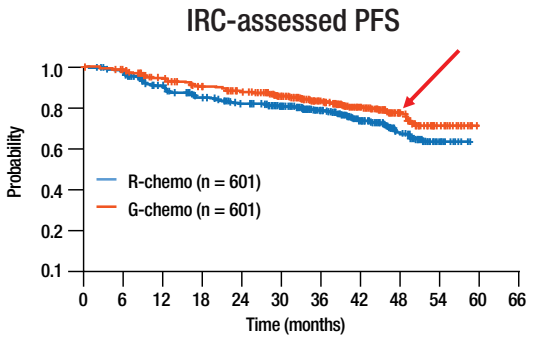
Another secondary analysis of the GALLIUM study evaluated the prognostic value of PET-CT-based responses at end of induction therapy in relation to PFS and OS outcomes.[24] According to Lugano 2014 criteria, 2.5-year PFS in complete metabolic responders (CMRs) was 87.4% and in non-CMRs was 54.9% (HR 0.2; 95% CI 0.1-0.3, p < 0.0001); non-CMR was seen in approx. 12% of the 508 patients in the landmark PET sub-study cohort, nevertheless, they had a 45.1% risk of disease progression at 30 months. Analysis by antibody arm and CMR, revealed that patients treated with obinutuzumab-chemotherapy who did not achieve a CMR at end of induction appear to have improved PFS over those receiving rituximab-chemotherapy who did not achieve a CMR at end of induction; 2.5-year PFS from end of induction 69.7% vs 43.5% (HR 0.5: 95% CI 0.2-1.3, p = 0.14). PET-CR status at end of induction in the GALLIUM study was highly prognostic for prolonged OS (96.6% vs 84.0%; HR 0.22; 95% CI 0.11-0.45, p < 0.0001).

Professor Hertzberg explained that the utility of PET imaging for improving outcomes in FL is still under debate.[25,26] That is, it is still unclear what to do with the group of patients who have a non-CMR, or even CMR, at the end of induction. The UK PET Response-Adapted therapy trial (PETReA) (that is also being undertaken at all Australasian Leukaemia and Lymphoma Group [ALLG] sites) will investigate in a randomised manner the utility of FDG-PET in response-adapted therapy by adding lenalidomide to rituximab maintenance in EOT non-CMR patients, and withholding maintenance rituximab in PET CMR patients.



No of patients at risk

G-chemo	601	561	505	464	438	396	267	149	77	18	
R-chemo	601	569	535	505	478	420	291	176	85	25	1



No of patients at risk

G-chemo	601	563	502	463	438	394	271	151	73	16	
R-chemo	601	571	532	597	476	414	287	179	79	22	

	R-chemo, n = 601	*G-chemo, n = 601*
3-yr PFS, % (95% CI)	75.0 (71.0, 78.5)	81.5 (77.9, 84.6)
HR (95% CI), p-value†	0.68 (0.54-0.87), p = 0.0016	

	R-chemo, n = 601	*G-chemo, n = 601*
3-yr PFS, % (95% CI)	78.9 (75.2, 82.1)	83.4 (79.9, 86.3)
HR (95% CI), p-value†	0.72 (0.56-0.93), p = 0.0118	

*ITT population; † stratified analysis; stratification factors = FLIPI, chemotherapy regimen

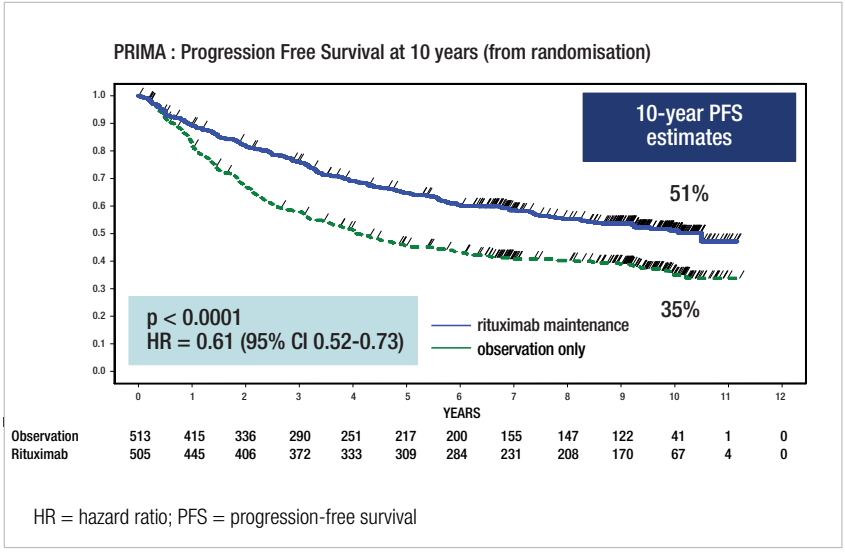
G-chemo = obinutuzumab-chemotherapy; INV = investigator; IRC = Independent Review Committee; PFS = progression-free survival; R-chemo = rituximab-chemotherapy

Figure 3. PFS after 41.1 months median follow-up in FL patients in the GALLIUM study [Adapted from Hiddemann W et al., 2017].[17]

What about maintenance therapy in FL?

The PRIMA study

The PRIMA study, involving 223 centres in 25 countries including ALLG sites (that contributed 15% of patients), investigated 2 years of rituximab maintenance therapy (375 mg/m^2 every 8 weeks) or observation in 1019 high-tumour-burden FL patients who had achieved a CR or PR after receiving one of three immunochemotherapy induction regimens used in routine clinical practice.[27] The study found that 2 years of rituximab maintenance in this patient group significantly improved PFS; 74.9% versus 57.6% in the observation group, HR 0.55 (95% CI 0.44-0.68, p < 0.0001). Long-term follow-up of PRIMA study participants showed an estimated PFS at 10 years of 51% in rituximab maintenance recipients versus 35% in the observation group; HR 0.61 (95% CI 0.52-0.73) (**Figure 4**).[28] The 10-year OS estimates were identical in each group at 80% (this was likely due to the ability to salvage patients). Safety analysis in the PRIMA study revealed a higher incidence of grade3/4 adverse events (mostly due to neutropenia and infections) and serious adverse events in rituximab maintenance recipients compared with the observation group (24% vs 17% and 21% vs 13%, respectively).[28]

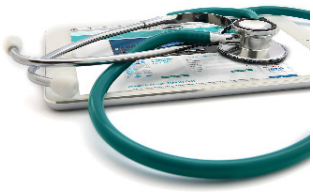


HR = hazard ratio; PFS = progression-free survival

Figure 4. Estimated PFS at 10 years in patients in the PRIMA study receiving rituximab maintenance or observation only [Adapted from Salles G et al., 2017].[28]

The BRIGHT study

In the BRIGHT study (discussed on page 2) rituximab maintenance was administered at the investigator's discretion, with approximately 50% of patients receiving such therapy.[29] In patients treated with BR induction therapy, duration of response was prolonged in the rituximab maintenance group (HR 0.50; 95% CI 0.26-0.95, p = 0.0298), with a 50% reduction in the risk of progression. Professor Hertzberg explained that these findings must be interpreted with caution, as this was not a pre-planned analysis and there may be investigator selection bias. Nevertheless, the data favours rituximab maintenance, with reassurance regarding fatal adverse event rates. Furthermore, the overall improvement in duration of response in rituximab maintenance patients appears to be at least as great following BR as following R-CHOP and R-CVP.



What about safety/toxicity concerns with bendamustine, obinutuzumab, and with maintenance therapy?

Professor Hertzberg explained that there have been some safety concerns around the toxicity of obinutuzumab, particularly in combination with bendamustine.

Infections and second cancers: Is there an issue?

The BRIGHT study

In the BRIGHT study, rates of secondary malignancy were higher in BR recipients than in R-CHOP/R-CVP recipients (19% vs 11%, p = 0.022), but after excluding for NHL and non-melanoma skin cancer, the rates were not significantly different (10% vs 6%, p = 0.133).[16]

The GALLIUM study

Professor Hertzberg explained that when interpreting study findings regarding toxicities and deaths, it is important to consider any differences in the baseline characteristics of the treatment groups. In the GALLIUM study, there was a higher incidence of high FLIPI score (≥3) and bulky disease (≥7 cm) in CHOP recipients than in bendamustine recipients (47% vs 40% and 52% vs 40%, respectively).[18] There were also more patients over the age of 80 years in the bendamustine group than in the CHOP group (3% vs 1%) and more patients in the bendamustine group had a comorbidity index ≥1 than in the CHOP group (24% vs 17%).

More grade 3-5 infections were observed in the bendamustine arms of the study than in the CHOP arms (23% vs 12%), and this difference occurred throughout induction, maintenance and observation, with little change in frequency over time.[18] Not surprisingly, there was a higher incidence of neutropenia in the CHOP group than in the bendamustine group (71% in obinutuzumab + CHOP and 55% in rituximab + CHOP recipients compared with 30% in obinutuzumab + bendamustine and rituximab + bendamustine recipients). Bendamustine was also associated with marked and prolonged reductions in CD4 T-cell numbers and these levels remained low for at least 2.5 to 3 years after bendamustine. Such a reduction in T-cells may account for the higher incidence of infections with bendamustine compared with CHOP.

Among the 45 deaths in the GALLIUM study, more fatalities occurred in the bendamustine cohort than in the CHOP cohort (total fatal adverse event rates were 4.4% with bendamustine, 1.8% with CHOP and 1.7% with CVP); 6 of these events (all in the bendamustine cohorts) were after patients started new cancer therapies and five of the six deaths were due to infections.[18] Among the remaining 39 fatal adverse events (20 in obinutuzumab recipients and 19 with rituximab), 30 occurred with bendamustine (75%). Interestingly, the rate of deaths before patients received anti-cancer therapies was higher in the bendamustine group in those aged over 70 years compared with those aged less than 70 years (13.4% vs 3%). These findings have caused some concern around the use of bendamustine, however,

when considering baseline characteristics it is clear that many of these deaths occurred in patients with significant comorbidities or older age, or impaired ECOG Performance Status.

Moreover, the causes of death in GALLIUM, especially in the bendamustine cohorts, were very diverse (including cardiac, thoracic/mediastinal, and nervous system disorders) and less than half were related to the highly biologically plausible causes of infections and secondary cancers. Indeed, of the six infectious deaths occurring before any new anti-cancer therapies, five occurred in the bendamustine cohorts while one CHOP recipient suffered such an event.[30] However, since twice the number of patients received bendamustine compared to CHOP, the difference in infectious deaths between the two groups (5 to 1, instead of 4 to 2) is perhaps not as great as has been suggested. Finally, of the total of 11 patients with fatal infections, nine received no G-CSF prophylaxis and seven received no anti-infective prophylaxis.[18] Unfortunately, such prophylaxis was not mandated in the study protocol. Similarly, there were 10 deaths due to second cancers, however, there was no signal that the incidence was higher among patients induced with bendamustine compared to CHOP (1% in both).

Bendamustine infection prophylaxis

According to Professor Hertzberg, infection prophylaxis for patients receiving bendamustine should include the following:

- *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis with Bactrim™ DS (double strength) especially in older pateints
- Viral prophylaxis with valaciclovir
- A low threshold for use of growth factors (especially in older patients).

While there are no definitive guidelines on when to cease infection prophylaxis, Professor Hertzberg would suggest continuing such treatment for 6-12 months beyond induction, or for 6-12 months beyond maintenance. He would also consider monitoring CD4 cell counts and continuing such prophylaxis until CD4 cell count is >200/μL.

Conclusions and discussion

Q. Given the increased grade 3-5 infections and deaths seen in bendamustine groups in GALLIUM, is the standard of bendamustine + anti-CD20 monoclonal antibody still a reasonable standard?

A. YES bendamustine is still a reasonable standard treatment, but we need to provide infection prophylaxis and consider G-CSF. For older patients (>75/80 years), a reduction in cycle number to 4 cycles may be considered.

Q. Given:

I. **Increased non-fatal adverse events seen in the GALLIUM study with obinutuzumab versus rituximab**

II. **The moderate absolute 2-year PFS benefit of obinutuzumab versus rituximab (approx. 5-6%)**

III. **A 32% relative reduction in risk of PFS event at 2 years (approx. 2.5 years longer PFS) with obinutuzumab versus rituximab**

IV. **A reduction in POD24 events by 46%, a 7% increase in MRD-negative rate, and a 5% increase in end of induction PET-CMR with obinutuzumab versus rituximab**

Should obinutuzumab replace rituximab as the preferred monoclonal antibody for the initial treatment of FL?

A. Probably yes, with either CHOP or bendamustine in most patients. Ideally we would like to see a longer follow up of the GALLIUM cohort.

Q. What is the role of maintenance monoclonal antibody therapy in FL?

A. Probably obinutuzumab after obinutuzumab-CHOP. Probably obinutuzumab after obinutuzumab-bendamustine. We need to provide infection prophylaxis and monitor closely for cytopenias and infection. Possibly withhold maintenance after obinutuzumab-bendamustine induction therapy in those select patients >70/75 years of age with an ECOG Performance Status >1 and/or multiple comorbidities.

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