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Lenalidomide Consolidation Added to Rituximab Maintenance Therapy in Patients Remaining PET Positive After Treatment for Relapsed Follicular Lymphoma: A Phase 2 Australasian Leukaemia & Lymphoma Group NHL26 Study

Judith Trotman[1,2], Peter Presgrave[3], Duncan P. Carradice[4], Douglas Stuart Lenton[5,6], Maher K. Gandhi[7,8], Tara Cochrane[9,10], Xavier Badoux[11], Julia Carlson[12], Gloria Nkhoma[12], Belinda Butcher[11,13], Armin Nikpour[2,14], Michael Fulham[2,14], Anna M. Johnston[15,16]

Correspondence: Judith Trotman (judith.trotman@health.nsw.gov.au).

Follicular lymphoma (FL), the most common indolent lymphoma, has a heterogeneous clinical course.[1] Positron emission-computerized tomography (PET) using ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is integral to response assessment in FL.[2] The inferior outcomes in patients who fail to achieve complete metabolic response provides a platfom to test response-adapted approaches.[3] Lenalidomide is an immunomodulatory drug with multiple mechanisms of antilymphoma effect.[4,5] Lenalidomide-rituximab (R^2) has shown significant clinical activity in both relapsed and untreated FL, with efficacy identical to immunochemotherapy.[6,7] Patients who remain PET-positive (PET +ve) after reinduction therapy have the greatest potential benefit from a consolidation approach added to conventional rituximab maintenance therapy. We hypothesized that adding lenalidomide to rituximab maintenance could convert PET +ve to PET-negative (PET –ve) with an acceptable toxicity profile.

The ALLG NHL26 study was a prospective multicentre Phase 2 study of patients treated for relapsed FL, with lenalidomide consolidation added to rituximab maintenance therapy (R^2), in those remaining PET +ve. The study was approved by each site's ethics committee and registered with the Australian New Zealand Clinical Trial Registry ACTRN12613000106730. The full protocol is provided as Supplement (S1). Eligible patients had received reinduction rituximab-chemotherapy for symptomatic bulky Stage II, or Stage III–IV relapsed FL and achieved at least stable disease applying computed tomography (CT)-response criteria[8] within 4–6 weeks of the last cycle of therapy. Key exclusion criteria were: receipt of ≥6 cycles of fludarabine, prior allogeneic transplant or lenalidomide therapy; histological transformation within 12 months; and another malignancy, unless free from disease for ≥3 years.

Each of 4 PET sites performed a phantom study, with volume of interest analysis, to validate the standard uptake value calibration and acquired 2 patient studies reviewed by the Core Lab. Scanner quality control was performed before all patient scans. The amount of injected ^{18}F-FDG was based on the participants' body mass index. Participants underwent PET within 8 weeks of D1 of the last cycle of reinduction rituximab-chemotherapy. Core Lab assessment, applying the Deauville 5-point scale (DS), with DS of ≥3 (lesion uptake greater than FDG uptake in the mediastinal blood pool), was used to determine PET +ve status.[9,10] This lower cut-off of DS ≥3 has been shown in a prospective study in the firstline setting to be predictive of outcome, albeit less so than a cut-off of DS ≥4.[11] In the context of relapsed disease where the pretest probability of subsequent relapse is higher, DS ≥3 was considered an appropriate cut-off. Two PET physicians independently read the scans, with PET status determined by consensus if assessments differed.

Patients remaining PET +ve were assigned R^2 to commence within 12 weeks of D1 last cycle of rituximab-chemotherapy. Lenalidomide doses were titrated from 10 mg/d, up to 15 mg/d for 21 days in a 28-day cycle over a planned 2 years (Supplement 1). Repeat PET and CT scans were scheduled for 6 months later.

[1]Haematology, Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia
[2]University of Sydney, Camperdown, NSW, Australia
[3]Department of Haematology, Wollongong Hospital, NSW, Australia
[4]Department of Haematology and Medical Oncology, Western Health and University of Melbourne, St Albans, VIC, Australia
[5]Orange Hospital, NSW, Australia
[6]University of Sydney, Orange, NSW, Australia
[7]Princess Alexandra Hospital, Brisbane, QLD, Australia
[8]Mater Research University of Queensland, Brisbane, QLD, Australia
[9]Department of Haematology, Gold Coast University Hospital, Southport, Australia
[10]Griffith University, Southport, Australia
[11]University of New South Wales, Sydney, NSW, Australia
[12]Australasian Leukaemia and Lymphoma Group, Richmond, VIC, Australia
[13]WriteSource Medical Pty Ltd, Lane Cove, NSW, Australia
[14]Department of Molecular Imaging, Royal Prince Alfred Hospital, Camperdown, NSW, Australia
[15]Department of Hematology, Royal Hobart Hospital, Hobart, TAS, Australia
[16]University of Tasmania, Hobart, TAS, Australia

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Patients who remained PET +ve without CT-defined progression were scheduled to have another PET scan after a further 6 months. CT scanning was every 6 months for the first 3 years, and annually thereafter, or if progressive disease (PD) was suspected. The primary objective was to determine the percentage of evaluable patients converting from PET +ve after reinduction immunochemotherapy, to PET –ve after 6 months of commencing consolidation. Secondary endpoints included PET conversion rates after 12 months, the toxicity and deliverability of R^2, and progression-free survival (PFS) and overall survival (OS) in both PET populations.

We assumed a ≥50% conversion to PET –ve 6 months after commencing lenalidomide consolidation was worthy of further evaluation, and a ≤20% conversion being unacceptable. Using a 1-sided exact test for proportions, 16 evaluable patients were required to achieve 80% power (alpha set at 0.05). Assuming 25% of patients would be PET +ve after reinduction, and up to 20% of PET +ve would not be evaluable, 80 patients were planned to be enrolled. Evaluable patients were defined as those receiving more than 3 cycles of lenalidomide and who had undergone a PET scan at 6 months or who had progressed after at least 3 cycles of lenalidomide. PFS was defined as the time from the first postinduction PET scan until relapse, progression, or death from any cause. OS was defined as the time from the first postinduction PET scan until death from any cause. OS and PFS were estimated using Kaplan-Meier methods.

Thirty-seven patients were recruited from November 2013 to January 2021 when the study was closed due to poor recruitment. Eighteen (48.6%) were PET +ve at the baseline PET scan: DS3 n = 7, DS4 n = 0, DS5 n = 11. The only difference in prechemotherapy risk factors was a higher rate of extranodal disease in PET +ve versus PET –ve (65% versus 16%), $P = 0.01$ (Table 1). One PET +ve patient, with reactivation of hepatitis B, did not meet the eligibility criteria and was excluded from response analysis. Thus 36 patients were included in the full analysis set. Median age was 67 years (range 36–83); 58% male; with a median 2 prior therapies (range 2–11), including the recent rituximab-chemotherapy before enrollment. Ten patients had high-dose chemotherapy before autologous transplant as their most recent treatment. Median follow-up was 38 months (range 0.8–76.4): 32 months (0.8–76.4) in PET +ve and 42 months (6.7–73.8) in PET –ve.

Of the 36 evaluable patients, 19 were PET –ve and received rituximab maintenance alone. Seventeen (47.2%) remained PET +ve and commenced lenalidomide in addition to rituximab. Of these 17 patients, 3 with DS5 were not evaluable due to early PD, with additional lesions identified on PET before commencement of lenalidomide. Thus 14 of 17 (82%) baseline PET +ve patients were evaluable for response to R^2: 6 of 14 with DS3 and 8 of 14 with DS5. Of these, 5 of 14 (36%; 95% CI, 11%-61%) became PET –ve at 6 months, thus not excluding a PET conversion rate of <20% ($P = 0.14$). PET conversion occurred in 4 of 6 (67%) patients with DS3 and 1 of 8 (13%) with DS5. Two patients with a persisting DS3 at 6 months achieved DS2 after 12 months of lenalidomide.

PD occurred in 14 of 36 patients: 11 of 17 (65%) of those who were postinduction PET +ve and 3 of 19 (16%) of the postinduction PET –ve cohort. Not all the patients who progressed were rebiopsied; however, 4 patients demonstrated histological transformation at the time of progression, confirming this as an important cause of treatment failure. Median PFS was 30.8 months (5.7–37.6) in PET +ve and not reached (NR; 95% CI, 42.3-NR) in PET –ve (HR = 7.8, 95% CI, 2.4-25.1, $P < 0.001$). Median OS was 68.1 mo (9.6-NR) in PET +ve and NR (95% CI, 42.3-NR) in PET –ve (HR = 3.4, 95% CI, 0.9-12.8, $P = 0.059$; Figure 1).

Deliverability of lenalidomide was limited by PD and adverse events (AEs), mainly cytopenias. The prior lines of treatment and recent high dose chemotherapy (8 patients) may have contributed to this. Mean adherence was 87.9% (SD 16.7%), median was 95.2%. At least 1 lenalidomide-related AE was reported in 16 of 17 (94%) patients, most commonly neutropenia (n = 10, 59%, grade [Gd] = 4, 24%, Gd = 5, 0%).

Table 1

Baseline Demographics and Clinical Characteristics

Demographic	PET –ve (n = 19)	PET +ve (n = 17)	*P* Value
Sex, n (%)			
Male	12 (63)	9 (53)	0.53
Female	7 (37)	8 (47)	
Age at registration (y), median (range)	68.2 (35.6–83.4)	66.2 (44.8–79.2)	0.35
Length of diagnosis (mo), mean (SD)	104.5 (59.3)	95.1 (87.4)	0.71
Histological diagnosis, n (%)			
Follicular lymphoma, grade 1–2	17 (89)	10 (35)	0.20
Follicular lymphoma, grade 3a	2 (11)	3 (18)	
Follicular lymphoma, grade 3b	0 (0)	1 (6)	
Other	0 (0)	3 (18)	
Bone marrow biopsy at diagnosis, n (%)			
Not done	5 (26)	5 (33)	0.46
Done, not involved	6 (32)	2 (13)	
Done, involved	8 (42)	8 (53)	
No. prior lines therapy, n (%)			
2	12 (63)	10 (59)	0.30
3	6 (32)	3 (18)	
4	1 (5)	0 (0)	
6	0 (0)	2 (12)	
7	0 (0)	1 (6)	
11	0 (0)	1 (6)	
No. prior lines therapy, median (range)	1.0 (1.0–4.0)	1.0 (1.0–11.0)	0.48
FLIPI risk category, n (%)			
Low risk	4 (25)	3 (18)	0.40
Intermediate risk	3 (19)	1 (6)	
High risk	9 (56)	13 (76)	
Extranodal disease after reinduction, n (%)	13 (68)	16 (94)	0.052
Prior ASCT	2 (11)	8 (53)	

ASCT= autologous stem cell transplant; FLIPI = follicular lymphoma international prognostic index; PET = positron emission-computerized tomography.

Eleven patients have died (8 PET +ve, 3 PET –ve). Seven died due to lymphoma (5 PET +ve, 2 PET –ve) and 3 (all PET +ve) due to pneumonia. One PET –ve patient died from metastatic non–small-cell lung carcinoma.

This study showed a high PET +ve rate of 49% (DS3–5) after reinduction rituximab- chemotherapy for relapsed FL. The almost 8-fold increased risk for progression and the trend toward a 3-fold greater risk of death in patients remaining PET +ve supports the need for consolidation therapy in this patient group. However, in this small, under-recruited study, R^2 was challenging to deliver and did not achieve a sufficiently high PET conversion rate to justify further study.

PET+ was defined as a DS3–5 in this study. This accounted for a higher postinduction PET +ve rate than our conservative prediction of 25%. Even accounting for a lower cut-off DS, 30% of patients had a DS5 after completing immunochemotherapy. Our postinduction PET +ve rate is similar to the 41% described before autologous stem cell transplant (ASCT) in 59 patients with relapsed FL, using the same cut-off.[12] The majority of conversions to PET –ve status occurred in patients with DS3 and only 1 of 8 DS5 patients converted to PET –ve. The greatest limitation of our study was slow recruitment resulting in inadequate power. Recruitment was hampered initially by clinician concerns about second primary malignancies with lenalidomide, the reduced rate of FL relapse with widespread adoption of rituximab maintenance, and more recently by competing studies with novel agents.

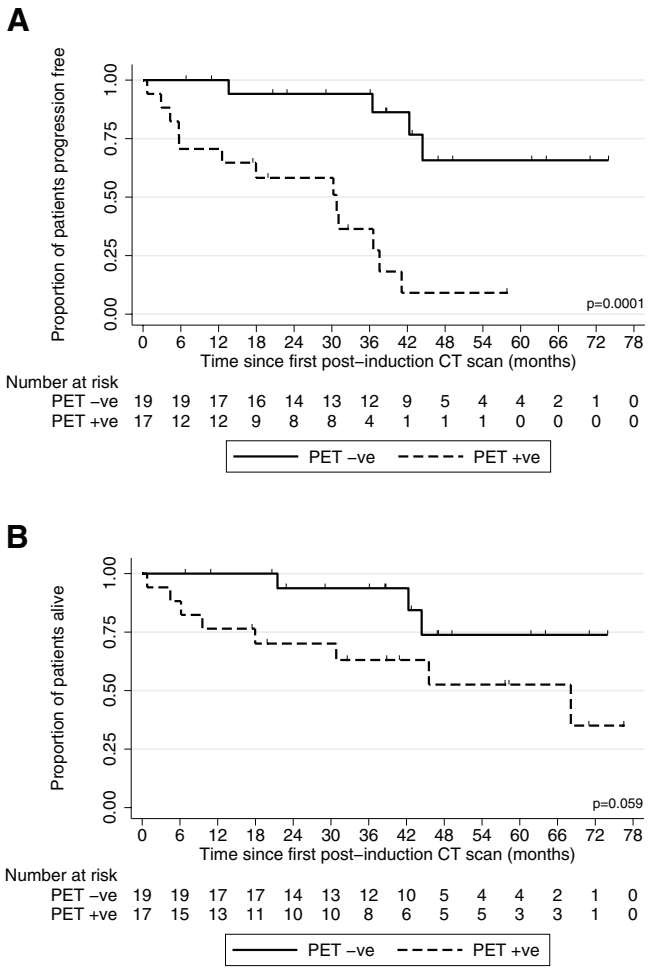

Figure 1. Progression free (A) and overall survival (B) of the cohort by post-reinduction therapy PET status. (A) Progression-free survival and (B) overall survival. CT = computed tomography; PET = positron emission-computerized tomography.

Other limitations were early PD in the PET +ve group. Ultimately 11 of 17 (65%) PET +ve patients progressed compared to only 3 of 19 (16%) of the PET –ve cohort. Although biopsy at progression was not mandated, a significant number were found to have histologic transformation at this time. The deliverability of R^2 was challenging in the relapsed setting where 7 of 17 (41%) of PET +ve patients had received more than 2 prior therapies and 8 of 17 (47%) had received ASCT, with neutropenia the most common toxicity. Observed toxicities in this study provided useful data to inform the design of the current UK-Australian PETReA study, a Phase 3 evaluation of PET-guided, Response-Adapted therapy in patients with previously untreated, high tumor burden FL.

The prolonged recruitment to our trial, provided informative survival predictions based on PET status for patients with relapsed FL. The poor PFS and OS in patients remaining PET +ve after second and subsequent lines of therapy justifies study of more aggressive consolidation approaches such as ASCT, or enrollment in bispecific antibody or CAR-T cell studies. Their inferior survival highlights the importance of continued investigation of novel approaches.

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AUTHOR CONTRIBUTIONS

JT, BB, and AMJ conceived and designed the study. All authors contributed data. MF and AN performed the PET analysis. BB performed the statistical analysis. JT and AMJ drafted the paper and all authors revised it critically and approved the final version for publication.

DISCLOSURES

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