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Article type : Letter to the Editor

Efficacy and infection morbidity of frontline immuno-chemotherapy in follicular lymphoma

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Running title: Outcomes of frontline FL therapies

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To The Editor:

Current UK standard of care in frontline advanced stage (III or IV) symptomatic follicular lymphoma (FL) is immuno-chemotherapy with anti-CD20 monoclonal antibodies (mAbs) rituximab (R) or obinutuzumab (O), in combination with cyclophosphamide, vincristine and prednisolone (CVP) or cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), or bendamustine (B)[1]. Maintenance R or O are commonly offered to patients who achieved an objective response to induction[1,2].

Patients currently receiving immuno-chemotherapy have a median OS of 15-20 years, with up to 80% demonstrating an age and gender-matched OS compared to the general population[3]. To achieve a desirable patient treatment journey, key priorities are to optimise therapy responses whilst minimising treatment-related toxicities.

GALLIUM reported increased toxicity with frontline O-based compared to R-based therapies, in particular: infusion reactions, neutropenia, neutropenic fever and infections[1]. The trial also demonstrated the effects of profound T-cell depletion associated with bendamustine therapy followed by anti-CD20 mAb maintenance, and reported a treatment-related mortality (TRM) of ~5% in bendamustine-treated patients[1,4].

In light of these data, we performed a retrospective cohort study of consecutive newly diagnosed FL patients (2009-2019) treated within Oxford's Tertiary Haematology Centre (UK), to assess efficacy outcomes and the 3-year infection morbidity/mortality following frontline therapy, and to identify factors associated with infective episodes. To our knowledge, there are no published data

describing these outcomes in UK routine care, where patients can present with advanced age and/or co-morbidities, which often exclude patients from prospective clinical trials. Study methodology is further described in the supplementary text.

Baseline patient, disease and treatment characteristics of 132 eligible patients are presented in Table 1. Median follow up of the whole cohort was 3 years (range: 0.08-3.00) for infections, 4.6 years (range: 0.5-11.3) for OS and 4 years (range: 0.3-8.9) for PFS. The 3-year PFS and OS were 69.7% (Fig 1A) and 89% (Fig 1B), respectively. Patients receiving R-CVP had an inferior 3-year PFS (Fig 1C) than other treatments (51.6% vs R-CHOP 79.8% vs BR 87.5% vs B-O 63.5%, p=0.001). R-CVP-treated patients also had an inferior 3-year OS (Fig 1D) (82.5% vs R-CHOP 100% vs BR 90.6% vs B-O 87.5%, p=0.015).

According to anti-CD20 mAb maintenance and across all patients, the 3-year PFS was 79.7% with maintenance compared to 52.9% without (p=0.001) (Fig 1E). There was a statistically significant 3-year OS difference in favour of maintenance use (97.4% vs. 75.1%, p=0.014) (Fig 1F).

Across the whole cohort, 74 patients experienced at least one infection (all grade) over a 3 year follow-up. Detailed infection-related outcomes are presented in Table 1S. There were a total of 131 documented infections (G1-5): 76 during induction (R-CHOP: 26, R-CVP: 21, B-R or B-O: 22, 2 each with hybrid BR/RCVP and hybrid RCVP/RCHOP, and 3 with R-GCVP). A total of 55 infections occurred during maintenance (R: 52, O: 3). Across the whole cohort, 40 patients experienced a total of 62 infection-related admissions (G3-5) during induction (R-CHOP: 22, R-CVP: 17, B-R or B-O: 16, hybrid BR/RCVP: 2, hybrid RCVP/RCHOP: 2, R-GCVP: 3), and 13 (of 83 maintenance patients) experienced a total of 16 episodes of ≥G3 requiring admission at maintenance (R: 14, O:2).

The regimen with the highest rate of patients experiencing any grade infection during the 3 year infection follow up was bendamustine-based (BR or BO) (63.4%: 26/41) which was comparable to R-CHOP (58.8%: 20/34), and the lowest was R-CVP (47.2%: 25/53) (p=0.200 for BR or BO vs. R-CVP). During maintenance, infection-related admissions were numerically higher in bendamustine-treated patients (22.6%:7/31) versus (R-CVP or R-CHOP: 16%: 8/50) (p=0.459).

Factors associated with an increased risk of all grade infections by UVA were having maintenance (odds ratio (OR): 2.09, p=0.05), and high CIRS-G (OR: 1.17, p=0.07). By MVA, compared to R-CVP, patients treated with BR (OR 3.77, p=0.02) and R-CHOP (OR 2.98, p=0.05) had a significantly higher risk of all grade infections, Table 2S.

Factors associated with an increased infective-related admissions by UVA included high CIRS-G (OR: 1.15, p=0.09). By MVA, significant factors were high CIRS-G (OR 1.34, p=0.05) and R-CHOP compared to R-CVP (OR 3.18, p=0.03), Table 2S.

In this study, R-CVP resulted in lower OS and PFS rates than other induction comparators, which is in part driven by patient selection, but also known to provide an inferior PFS compared to other standard immuno-chemotherapy regimens[5]. The 3-year PFS improvement with maintenance mAb is consistent with PRIMA data (79.7% vs. 74.9%)[2]. Our 10-year OS rate in non-maintenance patients was significantly lower (40.9%) compared to 80% in the non-maintenance arm of PRIMA[2], reflecting the nature of non-selective consecutive population-based data in patients with co-morbidities. Additionally, and in contrast with PRIMA, which showed no OS difference according to maintenance, our study demonstrated a significant OS advantage for maintenance, which likely reflects, at least in part, patient selection.

Despite the retrospective nature of our study, we have demonstrated the differences in infective morbidity according to the patient comorbidity status and immuno-chemotherapy choices which can inform decision making across different frontline FL therapeutic approaches. We show that B-treated patients suffer from a high infective morbidity, as described in the follow up toxicity reports from GALLIUM[1,4], and we demonstrated that infection-related hospitalisation was independently associated with R-CHOP and with a high baseline CIRS-G score.

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Author contributions:

FD, GPC and TAE designed the study. FD, FK and TAE collected data. LS, MML, FK and FD analysed data. FD and TAE wrote the manuscript, which all authors critically reviewed and approved.

Conflicts of interest:

FD: Amgen: Honorarium, Takeda: Honorarium, Travel to scientific conferences, Celgene: Honorarium, Research support, Travel to scientific conferences. FK: Nil. LS: Nil. MML: Nil. GPC: ADC Therapeutics: Consultancy, Honorarium, Research support. Gilead: Consultancy, Honorarium, Speakers Bureau. Amgen: Research support. Takeda: Consultancy, Honorarium, Speakers Bureau. Celgene: Research funding. Pfizer: Consultancy, Honorarium. Roche:

Consultancy, Honorarium, Speakers Bureau. MSD: Consultancy, Honorarium. Celleron: Consultancy, Honorarium. BMS: Consultancy, Honorarium, Research support. T.A. Eyre reports receiving other commercial research support from and is a consultant/advisory board member for Gilead, and reports receiving speakers bureau honoraria from Gilead, Abbvie, Janssen, and Roche

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Ethical approval:

The study received NHS service evaluation approval at the participating site.

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Table 1 title:

Baseline patient, disease and treatment characteristics

Table 1 legend:

R-CVP (rituximab with cyclophosphamide, vincristine and prednisolone), R-CHOP (rituximab with doxorubicin, cyclophosphamide, vincristine and prednisolone), B-R (bendamustine with rituximab), B-O (bendamustine with obinutuzumab), CISR-G (Cumulative Illness Rating Scale for Geriatrics), COPD (chronic obstructive pulmonary disease), ECOG (Eastern Cooperative Oncology Group), Hb (haemoglobin), LDH (lactate dehydrogenase), FLIPI (follicular lymphoma international prognostic index), BM (bone marrow), PD (progressive disease). Number of patients with unknown data in the total cohort: [a](1), [b](1), [c](2), [d](2), [e](52), [f](2), [g](1), [h](2), [i](33), [j](1), [k](58). *Four patients received other regimen: 1 hybrid BR/R-CVP, 2 hybrid R-CVP/R-CHOP and 1 R-GCVP (rituximab with gemcitabine, cyclophosphamide, vincristine and prednisolone).

Figure 1 title:

Kaplan Meier curves.

Figure 1 legend:

A: Progression-free survival (PFS) for all patients (3-year rate: 69.7% (95% confidence interval (CI): 60.6-77.1%)), **B:** Overall survival (OS) for all patients (3-year rate: 89% (95% CI 82.1-93.3%)), **C:** Progression-free survival (PFS) by regimen (3 year rate: RCVP 51.6% (95% CI 36.4-64.9%) vs R-CHOP 79.8% (95% CI 60.4-90.4%) vs BR 87.5% (95% 70-95.1%) vs B-O 63.5% (CI 23.8-86.6%) p=0.001), **D:** Overall survival (OS) by regimen (3 year rate: R-CVP 82.5% (95% CI 69-90.5%) vs R-CHOP 100% vs BR 90.6% (95% 73.7-96.9%) vs B-O 87.5% (95% CI 38.7-98.1%) p=0.015). RCVP vs. RCHOP vs. B-R vs. B-O), **E:** Progression-free survival (PFS) by anti-CD20 mAb maintenance (3 year rate: Yes 79.7% (95% CI 68.5-87.3%) vs No: 52.9% (95% CI

37.6-66%), p=0.001), **F:** Overall survival (OS) by anti-CD20 mAb maintenance (3 year rate: Yes 97.4% (95% CI 89.9-99.3%) vs No: 75.1%, (95% CI 60.2-85%), p=0.014).

Table 1S title:

Infection complications of frontline follicular lymphoma therapies over a 3 year follow-up

Table 1S legend:

R-CVP (rituximab with cyclophosphamide, vincristine and prednisolone), R-CHOP (rituximab with doxorubicin, cyclophosphamide, vincristine and prednisolone), B-R (bendamustine with rituximab), B-O (bendamustine with obinutuzumab), Tx (treatment), GCSF (granulocyte colony stimulating factor), PCP (pneumocystis pneumonia), FU (follow up): IVIG (intravenous immunoglobulin). Number of patients with unknown data in the total cohort: a(52),b(2),c(4),d(4),e(4),f(5),g(2),h(1),i(45). *Four patients received other regimen: 1 hybrid BR/R-CVP, 2 hybrid R-CVP/R-CHOP and 1 R-GCVP (rituximab with gemcitabine, cyclophosphamide, vincristine and prednisolone).

Table 2S title:

Univariate and multivariate analyses of factors associated with increased overall incidence of infection and with increased infection-related admissions

Table 2S legend:

CI (confidence interval), FLIPI (follicular lymphoma international prognostic index), CISR-G (Cumulative Illness Rating Scale for Geriatrics), COPD (chronic obstructive pulmonary disease), R-CVP (rituximab with cyclophosphamide, vincristine and prednisolone), R-CHOP (rituximab with doxorubicin, cyclophosphamide, vincristine and prednisolone), B-R (bendamustine with rituximab), B-O (bendamustine with obinutuzumab)

Table 1: Baseline patient, disease and treatment characteristics: R-CVP (rituximab with cyclophosphamide, vincristine and prednisolone), R-CHOP (rituximab with doxorubicin, cyclophosphamide, vincristine and prednisolone), B-R (bendamustine with rituximab), B-O (bendamustine with obinutuzumab), CISR-G (Cumulative Illness Rating Scale for Geriatrics), COPD (chronic obstructive pulmonary disease), ECOG (Eastern Cooperative Oncology Group), Hb (haemoglobin), LDH (lactate dehydrogenase), FLIPI (follicular lymphoma international prognostic index), BM (bone marrow), PD (progressive disease). Number of patients with unknown data in the total cohort: [a](1), [b](1), [c](2), [d](2), [e](52), [f](2), [g](1), [h](2), [i](33), [j](1), [k](58). *Four patients received other regimen: 1 hybrid BR/R-CVP, 2 hybrid R-CVP/R-CHOP and 1 R-GCVP (rituximab with gemcitabine, cyclophosphamide, vincristine and prednisolone).

Baseline Characteristics			R-CHOP (n= 34)	R-CVP (n= 53)	R-bendamustine (n= 32)	O-Bendamustine (n= 9)	Total cohort (n= 132)*
Patient	Diagnosis to treatment; median (range) in months		1.1 (0.03-109.8)	2.4 (0.1-98.1)	1.6 (0.3-54.2)	1.3 (0.5-58.4)	1.6 (0.03 - 109.8)
	Age pre-Tx, median (range)		62 (33-78)	71 (33-90)	56 (28-83)	58(46-76)	63 (28-90)
	Sex (Male)		17/34 (50%)	26/53 (49%)	14/32 (43%)	3/9 (33%)	62/132 (47%)
	CIRS Severity index, mean		0.8	1.4	0.8	0.8	1.1
	Neutrophil count, median (range)[a]		4.7 (1.7-13.1)	4.5 (1.0-12.3)	3.2 (0.3-12.7)	4 (1-5.3)	4.1 (0.3-13.1)
	Lymphocyte count, median (range)[b]		1.2 (0.5-17.1)	1.44 (0.1-7.6)	1.4 (0.3-6.2)	1.3(0.35-25.5)	1.3 (0.1 - 25.5)
	Bronchiectasis history[c] (Yes)		0/33 (0%)	0/52 (0%)	0/32 (0%)	1/9 (11%)	1/130 (1%)
	COPD history[d] (Yes)		0/33 (0%)	5/52 (10%)	2/32 (6%)	0/9 (0%)	7/130 (5%)
	Smoking history[e] (Yes)		2/20 (10%)	5/30 (16%)	4/19 (21%)	0/7 (0%)	11/80 (14%)
	ECOG score[f]	0-1	30/33 (91%)	47/52 (90%)	32/32 (100%)	9/9 (100%)	122/130(94%)
Disease	Ann Arbor staging	3-4	31/34 (91%)	45/53 (85%)	31/32 (97%)	9/9 (0%)	118/132(89%)
	Hb, median (range)[g]	<12	12/34. (35.3%)	9/52 (17.3%)	8/32. (25%)	3/9. (33.3%)	34/131 (26%)
	Raised LDH pre-Tx[h] (Yes)		15/34 (44%)	15/51 (29%)	12/32 (37%)	4/9 (44%)	47/130 (36%)
	Number of nodal sites	>4	23/34 (68%)	31/53 (58%)	27/32 (84%)	9/9 (100%)	91/132 (69%)
	FLIPI score	3-5	23/34 (68%)	29/53 (55%)	21/32 (66%)	8/9 (90%)	83/132 (63%)
	BM involvement[i] Yes		10/20 (50%)	21/40 (52%)	22/27(81%)	4/9 (44%)	58/99 (59%)
	Bulky disease (≥7cm)[j]	Yes	14/33 (42%)	11/53 (21%)	11/32 (34%)	2/9 (22%)	41/131 (31%)
	Raised β-2 microglobulin[k]	Yes	9/21 (43%)	10/23 (43%)	9/19 (47%)	4/9 (44%)	34/74 (46%)
Treatment	# of Rx cycles, median (range)		6 (4-8)	6 (1-12)	6 (2-7)	6 (5-6)	6 (1-12)
	Maintenance treatment	Yes	23/34 (68%)	27/53 (51%)	23/32 (72%)	8/9 (89%)	83/132 (63%)
	Number of maintenance cycles, median (range)*		12 (3-12)	12(1-13)	12(2-12)	6(1-12)	12(1-13)
	Early maintenance discontinuation?	Yes	6	12	3	5	26
		No	14	14	20	2	52
		ongoing	3	1	0	1	5
	Reason for early discontinuation	PD	0	6	2	3	11
		Toxicity	3	2	1	2	8
		Patient preference	0	1	0	0	1
		Death	0	2	0	0	2
		Other	3	1	0	0	4