Lenalidomide, dexamethasone and alemtuzumab or ofatumumab in high-risk chronic lymphocytic leukemia: final results of the NCRI CLL210 trial

Therapeutic response in chronic lymphocytic leukemia (CLL) is variable, with deletion or inactivating mutation of the *TP53* gene on chromosome 17p13 being strongly associated with chemotherapy resistance and short survival. The UK CLL206 and German/French CLL2O trials demonstrated the effectiveness of combining the anti-CD52 monoclonal antibody alemtuzumab with high-dose methylprednisolone (HDMP) or dexamethasone in high-risk CLL,[1,2] and these p53-independent drug combinations became the standard of care for such patients in many centers prior to the advent of novel agents such as ibrutinib, idelalisib and venetoclax.[3] The CLL210 trial was developed to evaluate the potential benefit of adding the cereblon-targeting drug lenalidomide to the alemtuzumab/glucocorticoid backbone. Lenalidomide was of interest owing to its established activity in 17p-deleted CLL coupled with its potential to act in synergy with the other two drugs in a p53-independent manner.[4,5] During the course of the study, alemtuzumab became unavailable and was replaced by the anti-CD20 monoclonal antibody ofatumumab, which has a reported efficacy similar to that of alemtuzumab.[6] Although the study showed that both regimens had therapeutic activity, the predefined co-primary endpoints for efficacy and toxicity were not met.

CLL210 was designed as a single-arm phase II trial with a randomisation to lenalidomide maintenance *versus* placebo for patients who responded to the induction phase. Patients were eligible if they had CLL requiring therapy by International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria and were high-risk defined by a previously documented 17p deletion or *TP53* mutation affecting at least 20% of CLL cells, or a history of not responding to or relapsing within 12 months of responding to fludarabine-containing combination therapy irrespective of *TP53* status.

The study treatment consisted of dexamethasone (40 mg on day 1-4 of alternate weeks from week 1-15), lenalidomide (5 mg daily during weeks 3 and 4 and then 10 mg daily during weeks 5-24) and alemtuzumab (30 mg by subcutaneous injection thrice weekly during weeks 7-22). Supportive care included aciclovir, pneumocystistis jiroveci prophylaxis, cytomegalovirus (CMV) PCR surveillance and granulocyte colony-stimulating factor (G-CSF) support. In the amended protocol, alemtuzumab was replaced by 12 doses of intravenous ofatumumab (300 mg on day 1 of week 7, then 1,000 mg weekly on day 1 of weeks 8-15, then fortnightly on day 1 of weeks 17-21). Patients who achieved a complete response (CR) or partial response were allowed to proceed to allogeneic haemopoietic stem-cell transplantation (HSCT) or were randomised to stopping treatment or continuing lenalidomide as maintenance therapy (10 mg daily until disease progression).

The efficacy and toxicity of induction therapy were evaluated using co-primary endpoints comprising CR rate and tolerability defined as absence of treatment-related grade 5 serious adverse events (SAE) and grade ≥3 SAE due to infection. The criteria for considering the study treatment to be of potential or definite interest were set at a CR rate of more than 10% or 20%, respectively, and an intolerance rate of less than 50% or 30%, respectively. Secondary outcomes included overall response (OR) rate, progression-free survival (PFS), overall survival (OS) and toxicity. Minimal residual disease (MRD) was assessed centrally by 4-color flow cytometry with a sensitivity of 10^{-4}. Efficacy data were assessed by an independent endpoint review committee using the 2008 National Cancer Institute/iwCLL (NCI/iwCLL) criteria.[7] Patients without progressive disease (PD) were deemed evaluable for response assessment if at least 10 weeks of study treatment had been administered. Toxicity assessment was in accordance with common terminology criteria for adverse events (CTCAE) v4.0 with the exception of hematological toxicity which was assessed using the 2008 NCI/iwCLL criteria.

Sixty-four patients were registered from 21 UK sites between February, 6 2012 and October, 8 2015. Sixteen patients were recruited to the original alemtuzumab protocol until September, 4 2012, after which 48 additional patients were recruited to the revised ofatumumab protocol from September, 13 2013. Baseline features of registered patients are summarized in Table 1 and were broadly as expected. Twenty-nine (45%) patients were treatment-naïve, while the other 35 (55%) had received

Table 1. Pre-treatment characteristics.

	Ofatumumab (N=48)	Alemtuzumab (N=16)	Total (N=64)
Age, median (IQR)	66 (59-70)	68 (57-74)	66 (59-70)
Sex, n (%)			
Female	15 (31%)	3 (19%)	18 (28%)
Male	33 (69%)	13 (81%)	46 (72%)
Binet stage, n (%)			
A	10 (21%)	7 (44%)	17 (27%)
B	12 (25%)	4 (25%)	16 (25%)
C	25 (52%)	5 (31%)	30 (47%)
Unknown	1 (2%)	0 (0%)	1 (1%)
IGHV Status*			
Mutated	13 (27%)	2 (12%)	15 (23%)
Unmutated	29 (60%)	11 (69%)	40 (63%)
Other**	6 (13%)	3 (19%)	9 (14%)
WHO performance status, n (%)			
0	25 (52%)	9 (56%)	34 (53%)
1	17 (35%)	7 (44%)	24 (38%)
2	6 (13%)	0 (0%)	6 (9%)
CIRS Total Score*** median (IQR)	2 (0-4)	2 (1-4)	2 (1-4)
CIRS Severity Index median (IQR)	1 (0-2)	1 (1-2)	1 (1-2)
Previous Treatment, n (IQR)			
No	21 (44%)	8 (50%)	29 (45%)
Yes	27 (56%)	8 (50%)	35 (55%)
TP53 defect****, n (%)			
No	8 (17%)	3 (19%)	11 (17%)
Yes	40 (83%)	13 (81%)	53 (83%)

*IGHV genes showing >98% homology to the germline DNA were classed as unmutated and the remainder as mutated. **Six patients had no clonal heavy-chain variable region identified and three patients had insufficient sample to assess for IGHV status. ***CIRS score did not include points for having CLL. ****Previously documented *TP53* defects were confirmed in pre-treatment blood samples from 47 of 53 (89%) patients and consisted of 17p deletion and *TP53* mutation (33 patients), 17p deletion only (eight patients) or *TP53* mutation only (six patients). IGHV: immunoglobulin heavy-chain variable region; IQR: interquartile range; WHO: World health organisation.

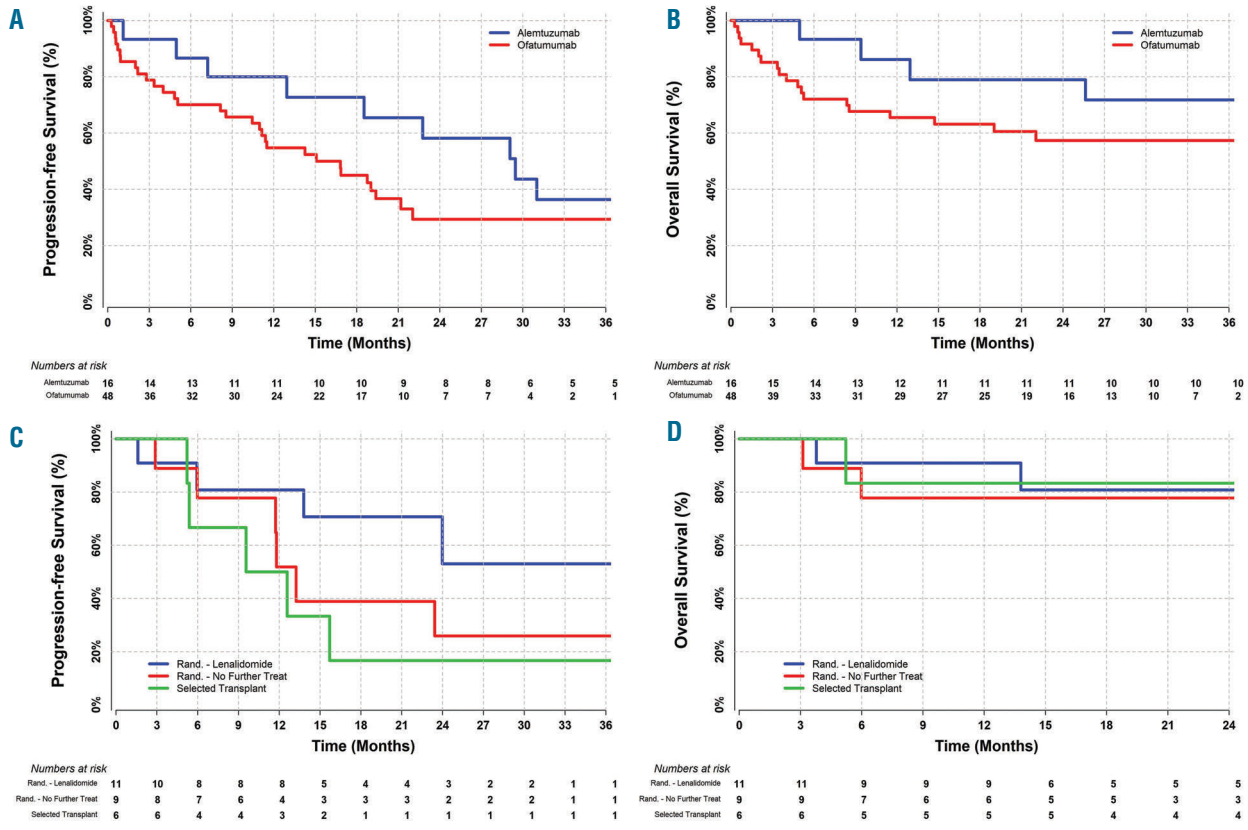

Figure 1. Kaplan-Meier plots showing progression-free and overall survival for the different induction and post-induction treatments. (A) Progression-free survival of the alemtuzumab and ofatumumab cohorts from study registration; (B) overall survival of the alemtuzumab and ofatumumab cohorts from study registration; (C) progression-free survival of patients who were randomised to lenalidomide maintenance or no further treatment or received a hematopoietic stem-cell transplant; (D) overall survival of patients who were randomised to lenalidomide maintenance or no further treatment or received a hematopoietic stem-cell transplant.

between one and three lines of prior therapy. Fifty-three (83%) patients had a previously recorded 17p deletion including all 29 treatment-naïve patients and 24 of 35 (69%) previously treated patients. Patient characteristics were generally well balanced between the alemtuzumab and ofatumumab cohorts.

Within the alemtuzumab cohort, 9 of 16 patients received all of the planned induction therapy, whereas treatment was terminated prematurely in 7 patients who received a median of 29 (interquartile range [IQR]: 12-54) percent of the planned treatment. Within the ofatumumab cohort (excluding one untreated patient who did not start trial treatment due to acute immune thrombocytopenia [ITP]), 24 of 47 patients received all the planned induction therapy, whereas treatment was terminated prematurely in 23 patients who received a median of 29 (IQR: 10-38) percent of the planned treatment.

Among the 16 patients in the alemtuzumab cohort, the CR/CRi, PR, SD and PD rates were 6%, 69%, 0% and 6%, respectively, while 19% were non-evaluable due to missing data and/or receiving less than 10 weeks of study treatment in the absence of disease progression. Among the 47 patients in the ofatumumab cohort, the CR/CRi, PR, SD and PD rates were 2%, 51%, 9% and 11%, respectively, with 28% being non-evaluable. Consequently, neither regimen met the predefined boundary for being of interest from an efficacy perspective. Of note, the 6% CR rate in the alemtuzumab cohort was substantially lower than the 36% CR rate observed in the CLL206 trial[1] which employed an 8-fold higher relative glucocorticoid dose.

Kaplan-Meier curves for PFS and OS are shown in Figure 1. Despite the lower-than-expected CR rate in the alemtuzumab cohort, the 2-year PFS rate was surprisingly good at 58% (95% confidence interval [CI]: 27-91%). This compares with ~17% in the CLL206 trial, 12% in the previously treated cohort of CLL2O and 56% in the treatment-naïve cohort of CLL2O (two thirds of whom received alemtuzumab maintenance or HSCT)[1,2] and suggests that adding lenalidomide to alemtuzumab and dexamethasone may prolong PFS without increasing the CR rate. In contrast, the 2-year PFS rate in the ofatumumab cohort of CLL210 was only 30% (95% CI: 18-49%) with a striking difference between previously treated *versus* treatment-naïve patients (9% and 52%, respectively). Two-year OS rates were higher for the alemtuzumab cohort compared to the ofatumumab one (79% *vs.* 57%).

Our findings revealed interesting differences between the responses induced by the alemtuzumab and ofatumumab regimens. In addition to being more effective in terms of OR rate (75% *vs.* 53%), CR rate (6% *vs.* 2%), 2-year PFS (58% *vs.* 30%), and 2-year OS (79% *vs.* 57%), the alemtuzumab regimen produced much higher rates of blood MRD negativity (37% *vs.* 0%) and morphological bone marrow clearance (50% *vs.* 8% of responders). In contrast, the two regimens were comparably effective at clearing nodal and splenic enlargement (25% *vs.* 20% of

Table 2. Summary of all grade ≥3 adverse events (AE) (reported as either serious AE [SAE] or non-serious AE) occurring with a frequency of >1%.

Toxicity	Induction phase		Post-induction phase			Total events
	Alemtuzumab group (n=16)	Ofatumumab group (n=47)	Lenalidomide arm (n=11)	Control arm (n=9)	Not randomized (n=18)	
Lung infection	8	13	3	3	3	30
Neutropenia	4	15	3		2	24
Sepsis	13	1			3	17
Infection, other	2	5	1	1	2	11
Febrile neutropenia	1	4	1		3	9
Neoplasms, other		2	6		1	9
Anemia	2	3		1	2	8
Hyperglycemia	3	3			1	7
Hypophosphatemia		4	2			6
Thrombocytopenia	2	3				5
Upper respiratory infection		4			1	5
Vomiting	1	3				4
General, other	3	1				4
Infusion related reaction		4				4
Bronchial infection	1	1	1	1		4
Infective enterocolitis	1	1			2	4
Hyponatremia	1		2		1	4
Hypercalcemia		4				4
Hypokalemia		1	2		1	4
Maculopapular rash	1	1	1		1	4
Thromboembolic event		4				4
Localized edema	1			1	1	3
Laryngitis	2	1				3

patients, respectively).

Twenty patients (5 from the alemtuzumab cohort and 15 from the ofatumumab cohort) were randomized to lenalidomide maintenance (11) *versus* placebo (9). The median duration of lenalidomide maintenance was 6 (IQR: 2-10) months. There was a non-significant trend for superior PFS in the lenalidomide arm compared to the control arm and HSCT group (Figure 1). However, these results should be interpreted with caution owing to the small number of patients in each group and the high post-induction drop-out rate.

A total of 252 grade ≥3 adverse events (AE) were identified from SAE and non-serious AE reports, among which infections (83), hematological alterations (61) and metabolic disturbances (30) were the most common (Table 2). Grade ≥3 SAE were reported in 13 of 16 (81%) patients in the alemtuzumab cohort and 28 of 47 (60%) patients in the ofatumumab cohort. These included eight treatment-related grade 5 SAE, of which two were in the alemtuzumab cohort (one infection and one neoplasm) and six in the ofatumumab cohort (four infections, one hematoma and one visceral arterial ischemia). The intolerance rate was 0.67 (95% CI: 0.51-0.80) for the alemtuzumab cohort and 0.38 (95% CI: 0.30-0.46) for the ofatumumab cohort. Consequently, neither regimen met the predefined boundary for being of interest from a tolerability perspective.

Neither of the two regimens evaluated in CLL210 compare favorably with newer drugs such as ibrutinib, idelalisib and venetoclax when applied as monotherapy to a similar patient population. For example, ibrutinib produced a 2-year PFS rate of 85% in a retrospective study of 108 patients with treatment-naïve 17p-deleted CLL[8] and 65% in a combined analysis of 230 patients with a 17p deletion who were recruited into three prospective clinical trials of relapsed/refractory CLL.[9] Similarly, the 2-year PFS rate among 46 patients with a 17p deletion or *TP53* mutation who were recruited into a prospective clinical trial of idelalisib in relapsed/refractory CLL was ~43%,[10] while the 2-year PFS for venetoclax in the pivotal study of 158 patients with predominantly relapsed/refractory 17p-deleted CLL was 54%.[11]

In summary, although the NCRI CLL210 trial showed that lenalidomide and dexamethasone combined with either alemtuzumab of ofatumumab is feasible and active in high-risk CLL, the study did not meet the pre-specified dual primary endpoints. Furthermore, interest in glucocorticoid/ antibody combinations has now been eclipsed by the emergence of highly effective and well-tolerated novel agents that target BCL-2 or components of the B-cell receptor signalling pathway.

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