A Randomised Study of F(C)R in Fit, Elderly Patients with Chronic Lymphocytic Leukaemia (CLL) shows high response rates and a dose intensity effect

Stephen P. Mulligan, Devinder Gill, Paul Turner, William Renwick, Maya Latimer, Naomi Mackinlay, Leanne Berkahn, David Simpson, Phillip Campbell, Cecily Forsyth, Gavin Cull, Rosemary Harrup, Melanie Sulda, Giles Best, Mathias Bressel, Juliana Di Iulio, Bryone Kuss for the CLL Australian Research Consortium (CLLARC) and Australasian Leukaemia and Lymphoma Group (ALLG).

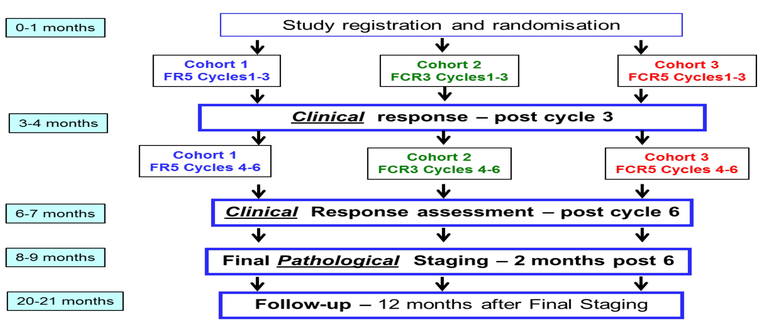
Introduction

Fludarabine (F), cyclophosphamide (C) and rituximab (R) gave superior progression free (PFS) and overall survival (OS) versus (vs) FC in the CLL8 Study. The median age in CLL8 was 61 years compared to 72 years for CLL overall. We aimed to assess the safety, tolerability and efficacy of FCR based therapy in elderly patients (pts).

Methods

Previously untreated pts with progressive CLL aged ≥65 were randomised to one of 3 therapy arms: (i) FR5: F 24mg/m2 po D1-5 + R (375mg/m2 cycle 1, 500mg/m2 cycles 2-6) iv D1, (ii) FCR3: F 24mg/m2 po and C 150mg/m2 po D1-3 + R iv D1 or (iii) FCR5: F 24mg/m2 po+ C 150mg/m2 po D1-5 + R iv D1 all at 4 weekly intervals for an intended 6 cycles. Cycles could be delayed up to 2 weeks for grade 3+ toxicity, and if unresolved by 2 weeks, pts were taken off study. All analyses were by intention to treat (ITT) and adjusted for pre-treatment Binet stage. .

Regimen	Oral Fludarabine	Oral Cyclophosphamide	IV Rituximab
Cohort 1 "FR5"	24 mg/m² Days 1-5		Cycle 1: 375mg/m² D0 Cycles 2-6: 500mg/m² D1
Cohort 2 "FCR3"	24 mg/m² Days 1-3	150 mg/m² Days 1-3	Cycle 1: 375mg/m² D0 Cycles 2-6: 500mg/m² D1
Cohort 3 "FCR5"*	24 mg/m² Days 1-5	150 mg/m² Days 1-5	Cycle 1: 375mg/m² D0 Cycles 2-6: 500mg/m² D1



Results

Recruitment of 120 pts was completed in July 2012. 117 fulfilled eligibility and 1 had no treatment or follow-up reducing the cohort to 116. Median age was 71 (range 65-82) years; 78 males (67%) and 39 females (33%). Binet stage was progressive A - 19 (16.2%), B – 55 (47.0%), C – 43 (36.8%). Response data are shown in table 1 and grade 3+ toxicity in table 2. All 6 protocol cycles were completed in 69% but less on FCR5 44% vs FR5 89% and FCR3 76% (p<0.001). FCR3 vs FR5 was not statistically significant (NSS). Reasons for non-completion were death, intercurrent illness, withdrawn consent, stable or progressive disease, unacceptable toxicity and doctor decision.

ORR was high in all 3 arms but CR rates were higher with FCR5 (p<0.001) vs FCR3 and FR5 (FCR3 vs FR5 NSS). When done, minimum residual disease at ~10-4 was negative in blood in 27/84 and in marrow 33/70 pts.. PFS (p=0.672) and OS (p=0.164) between treatment arms was NSS. PFS and OS at 12 months were 83% and 95%, and 18 months 69% and 90% respectively. At 18 months, PFS was FR5 65%, FCR3 75%, FCR5 65% and OS 97%, 90%, 83% respectively.

Table 1: Response - Final Pathological Staging 2 months Post-Rx or at Rx end	Treatment arm FR5 (*N*=37)	FCR3 (*N*=41)	FCR5 (*N*=38)	Total (n=116)
Complete remission (CR)	14 (38%)	21 (51%)	30 (79%)	65 (56%)
CR (Bone Marrow confirmed)	9 (24%)	13 (32%)	8 (21%)	30 (26%)
CR-i (BM confirmed)	1 (3%)	5 (12%)	9 (24%)	15 (13%)
CR-u (no BM, PB MRD-neg)	1 (3%)	2 (5%)	4 (11%)	7 (6%)
CR-i/u (no BM, PB MRD-neg)	3 (8%)	1 (2%)	9 (24%)	13 (11%)
Nodular Partial Remission (nPR)	11 (30%)	13 (32%)	3 (8%)	27 (23%)
Partial Remission (PR)	10 (27%)	5 (12%)	4 (11%)	19 (16%)
Stable Disease (SD)	1 (3%)	1 (2%)	0 (0%)	2 (2%)
Progressive Disease (PD) / early death	1 (3%)	1 (2%)	1 (3%)	3 (3%)
Overall Response Rate (ORR) (CR, CR-i, CR-u, CR-i/u, nPR, PR)	35 (95%)	39 (95%)	37 (97%)	111 (96%)

Table 2: Grade 3+ Adverse Events by Treatment Arm	Treatment arm FR5 (*N*=37)	FCR3 (*N*=41)	FCR5 (*N*=38)	Total (n=116)
Hematological	15 (41%)	26 (63%)	29 (76%)	70 (60%)
Neutropenia	14 (38%)	20 (49%)	24 (63%)	58 (50%)
Thrombocytopenia	2 (5%)	5 (12%)	12 (32%)	19 (16%)
Anaemia	3 (8%)	6 (15%)	6 (16%)	15 (13%)
Haemolytic Anaemia	0 (0%)	2 (5%)	3 (8%)	5 (4%)
Febrile Neutropenia / Infection	5 (14%)	6 (15%)	13 (34%)	24 (21%)
Skin/Allergy/Fatigue/hypersensitivity	0 (0%)	3 (7%)	8 (21%)	11 (9%)
Other (Cardiac/resp/neuro/metabolic)	5 (14%)	11 (27%)	11 (29%)	27 (23%)
At least 1 grade 3+ AE	21 (57%)	34 (83%)	35 (92%)	90 (78%)
Early cessation *due to toxicity*	2 (5.6%)	1 (2.4%)	13 (34%)	16 (14%)

Toxicity was lower with FR5 compared to FCR3 and FCR5 (p=0.004) (FCR3 vs FCR5 NSS). Dose delay occurred in 43 pts (37%): FR5 12 (32%), FCR3 14 (34%), FCR5 17 (44%) (p=0.653), but early cessation due to toxicity was more common with FCR5 (p<0.001). 11/13 pts stopping early due to toxicity received ≥3 cycles of therapy (mean 3.5). Cyclophosphamide with FR adds toxicity but improves CR rate. ITT full dose FCR5 CR rates were significantly higher (79%), but also higher rates of incomplete marrow recovery, haematological toxicity and earlier cessation of therapy.

Conclusions

Final analysis shows oral FCR therapy is generally safe and well tolerated in CLL pts aged ≥65 years requiring first-line treatment, when early stopping is utilised if prolonged toxicity occurs. Toxicity was mostly hematological and manageable.

Response rates were very high with ORR of 96% and CR rate of 56% (39% not including CRu).

Full dose FCR is highly effective and while cessation due to toxicity appears important, a dose intensity effect may exist. Dose reduced FCR provides a balance of effectiveness, safety and tolerability as first-line therapy for fit elderly pts.

This trial documents that FCR should be the standard of care for all fit patients with CLL.

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Stephen Mulligan
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