Oral Fludarabine and Intravenous Rituximab (FR) as First-Line Therapy for Chronic Lymphocytic Leukemia: Long Term Outcomes and Secondary Malignancies in 673 Patients Treated in British Columbia

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Introduction

- Oral fludarabine and intravenous rituximab (FR) was the standard first-line therapy for CLL or small lymphocytic lymphoma (SLL) patients in BC from 2003-2015. Ibrutinib for frontline treatment for patients with deletion 17p became publicly funded in October 2016.
- Cyclophosphamide was omitted from frontline therapy due to increased risk of AML/MDS observed with combination of fludarabine and alkylators[1]. The protocol was updated in 2014 based on first ever demonstration of mortality benefit with the FCR regimen[2]
- We evaluated outcomes of all CLL/SLL pts treated with frontline FR in BC from 2001-2017, including survival data and rates of second primary malignancies (SPM).

Methods

- Data was obtained from the BC Provincial CLL database with data cutoff of December 2022; BC Cancer Registry was used to identify secondary malignancies occurring after FR. Second malignancy data was available to December 2020.
- Initiated first-line FR from 2003-2017.
- Event free survival (EFS) defined as start of FR to next-line therapy or death.
- Variables examined for impact on OS/TFS included age at FR, gender, primary diagnosis (CLL vs SLL), B symptoms, advanced stage (Rai stage 3-4 CLL, Ann Arbor 1-2 SLL), baseline hemoglobin, lymphocyte count, platelets, LDH and FISH abnormalities.
- No patients with del17p initiate on FR after December 2015 when ibrutinib became funded.

Results

- 673 patients were identified. Median age 66 (range 26-91)
- Baseline characteristics are listed in Table 1.
- Median follow up from FR using reverse Kaplan-Meier method was 9.4 years (range 0.1-20.8 years).
- Median time from diagnosis to initial treatment 2.6 years (range 0 – 27.3 years)
- Median OS and EFS were 10.3 years and 3.5 years for the total cohort
- Median OS and EFS were 11.2 years and 3.6 years respectively if restricted to those who were known to not have del17p

Table 1. Baseline characteristics

Baseline Characteristics at Time of Treatment	
Median age at treatment, years (range)	67 (26-91)
Age > 65 years at treatment, n (%)	374 (56)
Male, n (%)	445 (66)
Primary Diagnosis	
CLL, n (%)	578 (86)
SLL, n (%)	95 (14)
High Combined Stage Group (Rai stage 3-4 or Ann Arbour stage 3-4) (n=652)	104 (16)
Median lymphocyte count at diagnosis, x10^9/L (range) (n=598)	12 (0-662)
Median hemoglobin at diagnosis, g/L (range) (n=593)	139 (52-249)
Median platelets at diagnosis, x10^9/L (range) (n=587)	194 (20-720)
LDH elevated, n (%) (n=388)	70 (18)
B symptoms, n(%) (n=631)	66 (10)
Deletion 17p, n (%) (n= 412)	33 (8)
Deletion 11q, n (%) (n= 410)	53 (12.9)
IGHV mutational status, n(%) (n=303)	14(5)

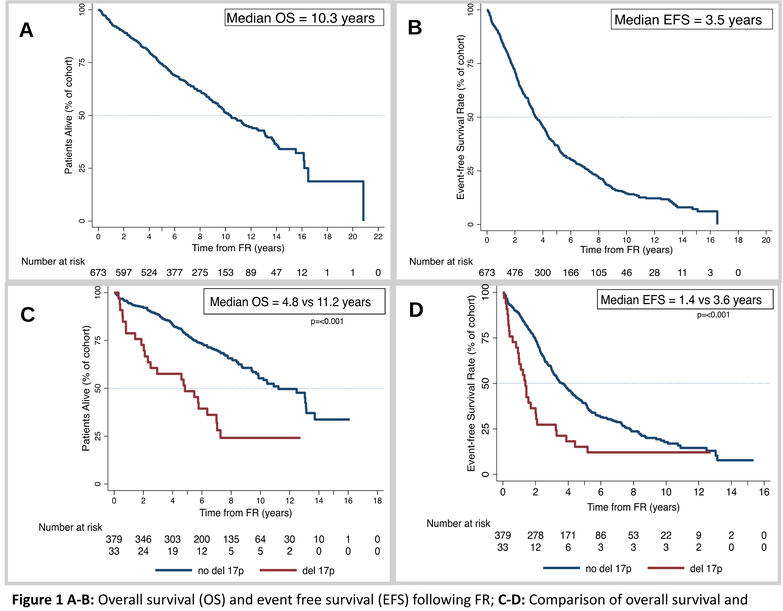


Figure 1 A-B: Overall survival (OS) and event free survival (EFS) following FR; **C-D:** Comparison of overall survival and event free survival in patients with (n=33) or without (n=377) 17p deletion

Table 2. Significant predictors of overall survival on univariate and multivariate analysis

Overall Survival (univariate analysis)		
Covariate	Median OS (yrs)	P
Male gender	9.8 vs. 13.1	0.0065
Abnormal LDH	5.7 vs. 13.1	<0.0001
Hb at FR (cont)	NA	0.032
Age at FR (cont)	NA	<0.0000
Age at FR > 65 yrs	8.4 vs 15.5	<0.0001
Deletion 17p	4.8 vs 11.2	<0.0001

Overall Survival (multivariate analysis)			
Covariate	HR	95% CI	P
Age (cont)	1.06	1.04-1.06	<0.001
Deletion 17p	3.72	2.07-6.69	<0.001

Table 3. Significant predictors of event free survival on univariate and multivariate analysis

Event Free Survival (univariate analysis)		
Covariate	Median EFS (yrs)	P
Male gender	3.3 vs 4.3	0.0482
Abnormal LDH	2.3 vs 4.2	0.0201
Age at FR (cont)	NA	0.0008
Age at FR > 65	3.1 vs. 4.2	0.0031
Deletion 17p	1.4 vs 3.6	0.0002
Deletion 11q	2.5 vs. 3.6	0.0001

Event Free Survival (multivariate analysis)			
Covariate	HR	95% CI	P
Deletion 17p	4.81	2.23-6.46	<0.001
Deletion 11q	1.72	1.19-2.52	0.004

Subsequent Malignancies

- Median follow up for SPMs was 8.8 years
- Total of 258 second primary malignancies in 216 patients (32.1%)
- Medan time to SPM was 3.0 years (95%CI 2.4-3.4 years; range 0.1-15.6 years)
- Richter's transformation (RT) occurred in 49 patients (7.3%) at median 3.1 years (range 0.1-16.1) from FR.
- Frequency of secondary malignancies are shown in Table 4.

Table 4. Summary of malignancies occurring after FR treatment; median follow up 8.8 years.

Malignancy	Number of Cases (% of cohort affected)
Non-melanoma skin cancer	76 (11.3)
Richter's transformation~	49 (7.3)
Lung	21 (3.1)
Colon	25 (3.7)
Melanoma	17 (2.5)
Prostate	15 (2.2)
Head and neck	10 (1.5)
Other heme malignancy (excluding AML)	11 (1.6)
Breast	8 (1.2)
Acute Myeloid Leukemia/Myelodysplastic syndrome*	**6 (0.9)**
Renal and bladder	5 (0.7)
Other malignancy &	5 (0.6)
Sarcoma	4 (0.6)
Pancreas	4 (0.6)
Liver	2 (0.3)
Total	**258**

~3 RT occurred after the data cut-off of December 31, 2020 and are not included in calculation of median follow up time
* Two patients received further alkylator therapy prior to AML diagnosis. 4 patients received FR only.
& Other malignancies includes: 3 metastatic diseases of unknown primary, 1 penile SCC, 1 penile warty carcinoma

Conclusion

- To our knowledge this is the largest cohort of individuals with CLL/SLL patients treated with first line FR reported to date.
- Despite a short median TFS of 3.5 years, we demonstrate a long OS after first line FR of 10.3 years.
- These data demonstrate the efficacy of FR and low rates of therapy related MDS and AML after this non-alkylator based chemoimmunotherapy regimen.

References

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Disclosures

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