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RESEARCH ARTICLE

Beyond Guidelines: Real World Treatment & Outcomes of Chronic Lymphocytic Leukemia at a Tertiary Indian Cancer Centre

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ABSTRACT

Background: Chronic Lymphocytic Leukemia (CLL) is the most common type of leukemia diagnosed in the United States and accounts for about one-quarter of the newly diagnosed cases while it is one of the least common leukemias in India (< 5% of all leukemias) with incidence rates ten times lesser than in the US. There is a dearth of data on regional characteristics and treatment outcomes of the disease; especially from India

Methods: This is a retrospective single centre study conducted among 63 newly diagnosed CLL patients at a tertiary cancer care centre in India from January 2020 to December 2023. The various demographic, clinicopathological characteristics and response to various treatment regimens were recorded. Relapse-free survival, Time to next treatment and Overall survival were the end points studied. The median follow up period was 17 months.

Results: In contrast to the Western data, majority of our patients presented in the younger cohort, with patients aged<= 55 years comprising 36.5% of the total patient population, with a median age of 60 years (about a decade lesser than our Western counterparts). Majority of our patients (88.9%) were symptomatic for the disease at presentation and required initiation of treatment.

Deletion 13q(del 13q) was the most common genetic abnormality seen in our population and deletion 11q(del 11q) the least. Deletion 17p(del 17p) was positive in 30.2% cases upfront and the hazard ratio for relapse was found to be 11.26(95% CI: 2.9,42.7; p=0.0001) in those patients.

The various regimens used in the study were primarily Bruton Tyrosine Kinase inhibitors (BTKis), Bendamustine-Rituximab regimen (BR)and Chlorambucil-Wysolone combination.

All the patients treated with Ibrutinib (BTKi) achieved a complete response (CR) at the end of 6 months, with no documented relapses. BR regimen was the most common regimen found to have been used among the relapsed cases and the hazard ratio for relapse in patients treated with BR regimen was found to be 3.37(95% CI: 0.90,12.5; p=0.069) with a trend towards statistical significance.

Median relapse free survival was found to be 17.6 months & median time to next treatment was found to be 10.9 months. The Median Overall survival was not reached in this study.

This study concludes that Chronic Lymphocytic Leukemia seems to be more aggressive in Indian patients with younger age of presentation, higher disease burden, higher incidence of del 17p, shorter time to first treatment, more frequent relapses and lesser time to next treatment. BTKis seem to be the best treatment regimen for CLL patients. Chlorambucil-wysolone regimen was found to have better survival benefit as compared to the BR regimen.

Keywords: chronic lymphocytic leukemia, tertiary indian cancer centre, treatment outcomes, relapse-free survival, bruton tyrosine kinase inhibitors, demographic characteristics

1. Introduction

Chronic Lymphocytic Leukemia(CLL) is the most common type of leukemia diagnosed in the United States[1] and accounts for about one-quarter of the newly diagnosed cases while it is one of the least common leukemias in India (< 5% of all leukemias) with incidence rates ten times lesser than in the US. The reason for the disparity in the disease frequency between the population of primarily European descent and that of the Orient, Asian and Mediterranean populations still continue to be a mystery[2]. The fact that this trend persists in migrants to other countries, continuing into subsequent generations, shows that genetic predisposition is a likelier reason than environmental factors.

The characteristics of the disease including demographics, clinical presentation, treatment options, and outcomes also tend to vary between subcontinents and studies suggest that the course of the disease tends to be more aggressive in the South Asians with younger age of presentation, shorter time to first treatment and more frequent relapses with lesser time to next treatment (TTNT)[3,4].

The diagnosis of CLL requires sustained elevation of clonal B lymphocytes to >=5∗109/L for at least 3 months [5]. Flowcytometry is used to demonstrate immunoglobulin light chain restriction and thus, clonality. The peripheral smear picture in CLL is described as small, mature lymphocytes with a rim of cytoplasm and a large nucleus lacking discernable nucleoli and partially aggregated chromatin. Smudge cells or gumprecht nuclear shadows are commonly associated with CLL. CLL cells co-express the surface antigen CD5 together with the B-cell antigens CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared with those found on normal B cells. Each clone of leukemia cells is restricted to expression of either kappa or lambda immunoglobulin light chains. Chromosomal abnormalities in chronic lymphocytic leukemia (CLL) are detected in roughly 80% of patients. Among them, deletions of 11q, 13q, 17p, and trisomy 12 have a known prognostic value in CLL[6].

Certain genetic abnormalities have been found to be associated with adverse outcomes in response to standard chemoimmunotherapy regimens in some prospective trials. For example, patients that carry del 17p and/or TP53 mutations have been found to have better clinical outcomes when treated with nonchemotherapeutic agents, such as small molecule inhibitors of BTK, phosphatidylinositol 3-kinase, or BCL2[7].

CLL has been hypothesized to be a B cell receptor (BCR) signaling dependent malignancy. Mutated IGHV gene has been found to be associated with better prognosis as compared to patients with an unmutated IGHV gene (defined as 98% or more sequence homology to the nearest germline gene) Moreover, the presence of mutated IGHV gene is associated with excellent outcomes following chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab[8].

For CLL/SLL without del 17 p, BTKis with or without anti-CD20 mAb (continuous treatment) or Venetoclax + obinutuzumab (fixed duration treatment) or Chemoimmunotherapy (CIT) or immunotherapy (in special circumstances like IGHV-mutated CLL in patients aged < 65 years) are indicated in the first line setting[9].

In situations where BTKis and venetoclax are not available or contraindicated or rapid disease debulking needed, the options are:

- Bendamustine with anti-CD20 mAb
- Obinutuzumab with or without chlorambucil
- High-dose methylprednisolone (HDMP) with anti-CD20 mAb

For CLL cases with 17p deletion, CIT is not recommended since del 17p/TP53 mutation is associated with low response rates[7]

At our centre, the choice of treatment was at the discretion of the treating physician based on the performance status of the patient along with their financial and supportive care status.In general, fit patients who could afford the drug were offered the option of BTK inhibitors (especially if they were found to be TP53 mutated), while the fit, albeit financially unaffordable patients were offered BR regimen and the clinically unfit patients were offered chlorambucil with or without prednisolone based therapies.

With this study, we aim to describe the demographic, clinicopathological and treatment characteristics of CLL patients. While acknowledging the fact that our treatment strategy is different from the currently practised CLL guidelines due to financial limitations, we would like to describe the outcomes of the same in this paper.

2. Methods

This is a retrospective single centre study of newly diagnosed CLL patients conducted in the Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru from the year 2020 to 2023. The diagnosis, risk stratification, indication for treatment, response criteria, and adverse events were recorded as per International Workshop on Chronic Lymphocytic Leukemia guidelines[5].

2.1 ELIGIBILITY

All consecutively diagnosed patients with CLL, above the age of 18 years, registered under the Department of Medical oncology were enrolled in the study.

2.2 BASELINE EVALUATION OF PATIENTS WITH CLL

Diagnostic tests

1. Tests to establish the diagnosis: CBC and differential count Immunophenotyping of peripheral blood lymphocytes
2. Assessment before treatment: History and physical examination, performance status CBC and differential count Serum biochemistry, Direct antiglobulin test, Viral markers (HBsAg, HIV, Anti-HCV), Marrow aspirate and biopsy, CECT scan of neck, chest, abdomen, and pelvis
3. Additional tests before treatment: Molecular cytogenetics (FISH) for del 13q, del 11q, del 17p, trisomy 12, IGHV mutational status

Based on information from the above tests, patients were grouped as Rai Stage 0-IV

Rai Staging

Rai 0 - Lymphocytosis with Absolute leucocyte count > 5 * 10^9/L

Rai I - Lymphocytosis with lymphadenopathy

Rai II - Hepatomegaly and/or splenomegaly with/without lymphadenopathy

Rai III - Lymphocytosis and Hb <; 11 g/dL with/without lymphadenopathy/ organomegaly

Rai IV - Lymphocytosis and platelets < 100 * 10^6/dL with/without lymphadenopathy/Organomegaly

2.3 INDICATION FOR TREATMENT

To initiate treatment in CLL, atleast 1 of the following criteria needed to be met:

1. Worsening marrow failure in the form of Hb <10 g/dL and/or platelet counts < 100 * 10^9/L
2. Massive (ie, >= 6cm below the left costal margin) or progressive or symptomatic splenomegaly.
3. Bulky lymphnodes (ie, >=10 cm in longest diameter) or progressive or symptomaticlymphadenopathy.
4. Increasing lymphocytosis with an increase of >= 50% over 2 months, or with a lymphocyte doubling time (LDT) <6 months; after excluding other causes of lymphocytosis
5. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
6. Symptomatic or functional extranodal involvement (eg: skin, kidney, lung, spine).
7. Disease-related symptoms as defined by any of the following:
   a. Unintentional weight loss >= 10% within the previous 6 months.
   b. Significant fatigue (ie, ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
   c. Fevers >= 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
   d. Night sweats for >= 1 month without evidence of infection.

2.4 SELECTION OF CHEMOTHERAPY REGIMENS

- The choice of treatment was at the discretion of the treating physician based on the performance status of the patient along with their financial and supportive care status.
- In general, fit patients with some financial support, were offered the option of BTK inhibitors (especially if they were found to be TP53 mutated), while the fit, albeit financially unaffordable patients were offered bendamustine-rituximab (BR) regimen and the clinically unfit patients were offered chlorambucil with or without prednisolone-based therapies.

Patients in the BTKi group recieved Ibrutinib at a dose of 420 mg/day. Patients in the BR group recieved Inj.Bendamustine 90 mg/m2 on D1 and D2 along with Inj.Rituximab 375 mg/m2 on D1 (for the first cycle) and 500 mg /m2 for subsequent cycles; q28 days. Patients in the Chlorambucil with Wysolone group received T.Chlorambucil 10 mg BD (D1-D7) with T.Prednisolone 40 mg OD (D1-D7) PO; q28 days. Toxicities were recorded and managed as per iwCLL guidelines.

2.5 RESPONSE ASSESSMENT

The response was assessed at 6 months after completion of the treatment as per iwCLL criteria. A complete History and Physical examination was done along with CBC and Serum Biochemistry. Computed tomography (CT) imaging was repeated. Bone marrow examination was not done in all patients. Hence, responses were documented as unconfirmed complete response (CRu).

2.6 TIME TO NEXT TREATMENT, RELAPSE-FREE SURVIVAL & OVERALL SURVIVAL

Relapse-free survival was defined as the interval between the last treatment day to the first sign of disease progression or death from any cause. Overall survival was defined as the interval between the first treatment day to death. Time to next treatment was defined in our study as the interval between the day of last treatment until the initiation of subsequent therapy for progressive CLL.

3. Statistical Methods

Categorical variables are reported as number and percentage and continuous variables as median and quartiles. Differences in proportions were assessed using the X^2 or Fisher exact test. Cox Proportion Hazard model was used to compare relapse between various categories. Hazard ratio with 95% CI is reported. The time to relapse is presented using Kaplan-Meier analysis. A p value <= .05 was taken as statistically significant. Statistical analysis was performed with STATA version 16.0

4. Results

63 patients who were serially recruited from the year 2020 to 2023, with a median follow up period of 17 months (range: 6 to 36 months) and their demographic profiles are described:

Table 1: Demographic characteristics of Patients with Chronic Lymphocytic Leukaemia at Diagnosis (n=63)

Characteristics	Category	Frequency	Percent
Age	<= 55	23	36.5
	56-60	14	22.2
	61-70	19	30.2
Gender	Male	34	54.0
	Female	29	46.0
Year of Registration	2020	19	30.2
	2021	12	19.0
	2022	11	17.5
	2023	21	33.3
Comorbidities	No Comorbidities	42	66.7
	HTN	14	22.2
	DM	12	19.0
	IHD	3	4.8
	Pulmonary Koch's	2	3.2
	CKD	1	1.6
Addictions	No Addiction	54	85.7
	Smoker	4	6.3
	Alcoholic	2	3.2
	Tobacco Chewing	2	3.2
	Smoker & Alcoholic	1	1.6

As charted in Table 1, the median age at presentation was 60 years; with majority of our patients presenting in the "younger" cohort, with patients aged <= 55 years comprising 36.5% of the total patient pool. There was a slight male preponderance and the majority of the patients recruited had no comorbidities.

Table 2: Presenting complaints (n=63)

Presenting complaints	Frequency	Percent
Neck Swelling	26	41.3
Fatigue	24	38.1
Abdominal Pain	5	7.9
Asymptomatic	7	11.1
Weight Loss	1	1.6

As represented in Table 2, Majority of the CLL patients presented with symptomatic lymphadenopathy followed by significant fatigue and symptomatic organomegaly, with asymptomatic patients constituting only 11.1% of the study group.

Table 3: Median values of blood parameters

Parameters	Median Values
Total Leukocyte Count	71,300/microL
Absolute Lymphocyte Count	60,605/microL
Lymphocyte percentage	85%
Haemoglobin	11.1gm%
Platelet Count	80,000/microL
Serum Creatinine	0.8 mg/dL
LDH	230
Uric acid	4.50 mg/dL

As evident in Table 3, among the 63 patients, the median value of TLC was found to be 71,300; with median S.Creatinine and Uric acid levels being in the normal range. No patient presented with Clinical or Laboratory TLS (Tumour Lysis Syndrome).

Table 4: Clinical characteristics of Patients with Chronic Lymphocytic Leukaemia at Diagnosis (n=63)

Characteristics	Category	Frequency	Percent
B-Symptoms	No	40	63.5
	Yes	23	36.5
Family History	No	61	96.8
	Yes	2	3.4
ECOG PS	1	56	88.9
	2	7	11.1
	3	0	0
	4	0	0
Lymphadenopathy	Yes	44	71.6
	No	19	28.4
Hepatomegaly	No	53	84.1
	Yes	10	15.9
Splenomegaly	Yes	37	58.7
	No	26	41.3
Viral Markers	Negative	62	98.4
	HBsAg+ve	1	1.6
DCT/ICT	Negative	57	90.5
	Positive	6	9.5
Rai Stage	0	3	4.8
	I	7	11.1
	II	16	25.4
	III	11	17.5
	IV	26	41.3

As mentioned in Table 4, majority of patients had no B symptoms at presentation (63.5%). All the patients studied had an ECOG PS of 2 and below. The two patients with a positive family history had a first degree relative with CLL. CECT N/T/A/P revealed generalised lymphadenopathy in 71.6% of cases, hepatomegaly in 84.1% of cases and splenomegaly in 58.7% of cases. Only 6 opatients were found to have DCT/ICT positivity and majority of the patients presented in Rai stage IV.

Table 5: Clinical characteristics of Patients with Chronic Lymphocytic Leukaemia at Diagnosis (Continued)

Characteristics	Category	Frequency	Percent
Del 17p	Negative	44	69.8%
	Positive	19	30.2%
IGHv mutated (n=34)	Negative	21	61.7%
	Positive	13	38.3%
Del 13q	Negative	37	58.7%
	Positive	26	41.3%
Del 11q	Negative	52	82.5%
	Positive	11	17.5%
Trisomy 12	Negative	50	79.3%
	Positive	13	20.7%
Indication for treatment	B Symptoms	18	28.6%
	Fatigue	15	23.8%
	Symptomatic organomegaly	9	14.3%
	LDT 6 months	7	11.1%
	Bulky lymph nodes	7	11.1%
	No indication	7	11.1%
Treatment Given	BR	27	42.8%
	Chlorambucil+Wysolone	18	28.5%
	Ibrutinib	11	17.4%
	Observation	7	11.1%
Toxicities	Nil	48	76%
	Febrile neutropenia	14	22%
	TLS	1	1.5%

As per Table 5, out of the 63 patients that were studied, 44 patients had chromosomal abnormalities (69.8%) Del 13 q was the most common chromosomal abnormality seen (41.3%). Del 17 p was positive in 30.2% cases, Trisomy 12 in 20.7% of cases and Del 11 q was the least common abnormality (seen in only 17.5% of cases). IGHv

mutation status was checked for in only 34 cases, out of which 38.3% (13 patients) were positive. The presence of B symptoms was the most common reason to initiate treatment in CLL (28.6%) followed by fatigue (23.8%) and symptomatic organomegaly (14.3%) with only 7 patients in the the observation cohort. The majority of patients received the BR regimen (42.8%) followed by Chlorambucil with Wysolone regimen (28.5%) and only 11 patients received Ibrutinib (17.4%). Majority of our patients did not develop any toxicities after initiation of treatment. However, among the patients who developed febrile neutropenia (22%), BR regimen was found to cause more FN(78%) as compared to Chlorambucil with Wysolone regimen. TLS was reported in one of the patients (who received BR regimen as the initial treatment).

Table 6: Response to Treatment of Patients with Chronic Lymphocytic Leukaemia (n=63)

Characteristics	Category		Frequency	
	Complete response		16	28.5%
Response (n=56)	*Cases treated with Ibrutinib*	*Cases treated with BR regimen*	*n=10*	*n=6*
	Partial Response or Stable disease		40	71.4%
	Cases treated with BR regimen	*Cases treated with Chorambucil with Wysolone regimen*	*n=22*	*n=18*
Relapse (n=56)	Yes		12	21.4%
	No		44	78.6%
Relapsed cases (n=12) & their Genetic associations	Del 17p		9	75%
	Del 13q		5	41.6%
	Del 11q		3	25%
	Trisomy 12		5	41.6%
Relapsed cases (n=12) & their Association with Initial Treatment Regimens used	BR regimen		9	75
	Chlorambucil + Wysolone		3	25%
	Ibrutinib		0	0
Status present (n=63)	Alive		55	87.3%
	LFU		5	7.9%
	Dead		3	4.7%

In Table 6 out of the 56 cases for whom treatment was initiated, complete response was achieved in 16 cases (28.5%); majority of whom were treated with Ibrutinib. All patients initiated on Ibrutinib achieved CR at the end of 6 months. Among the 40 cases in which PR or SD was achieved, 21 cases were treated with BR regimen and 18 cases were treated with Chlorambucil+ Wysolone.

The associations of relapsed cases (n=12) with the molecular cytogenetic panel and with the initial treatment regimens were studied and Del 17 p was found to be the most common cytogenetic abnormality associated with relapse (75%) followed by Del 13q and Trisomy 12. The most common regimen associated with relapse was found to be BR regimen (75%) followed by Chlorambucil with Wysolone, with no relapses seen in the Ibrutinib cohort.

5. Discussion

CLL in the Western world is rare before the fourth decade of life with a median age of diagnosis of 72 years[10]. The upper age limit for definition of patients with CLL as "younger" has varied between 50 and 55 years in published reports[11,12] and accounts for only about 10-20% of newly diagnosed patients[13]. In contrast to the Western data, majority of our patients presented in the younger cohort, with patients aged<= 55 years comprising 36.5% of the total patient population, with a median age of 60 years (about a decade lesser than our Western counterparts).

These findings closely correlate with other published Asian and Indian data on CLL [3,14-17]. Risk of developing CLL is about two-times higher for men than for women[18,19] as per Western data but among our patients, the disease seems to be almost equally distributed between men and women, with only a slight predilection for men.

According to Western data, majority of patients at presentation do not require treatment and are asymptomatic[20].However, majority of our patients presented with a clinical history of symptomatic lymphadenopathy followed by significant fatigue, with asymptomatic patients constituting only 11.1% of the study group.

Even though our patients presented with greater disease burden (in the form of higher stages of Rai at presentation) with most of them requiring upfront treatment, their hematological and biochemical parameters, however, were grossly normal, with median TLC value of 71,300. This must probably be the reason why none of our patients presented with spontaneous TLS . However, the median platelet count was found to be 80,000/ microL , owing to the fact that majority of our patients presented in Rai Stage IV.

Only a minority of patients had DCT/ICT positivity (6 patients) and this hence explains the median LDH being in the normal range. For such patients, we initiated a short course of oral steroids (wysolone) at 1mg/kg/total body weight and confirmed marrow involvement with bone marrow aspiration and biopsy before grouping them as Stage III/IV disease.

All the patients studied had an ECOG PS of 2 and below, probably owing to the younger age at presentation and lack of comorbidities. Majority of our patients presented as Rai stages III and IV, signalling high morbidity and also probably accounting for early relapses and lesser TTNT.

Del 13q was the most common genetic abnormality seen in our population as well (similar to the Western data available)[6]. However, the incidence of deletion 17p (considered as a poor risk marker) and Trisomy 12 (considered as an intermediate risk marker) were higher in our population – probably accounting for the aggressiveness of the disease at presentation.

According to Western data, deletion of 17p is found in approximately 3–8% of CLL patients at diagnosis and can account for up to 30% in patients treated with chemotherapy[6,21]. However, in our population, it was positive in 30.2% cases upfront. Del 11q was the least common genetic abnormality seen.

BR regimen was the most common regimen used (42.8%) followed by Chlorambucil with Wysolone and Ibrutinib. Among the patients who received BR regimen, febrile neutropenia and TLS were observed as toxicities. Chlorambucil with Wysolone regimen also resulted in febrile neutropenia, albeit in lesser frequency as compared to the BR regimen. This is accounted for by the fact that both regimens contain alkylating agents. The patients treated with Ibrutinib had no incidence of febrile neutropenia or TLS, since both the side effects are traditionally considered as chemotherapy–induced[22]and is not known to be caused by Ibrutinib. There were no Ibrutinib –specific side effects observed in our patients[23].

All the patients treated with Ibrutinib achieved a CR at the end of 6 months, with no documented relapses , thereby reiterating the fact that BTKis are indeed, superior to CIT or Chemotherapy.

Among the relapsed cases, del 17 p was found to be the most common genetic abnormality followed by del 13q and Trisomy 12. BR regimen was the most common regimen found to have been used among the relapsed cases. This is probably because most of the patients who received BR regimen had del 17 p as well (7 out of 9 patients; 77%). These are the patients who should have ideally received BKTis or other nonchemotherapeutic agents as del 17p is found to be relatively resistant to chemotherapy[7,24]. None of the patients who received BTKis relapsed, thus driving home the fact that they yield long lasting remissions, when compared to chemotherapy or chemoimmunotherapy.

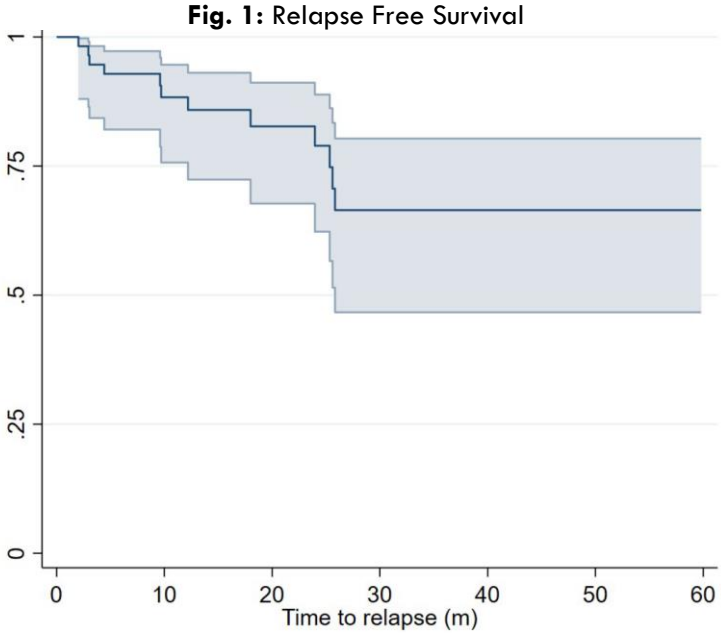
In this study, the Median Overall survival was not reached.

Table 7: Comparison between our findings and other published Indian studies on CLL

	Present Study	**Tejaswi** *et al*[12]	**N Agrawal** *et al*[13]
Median Age	60 years	61 years	61years
Young CLL (age <= 55 years)	36.5%	31.8%	31.6%
M:F Ratio	1.2:1	2.4:1	3.75:1
Asymptomatic patients at presentation	11.1%	42.3%	7%
Rai Stage IV at presentation	41.3%	21.8%	18%
Incidence of Del 17 p at presentation	30.2%	10.5%	-
Percentage of patients who achieved CRu with BR regimen	28.5%	77.2%	-
Percentage of partial response with Chlorambucil-Wysolone based therapy	71.4%	71.3%	-
Percentage of relapse	21.4%	35.5%	-

Median age at presentation was comparable between the studies and the "young CLL" cohort constituted roughly 35% of the main subset. Our study found a relatively equal distribution of the disease in both sexes while Tejaswi et al and N Agrawal et al had higher prevalence among males.The prevalence of Stage IV disease and Del 17 p at presentation appear to be higher in our study. Our patients did poorly with BR regimen as compared to the study by Tejaswi et al; with similar responses to Chlorambucil-wysolone regimen.Our patients seemed to have lesser relapses as compared to the other published studies.

Fig. 1: Relapse Free Survival



Relapse free survival (n=56) observed in the patients post their respective initial treatment regimens was found to be 17.6 months (Interquartile range of 8.7 to 26.7 months). Median Time to Next Treatment (TTNT) was found to be 10.9 months (Interquartile range of 3.7-24.7 months).

Table 8: Hazard ratio for relapse in 17p deletion

_t	Hazard Ratio	Std. Err.	z	P > |z|	95% Confidence Interval
Del_17_p	11.26095	7.660359	3.56	0.000	2.968503 42.71814

Table 9: Hazard ratio for relapse in Trisomy 12

_t	Hazard Ratio	Std. Err.	z	P > |z|	95% Confidence Interval
Trisomy_12	5.313061	3.330002	2.66	0.008	1.55542 18.14855

In Tables 8 and 9, according to the Cox proportional hazard model, the hazard ratio for relapse was found to be 11.26 (95% CI:2.9, 42.7, p = 0.0001) in patients with Del 17 p, and 5.3 (95% CI: 1.5, 18.1, p = 0.018) for Trisomy 12. These two variables were considered together in Table 10, in the Cox proportional regression model and del 17p remained statistically significant with p value of 0.001

Table 10: Hazard Ratio for relapse in 17p deletion and Trisomy 12, when considered together

_t	Hazard Ratio	Std. Err.	z	P > |z|	95% Confidence Interval
Trisomy_12	3.541117	2.328217	1.92	0.054	0.9760938 12.84662
Del_17_p	9.652345	6.731154	3.25	0.001	2.460591 37.86398

Fig.2(a) Kaplan Meier survival estimate for patients with del 17 p

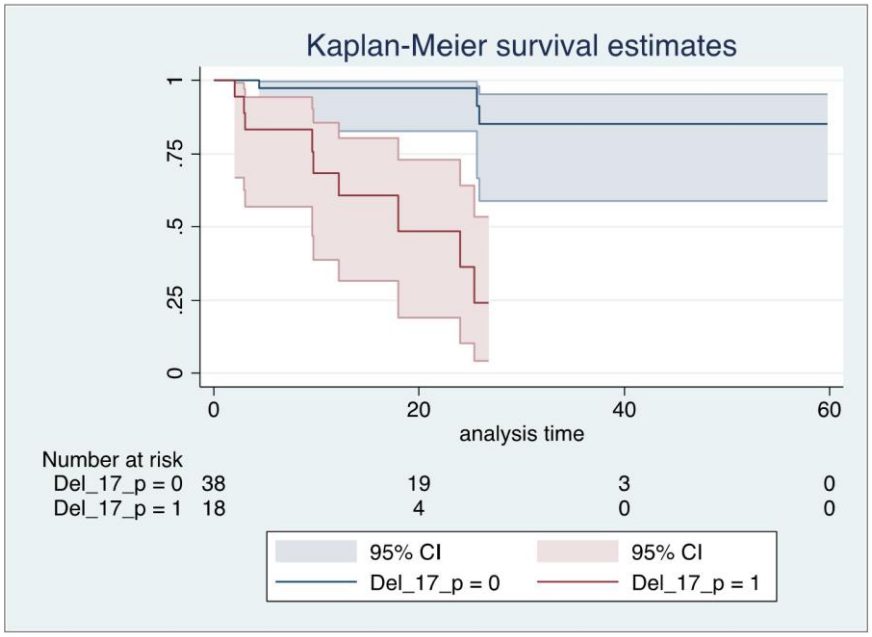
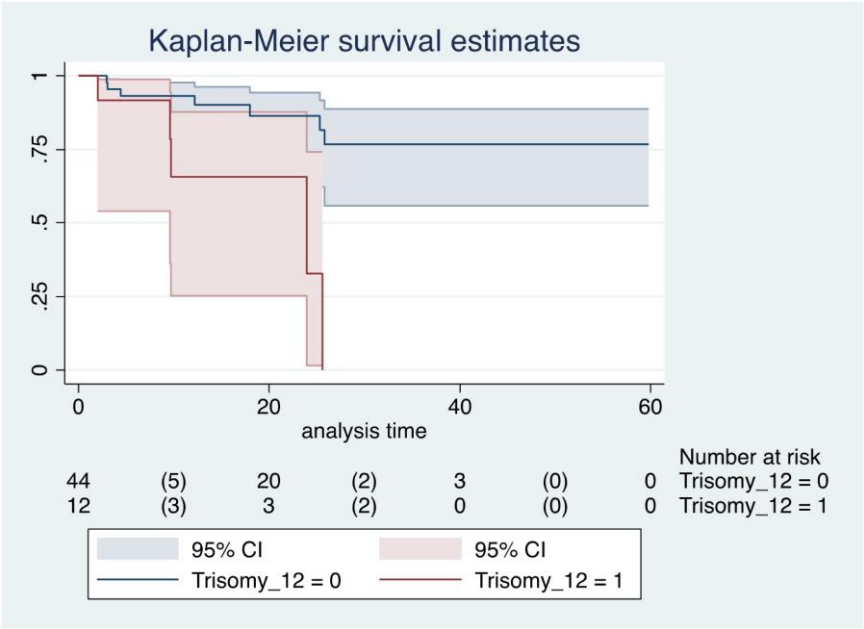
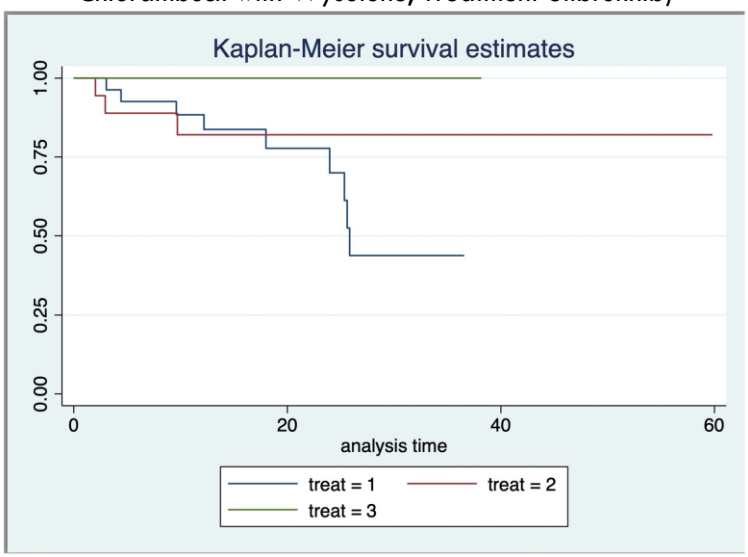


Fig.2(b) Kaplan Meier survival estimate for patients with Trisomy 12



The Kaplan-Meier survial estimate with 17p deletion and Trisomy 12 are graphically represented in Figures 2a & 2b.

Fig.3 Kaplan Meier survival estimates for the various regimens used (Treatment 1: BR Regimen,Treatment 2: Chlorambucil with Wysolone, Treatment 3:Ibrutinib)



The survival of patients post initial treatment with BR, Chlorambucil-Wysolone, Ibrutinib regimens have been graphically represented in Figure 3a.

Table 11: Hazard Ratio for relapse in patients treated with BR Regimen

_t	Hazard Ratio	Std. Err.	z	P > |z|	95% Confidence Interval
1.treat1	3.378435	2.264441	1.82	0.069	0.9082106 12.56738

In Table 11, the hazard ratio for relapse in patients treated with BR regimen was found to be 3.37(95% CI: 0.90,12.5; p = 0.069) with a trend towards statistical significance.

6. Conclusion

CLL seems to be more aggressive in our population with younger age of presentation, higher disease burden (in the form of higher Rai stage), shorter time to first treatment (Majority of our patients presented upfront with indications for treatment initiation), higher incidence of del 17 p upfront and more frequent relapses with lesser time to next treatment. Del 17 p remains a risk factor in our population with statistically significant lesser RFS in patients. Bruton Tyrosine Kinase inhibitors (BTKis) seem to be the best regimen for CLL patients in that it had no documented adverse effects, and yielded complete responses and long lasting remissions. Chlorambucil + wysolone remains a good option in resource limited settings and had lesser relapse rates than the cohort treated with BR regimen, with lesser adverse effects. The regimen however did not result in complete response in any of the patients.

Declarations

6.1 ETHICAL APPROVAL

Ethical Committee clearance was not required for this study as per institutional protocol since it is a retrospective study.

6.2 FUNDING

This study was not funded by any organization or body.

6.3 COMPETING INTERESTS

There are no financial or non-financial competing interests in this study. The authors of this study, are only affiliated to the institution where the study was held.

6.4 DATA AVAILABILITY

Not Applicable.

7. References

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