Evolution of natural history and prolongation of overall survival in patients with chronic lymphocytic leukemia: analysis of a long-term follow-up of an unselected cohort in the Hradec Králové district, Czech Republic.

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1. Introduction

* Therapy of chronic lymphocytic leukemia (CLL) has udergone a revolutionary progress over the last 20 years:
* Chemotherapy ➔ chemoimmunotherapy (CIT) ➔ oral targeted inhibitors (especially Bruton tyrosine kinase inhibitors and bcl-2 inhibitor venetoclax).

* However, analyses of the long – term changes of the clinical course and patients´prognosis at large centres are often hampered by the referral bias from regional hospitals which usually refer only patients with progressive CLL requiring therapy.

* Our project eliminated referral by analyzing an unselected cohort of CLL patients from a well – defined region (the Hradec Králové district, Czech Republic). Here, all new CLL cases could be recorded at our department.

2. Aims of the project

1. Retrospective evaluation of the natural history of CLL and evolution of time to first – line therapy (TTFT) and overall survival (OS) over time.
2. Assessment of the impact of introduction of first – line chemoimmiunotherapy and novel targeted inhibitors during the course of the disease.

3. Patients and Methods

Between 1999 – 2019, we diagnosed 311 CLL patients (median age, 69; Binet A/B/C, 85/7/7 %, median follow-up, 127 months) in the Hradec Králové district.

To compare baseline characteristics and clinical course, we divided our cohort into three subgroups according to the years of diagnosis: Group 1 (1999-2005) where chemotherapy dominated (n=97), Group 2 (2006-2012) when chemoimmunotherapy was introduced (n=101) and Group 3 (2013-2019) when the chemoimmunotherapy prevailed (n=113). Basic characteristics and prognostic factors of these subgroups are listed in Table 1. Statistical analysis was performed using MedCalc v. 20.109 (Medcalc, Mariakerke, Belgium). Fisher´s exact test was employed to compare differences in proportions. TTFT and OS were assessed using the log-rank test and Kaplan-Meier curves were constructed. Multivariate Cox regression analysis was performed as well. P values were double – sided and considered significant if < 0.05.

4. Results

Table 1. Basic characteristics

Variable	Years of CLL diagnosis		
	1999-2005	2006-2012	2013-2019
Number of patients	97	101	113
Median age (years)	71	68	68
Males, %	59	62	58
Binet stage A/B/C, %	84/5/10	86/7/7	86/9/5
Unmutated IGHV, %	49	56	32
Serious comorbidity, %	53	38	41
Treated for CLL, %	50	47	38
Died, %	89	54	25
Median follow - up, months	228	149	97

Differences in variables between subgroups

With the exception of significantly borderline younger age in the Group 3 vs. Group 1 (68 vs 71 years, p=0,043) and higher proportion of unmutated IGHV in Group 1 vs Group 2 (49 vs. 32%, p=0,01), there were no other significant differences between the three subgroups. It is important to note, however, that IGHV was available in 34% and 53% in Groups 1 and 2; similarly, low % of FISH was known for historical reasons.

Univariate analysis

There were no differences between the 3 groups regarding TTFT (p=0.32, Fig. 1). However, there was a highly significant improvement in overall survival from the time of diagnosis (Group 1 vs. 2 vs. 3, median 80 vs. 143 months vs. not reached, p<0.0001; Fig. 2). OS from the initiation of first-line (1L) therapy was significantly prolonged in Groups 2 and 3 (median 41 vs. 92 months vs. not reached, p=0.0001, Fig. 3). Patients who received first – line CIT had significantly longer OS from treatment start than those treated by chemotherapy (median 112 vs. 43 months, p<0.0001, Fig. 4).

Univariate analysis (continued)

In addition, patients who were treated during their course of CLL by targeted inhibitors had markedly better OS from initiation of 1L than those who were not (median 129 vs. 50 months, p<0.0001; Fig. 5). Please see hazard ratios and 95% confidence intervals in the Figures.

Fig. 1 Time to first – line therapy based on the year of diagnosis

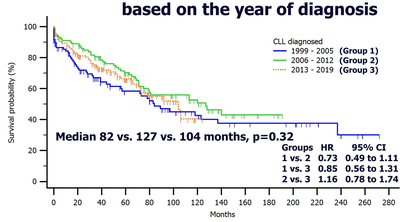


Fig. 2 OS from diagnosis based on the year of diagnosis

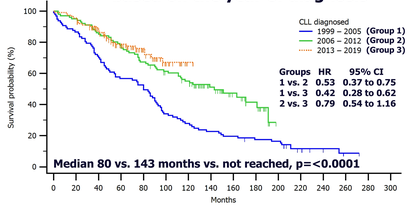


Fig. 3 OS from first – line therapy

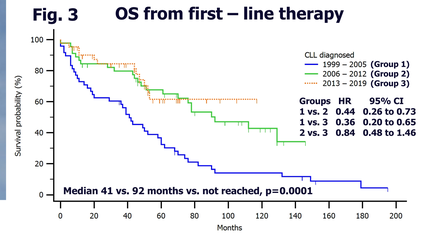


Fig. 4 OS from first – line therapy: the role of chemoimmunotherapy

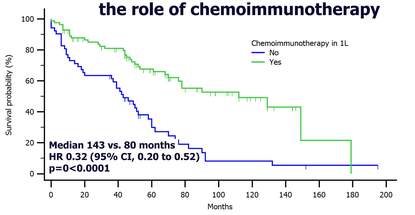
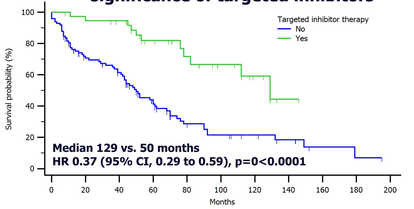


Fig. 5 OS from first – line therapy: significance of targeted inhibitors



Multivariate analysis of OS from first – line therapy

The use of chemoimmunotherapy in 1L (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0,30 to 0.77; p=0.0025) and targeted oral inhibitors anytime during the course of the disease (almost exclusively in the relapsed / refractory CLL) (HR, 0.40; 95% CI, 0.21 to 0.79; p=0.0079) retained their significance as independent factors of longer OS in multivariate analysis. Further independent factor for longer OS was female gender (HR 0.61, 95% CI, 0.38 to 0.99, p=0.046). In contrast, higher age was independent predictor of shorter OS (HR 1.05, 95% CI, 1.02 to 1.08; p=0.0006). We could not include IGHV and FISH results in the multivariate analysis model due to high proportion of missing data.

5. Conclusions

1. Analysis of a large, unselected CLL cohort with > 10 year follow - up revealed significantly lower age at diagnosis in Group 3, possibly pointing to earlier CLL diagnosis.
2. While TTFT did not change over time, OS was markedly longer both from diagnosis and start of first - line therapy.
3. Univariate and multivariate analyses indicate that improvement of OS was achieved mainly due to use of CIT vs. chemotherapy in the 1L and targeted agents for relapsed / refractory disease.

6. Acknowledgements

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7. Conflict of interest statement

The authors declare no relevant conflict of interest related to this project.