Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Research Article

Beta-Blockers Therapy is Associated with Shorter Time to First Treatments in Early-Stage Chronic Lymphocytic Leukemia

Tamar Tadmor[1*], Guy Melamed[2], Hilel Alapi[2], Sivan Gazit[2], Tal Patalon[2], Lior Rokach[3]

[1]Department of Medicine, Bnai Zion Medical Center, Haifa, Israel; [2]Department of Medicine, Kahn Sagol Maccabi Research & Innovation Center, Tel-Aviv, Israel; [3]Department of Software and Information Systems Engineering, Ben-Gurion University of the Negev, Beer-Sheva, Israel

ABSTRACT

Introduction: Beta blockers are among the most used class of drugs for the treatment of hypertension, arrythmias and congestive heart failure. Chronic Lymphocytic Leukemia (CLL) is the most frequent leukemia in western countries, and it involves elderly patients, who presents with past medical history including hypertension, arrythmias and heart disease.

Methods: In the current study, we aimed to retrospectively explore the effect of the use of beta-blocker, on Time To First Treatment (TTFT) in a large cohort of 3,474 patients with asymptomatic CLL who were under watch and wait approach. Data obtained from electronic medical records of Maccabi Healthcare Services (MHS) members, after receiving approval from the institution's ethical committee.

Results: Median follow-up of the entire cohort was 1745 days (57 months), and during this wait and watch period, 884 patients (25.4%) received a beta-blocker agent, for a minimum of 6 months. Bisoprolol Fumarate and Atenolol emerge as prominent treatments, representing 87.9% out of all of beta-blocker exposure. We report that utilization of any beta-blocker was associated with a shorter Time To First Treatment (TTFT), indicated by a hazard ratio of 1.5985 with a p-value of less than 0.001. The ten years treatment free ratio is 83.9% among beta-blockers users, while among non-beta-blocker users it is 90.4%.

Conclusion: The clinical observation, using a long-term retrospective study demonstrates that the administration of beta-blocker to patients with CLL in a watch and wait active surveillance is significantly associated with a shorter time to first treatment.

Keywords: Chronic Lymphocytic Leukemia (CLL); BETA Blockers; Time To First Treatment (TTFT); Hypertension

INTRODUCTION

Beta blockers are among the most used class of drugs for the treatment of hypertension, arrythmias and congestive heart failure. They act as competitive antagonistic on adreno-receptors expressed on cell membrane [1]. Their role in cancer patients and on malignant disease course have been investigated mainly from clinical point of view, with some controversial results. Some studies involving patients with breast, pancreatic and liver cancers they have beneficial and anti-tumor effect [2,3]. While others results are less convincing, as the study by Livingstone et al., that reported a relative lower survival for β-blocker users than in non-users amongst melanoma patients [4]. The main mechanism of action of this class of drugs is on the adrenergic system through inhibition of beta-adrenergic receptor. But, beta-blockers are reported to be involved in other mechanisms including tumorigenesis, angiogenesis, and tumor metastasis [2]. In regards to the lymphatic system: It has been reported that healthy human peripheral blood lymphocytes also express adrenergic receptors and uses of beta-blocking agents, may induce a polyclonal activation of lymphocytes [5-7]. In regards to malignant lymphocytes: It was demonstrated that when adding beta blockers *in vitro* to Chronic Lymphocytic Leukemia (CLL) cells-they induces signaling defect when compared to signaling in healthy lymphocytes [7,8]. Whether beta-blocker affects the clinical course of CLL patients, remains an open question. In the current study, we aimed to retrospectively explore the effect of beta-blocker, on Time To First Treatment (TTFT) in a large cohort of patients with asymptomatic CLL, who were under watch and wait approach.

Correspondence to: Tamar Tadmor, Department of Medicine, Bnai Zion Medical Center, Haifa, Israel, USA, E-mail: tamartadmor5@gmail.com

Received: 26-Jul-2024, Manuscript No. JLU-24-33219; **Editor assigned:** 29-Jul-2024, PreQC No. JLU-24-33219 (PQ); **Reviewed:** 12-Aug-2024, QC No. JLU-24-33219; **Revised:** 20-Aug-2024, Manuscript No. JLU-24-33219 (R); **Published:** 27-Aug-2024, DOI:10.35248/2165-7556-24.12.387

Citation: Tadmor T, Melamed G, Alapi H, Gazit S, Patalon T, Rokach L (2024). Beta-Blockers Therapy is Associated with Shorter Time to First Treatments in Early-Stage Chronic Lymphocytic Leukemia. J Leuk. 12:387.

Copyright: © 2024 Tadmor T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

MATERIALS AND METHODS

The cohort is based on anonymized data obtained from electronic medical records of Maccabi Healthcare Services (MHS) members, after receiving approval from the institution's ethical committee. MHS is the second-largest healthcare organization in Israel, with 2.5 million insured patients.

The study included data from 1st January, 2000, to 1st December, 2022. By using the ICD-9 coding system, we identified 4098 patients who received a diagnosis of CLL during this period. Following the approach of previous retrospective studies of CLL conducted on the MHS database, we excluded 430 patients who did not meet these specific criteria: A) the diagnosis was confirmed by an expert hematologist, B) the diagnosis was recorded in the MHS registry for hematologic neoplasm diseases, C) Meeting either of the following conditions. (i) Receiving anti-CLL therapy at least once after diagnosis, or (ii) if treatment-naive, have at least one complete blood count result indicative of an absolute lymphocyte count above 5×10^9/L at any time during the study. Furthermore, 194 patients were excluded from the cohort as they required immediate therapy following diagnosis. Consequently, the final study cohort included 3474 patients [9].

Statistical analysis

We used a multivariable time-dependent cox proportional hazards model adjusted for age and sex to accommodate variations in Beta-blocker intake during the follow-up period. This cox model considers the usage of beta-blocker as a time-varying covariate measured monthly, allowing for variations in a patient's exposure status throughout the follow-up period. This approach enhances statistical power for detecting moderate effects and reduces the likelihood of biases, such as immortal time bias. Please refer to Appendix A for detailed information regarding the statistical procedure used.

RESULTS AND DISCUSSION

Our cohort included 3,474 patients with CLL who are treatment naïve, and the median follow-up duration for the entire cohort, from the beginning of the study until the time of first treatment or death, was 1745 days (602-3700). Among the 3,474 patients included in the study, 884 patients (25.4%) received a beta-blocker, for a minimum of 6 months during the watch-and-wait period. Within the 884 patients, 62% have already begun receiving beta-blocker, within the first six months of the watch and wait period.

Those utilizing beta-blockers are typically of slightly older age (69.8 *vs.* 66.7 years). We also examine the effect of medical history as covariant for TTFT: Only two conditions were found to be associated with TTFT: Atrial fibrillation and valvar diseases. Additional information is available in Table 1 which outlines demographic laboratory and clinical profiles of individuals categorized as beta-blocker users and non-users. Table 2 displays the outcomes presented as Hazard Ratios (HRs) alongside their respective 95% Confidence Intervals (CIs) derived from fully adjusted multivariable analyses incorporating fixed and time-dependent covariates. The assessment period for measuring exposure commenced from the CLL diagnosis and extended until the conclusion of the follow-up period (Table 1) [10,11].

Table 1: The characteristics of the cohort and the differences among the Beta-blocker users and non-beta-blocker users.

Variable	Non-Beta blocker users (N=2590)	Beta blocker users (N=884)	p-value
Age at diagnosis	66.71 (57.87, 7.18)	69.8 (62, 76.92)	<0.001
Sex: Male	1486 (57.4%)	514 (58.1%)	0.694
Binet Stage=C	179 (6.9%)	55 (6.2%)	0.504
Blood tests			
Albumin	4.300 (4.100, 4.400)	4.300 (4.100, 4.400)	0.495
Calcium	9.300 (9.100, 9.500)	9.300 (9.100, 9.500)	0.487
Elevated LDH1	Elevated: 90.2%	Elevated: 89.9%	0.765
Platelet	209.528 (167.000, 243.000)	203.748 (161.000, 239.000)	0.015
Hemoglobin	13.5 (12.600, 14.400)	13.5 (12.500, 14.500)	0.208
WBC	14.900 (11.592, 21.000)	14.900 (11.400, 20.600)	0.943
% Lymp	59.375 (47.450, 69.906)	59.100 (47.525, 69.825)	0.852
Medical history			
Rheumatic disease	7 (0.3%)	3 (0.3%)	0.722
Acute stroke	84 (3.2%)	43 (4.9%)	0.029
Arrhythmias	83 (3.2%)	34 (3.8%)	0.388
Atrial fibrillation	272 (10.5%)	145 (16.4%)	<0.001
Cardiac conduction disorders	47 (1.8%)	33 (3.7%)	0.002
Cardiomyopathic diseases	32 (1.2%)	17 (1.9%)	0.139
Heart failure	182 (7.0%)	99 (11.2%)	<0.001
Diseases of the peripheral blood vessels	141 (5.4%)	60 (6.8%)	0.156
Endocarditis	8 (0.3%)	6 (0.7%)	0.135
Hypertension	1525 (58.9%)	661 (74.8%)	<0.001
Ischemic heart disease	263 (10.2%)	132 (14.9%)	<0.001
Myocardial infarction	183 (7.1%)	93 (10.5%)	0.001
Myocarditis	33 (1.3%)	8 (0.9%)	0.472
Pace maker	83 (3.2%)	35 (4.0%)	0.283
Transient stroke	65 (2.5%)	24 (2.7%)	0.713
Valvular diseases	43 (1.7%)	33 (3.7%)	<0.001

We report that utilization of any beta-blocker was associated with a shorter Time To First Treatment (TTFT), indicated by a hazard ratio of 1.5985 with a p-value of less than 0.001. Figure 1 presents the expected TTFT curves after adjustment for age and sex using the method discussed [12]. The intake of beta-blocker was found to be associated with a shorter TTFT, after adjustment for immortal time bias (p-value=0.02). Among beta-blocker users, the ten years treatment free ratio is 83.9%, while among non-beta-blocker users it is 90.4%. In order to examine if beta blocker is merely proxy to the patients' conditions, we used calcium channel blockers as a control variable and checked if it has similar impact on TTFT. Calcium channel blockers were determined to have no statistically significant impact on TTFT (Table 2) (Figure 1).

Table 2: Multivariable Cox Regression analysis for time to first treatment in a cohort of treatment naïve patients with CLL (time-dependent covariates).

Time to first treatment		
Variable	**Hazard ratio**	**p-value**
Age during diagnosis	0.9678 (0.96-0.98)	<0.0001****
Sex=Male	2.1586 (1.6-2.92)	<0.0001****
Binet stage=C	1.8916 (1.26-2.85)	0.002211**
Albumin	1.0519 (1.02-1.08)	0.000591***
Calcium	1.1075 (0.97-1.26)	0.130646
Elevated LDH	1.773 (1.21-2.6)	0.003526**
Platelet	0.9953 (0.99-1)	0.000152***
Hemoglobin	0.7206 (0.69-0.76)	<0.0001****
WBC	1.0024 (1.002-1.003)	<0.0001****
Atrial fibrillation	1.7106 (1.17876-2.4825)	0.004720 **
Valvular diseases	0.4710 (0.25219-0.8797)	0.018170*
Beta blocker (Yes/No)	1.5985 (1.22-2.09)	0.000603***
Calcium channel blocker (Yes/No)	0.8650 (0.68941-1.0854)	0.210386
By Beta Blocker use and dose		
Acebutolol (Yes/No)	4.4347 (2.2420-8.7720)	<0.0001****
Acebutolol dosage	Not available	NA
Atenolol (Yes/No)	2.8858 (1.1876-7.0124)	0.019307*
Atenolol dosage	0.9783 (0.9463-1.0114)	0.196363
Bisoprolol fumarate (Yes/No)	2.5036 (1.5062-4.1615)	0.000401***
Bisoprolol fumarate dosage	0.9189 (0.8115-1.0406)	0.18256
Carvedilol (Yes/No)	4.6718 (2.4078-9.0645)	<0.0001****
Carvedilol dosage	0.7912 (0.6634-0.9437)	0.009221 **
Labetolol HCL (Yes/No)	4.4347 (2.2420-8.7720)	<0.0001****
Labetolol HCL dosage	0.8731 (0.8614-0.8850)	<0.0001****
Metoprolol (Yes/No)	3.9322 (1.9449-7.9501)	0.000138 ***
Metoprolol dosage	1.0005 (0.9930-1.0081)	0.000138 ***
Propranolol (Yes/No)	3.5983 (1.7491-7.4023)	0.000503 ***
Propranolol dosage	0.9691 (0.9029-1.0401)	0.383572
Sotalol (Yes/No)	4.4347 (2.2420-8.7720)	<0.0001****
Sotalol dosage	0.8190 (0.8107-0.8274)	<0.0001****

Note: Significance 0.0001****, 0.001***, 0.01**, 0.05

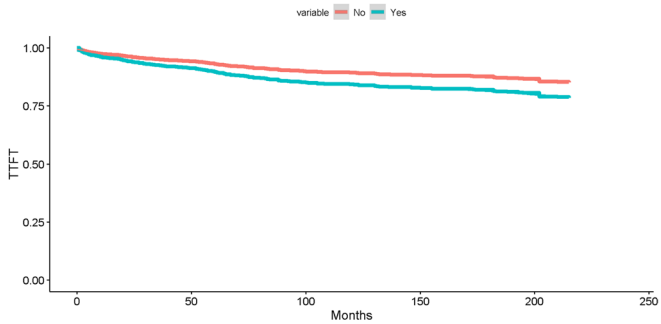

Figure 1: Time To First Treatment (TTT) in a large cohort of treatment naïve patients with CLL, after adjustment to age, sex and other co-founders based on the method presented in (14) Comparing BETA blockers users and non-users.

Subsequently, we conducted separate analyses to assess the significance of usage and dosage for each beta-blocker type. To achieve this, we conducted multivariable analyses on a sub-cohort comprising all patients exposed to the specific drug along with those who never received any beta-blocker. The usage of all drugs was found to be statistically significant, while the dosage was found to be statistically significant only for carvedilol, labetolol, metoprolol and sotalol. We analyzed the duration of patient exposure, measured in months, to different types of beta-blockers along and their corresponding dosages (Table S1).

Notably, Bisoprolol fumarate and Atenolol emerge as prominent treatments, collectively representing 56,185 months of exposure out of a total of 63,931 months of beta-blocker exposure (87.9%). Our study is based on a large cohort of "treatment naïve" patients with CLL, who were identify from the electronic medical records of Maccabi Healthcare Services (MHS) members. Our analysis has the advantage to involve a "non-selected" cohort of all patients who receive the diagnosis of CLL. We observed that more than a quarter of these CLL patients are taking routinely beta blockers for their other medical diseases, mainly hypertension, arrythmias or heart disease. The effect of this class of drugs on CLL course was never evaluated, an as a result it is unknown, and probably not taken into consideration when its being prescribed.

We demonstrated that utilization of any beta-blocker was associated with a shorter Time To First Treatment (TTFT), indicated by a hazard ratio of 1.5985 and that the ten years treatment free ratio is 83.9% among beta-blockers users, while among non-beta-blocker users it is 90.4%. This effect of shorter TTFT was not observed when we perform the same analysis on another class of drugs: The calcium blockers. As both beta

blockers and calcium channel blockers are being prescribed for some overlap indications as hypertension or arrythmias, it may be rational to favor the use of the second group in several circumstances for patients with CLL who is in active surveillance. Our study has several limitations. Firstly, its retrospective nature may introduce inherent biases. Secondly, we acknowledge the assumption that patients who purchased beta-blockers indeed took them, which may not always be accurate. Moreover, besides complete blood count, all other lab tests were not performed regularly, thus limiting their role as time-dependent confounding factors.

CONCLUSION

The main limitation of our study is its observational nature, as it does not add any mechanistic explanation or the pathogenesis of our reported clinical outcome which favor CLL progression and need to start treatment when using beta-blockers drugs. We may only speculate based on *in vitro* studies that b-blockers may influence or activate CLL cells using their beta-adrenergic receptors. Our long-term retrospective study demonstrates that the administration of beta-blocker to patients with CLL in a watch and wait active surveillance is significantly associated with a shorter time to first treatment. A prospective clinical trial is needed to validate results.

ACKNOWLEDGEMENT

The research was supported by a grant from Maccabi Healthcare Services

AUTHORSHIP CONTRIBUTIONS

TT designed, organized and wrote the manuscript. HA and GM prepared and preprocessed the data, LR performed the statistical analysis and wrote the manuscript. SG and TP critically reviewed the manuscript and supervised the research.

REFERENCES

1. Gorre F, Vandekerckhove H. Beta-blockers: Focus on mechanism of action Which beta-blocker, when and why?. Acta cardiologica. 2010; 65(5):565-570.
2. Peixoto R, Pereira MD, Oliveira M. Beta-blockers and cancer: Where are we?. Pharmaceuticals. 2020;13(6):105.
3. Tabassum M, Chikermane SG, Johnson C, Abdulkareem NM, Wang EM, Johnson ML et al. Comparing the effects of various β-blockers on cardiovascular mortality in breast cancer patients. Cardio-Oncology. 2024;10(1):1-17.
4. Livingstone E, Hollestein LM, Van Herk-Sukel MP, Van de Poll-Franse L, Nijsten T, Schadendorf D, et al. β-Blocker use and all-cause mortality of melanoma patients: Results from a population-based Dutch cohort study. Eur. J. Cancer. 2013;49(18):3863-71.
5. Ricci A, Bronzetti E, Conterno A, Greco S, Mulatero P, Schena M, et al. α1-Adrenergic receptor subtypes in human peripheral blood lymphocytes. Hypertension. 1999;33(2):708-712.
6. In S, Dueymes M, Fournié GJ. Beta blockers may induce in C57BL/6 mice a polyclonal activation of lymphocytes which is not mediated by beta adrenergic receptors. Int. J. Immunopharmacol. 1988;10(7):901-6.
7. Krasnikova TL, Kozlova MV, Kalentchuk VU, YuI S, Parfenova EV, Radiukhin VA, et al. Beta-blocker action on lymphocyte proliferative response in essential hypertension. Cor et vasa. 1988;30(2):110-114.
8. Kamp T, Liebl B, Haen E, Emmerich B, Hallek M. Defects of β2-adrenergic signal transduction in chronic lymphocytic leukaemia: Relationship to disease progression. European journal of clinical investigation. 1997; 27(2):121-127.
9. Goin JC, Sterin-Borda L, Borda ES, Finiasz M, Fernandez J, De Bracco MM. Active alpha2 and beta adrenoceptors in lymphocytes from patients with chronic lymphocytic leukemia. Int. J. Cancer Res. 1991; 49(2):178-181.
10. Chesnaye NC, Stel VS, Tripepi G, Dekker FW, Fu EL, Zoccali C, et al. An introduction to inverse probability of treatment weighting in observational research. Clin. Kidney J. 2022; 15(1):14-20.
11. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Statistics in medicine. 2013; 32(16):2837-2849.
12. Thomsen BL, Keiding N, Altman DG. A note on the calculation of expected survival, illustrated by the survival of liver transplant patients. Statistics in Medicine. 1991;10(5):733-748.