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COST OF CHRONIC MYELOID LEUKEMIA FROM THE PAYER'S PERSPECTIVE IN TÜRKIYE: RESULTS OF A DELPHI PANEL ANALYSIS

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a slowly progressing blood-cell cancer that originates in the bone marrow. The disease is classified into three different phases: chronic phase (CP), accelerated phase and blast phase. The standard treatment for chronic phase CML (CP-CML) is tyrosine kinase inhibitors (TKIs) and the introduction of the first generation of TKI, imatinib, has shifted the treatment paradigm of the disease. Despite the introduction of other TKIs for patients with resistance or intolerance, the high cost of these products is a cause for concern for healthcare systems and payer organizations.

Aim: This study aims to estimate the financial burden of CP-CML on the Social Security Institution (SSI) of Türkiye.

Methodology: A modified Delphi Panel approach was used to estimate the cost of CP-CML to the SSI. The panel was comprised of six leading hematologists who answered a Health Care Resource Utilization Questionnaire to identify the type, patient ratio and frequency of resources used in the diagnosis and treatment of the disease. The answers to these questions were discussed in a face-to-face meeting with the experts and a final consensus was reached. Following this, the costs of treatment at each treatment line and for patients with the T315I mutation were calculated based on the reimbursement prices and rules of the SSI.

Results: The annual total cost of CP-CML to SSI was estimated to be 1,283,203,114TRY (€36,643,159). The share of second line treatment in total costs is 38%, for the first line 31% and for the 3+line 21%. In terms of annual per patient costs, the highest cost per patient was for those with the T315I mutation (at 1,405,281 TRY,

€40,129). The annual cost per patient for first line treatment was 100,142 TRY (€2,859), while for second and third + line treatments the annual costs per patient were 320,490 (€9,151) and 357,870 (€10,219) respectively. These results indicate that the share of CP-CML treatment within the total expenditures of SSI in 2023 was 0.2%.

Conclusion: Our findings suggest that there is still a room to include more recent and effective TKIs on the SSI's reimbursement list.

KEYWORDS

Chronic phase Chronic Myeloid Leukemia, Cost, Türkiye, Delphi Panel.

INTRODUCTION

Chronic myeloid leukemia (CML) is a slowly progressing blood-cell cancer that originates in the bone marrow, with an estimated prevalence of 6.0 per 100,000 individuals and an incidence of 1.25 per 100,000 reported in Europe in 2023(1). The 5-year relative survival is estimated to be 70.0% in the US with an annual death rate of 0.3% per 100,000. The disease is most frequently seen in males in the later stages of life with the median age at diagnosis being 66(2). CML is classified into three different phases: chronic phase (CP), accelerated phase and blast phase(3). The chronic phase is the earliest phase and generally has the best response to treatment while the accelerated phase is a transitional phase when the disease becomes more aggressive. Finally, the blast phase is the most severe and aggressive phase of the disease when it becomes life-threatening. Most patients are diagnosed with CP-CML (90-95%)(3). The standard treatment for chronic phase CML (CP-CML) is tyrosine kinase inhibitors (TKIs)(3,4) and the introduction of the first generation of TKI, imatinib, has shifted the treatment paradigm of the disease(5–7). The introduction of generic versions of imatinib had an impact on reducing the cost of treatment(8). For patients with a failure in first-line treatment due to TKI resistance or

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intolerance, options include increasing the dose of the current TKI (for TKI resistant patients), switching to another TKI, the use of interferon therapy or chemotherapy, and stem cell transplantation(9). The rates of treatment failure increase from approximately 50% in patients receiving second-line treatment to 75-80% in patients receiving third line treatments(10). Although the majority of the patients respond to first-line treatment and stay in the CP for a long time and although the survival rates are higher compared to other cancer types, the burden on the quality of life of the patient and the burden on the health care systems due to higher costs of treatment are major concerns from a public health perspective. Second generation TKIs, bosutinib, dasatinib, and nilotinib were developed later to meet the needs of patients with resistance or intolerance to imatinib in the second line. Ponatinib and asciminib are third generation TKIs. It is stated that the choice of TKIs depends on a number of factors such as tolerability and adverse event profile, disease phase, mutation profile and the presence of comorbidities(11).

Several studies have been conducted on CML in Türkiye as well (6,11–13). Şahin et al analyzed the demographic features, disease status, response and resistance to treatment, and the use of second generation TKIs in a retrospective study covering 1,133 patients(6). Contrary to general findings, the majority of the patients in this study were female (50.7%) and the mean age for the entire patient population was 46.1 ± 14.8. 94.9% of the patients were in the chronic phase and 4.1% were in the accelerated phase. All patients received imatinib as the first line of therapy. According to the study results, 95.7% of the patients had a complete hematological response and 63.8% had a cytogenetic response at certain time points. Out of 1,133 patients 114 (10.1%) progressed to the accelerated or blastic phase with a median time for progression of 58.5 ±30.1 months. The first choice of treatment for switching therapy was dasatinib (58.8%) followed by nilotinib (41.2%). The findings of this study are of special value as it covers a large segment of the population from 11 centers.

In another study(11) covering 13 centers with 861 CP-CML patients, 50.4% of the patients were found to be male. The median age was 52 (40-64) and 31 % of the patients had at least one co-morbidity. Imatinib was the most frequently used first line treatment (97.6%). The rate of switching to second line treatment was 48.7% and the main reason for switching was absence/loss of response (60%). 25.7% of the patients switched to third line treatment with the main reason being side-effects (50.9%). 2.9% of the patients needed to switch to fourth line treatment. In another retrospective study conducted at Trakya University records of 102 patients between January 2003 and October 2019 were analyzed. In line with global trends, the majority of the patients were male (58.8%) and in the chronic phase (93.1%)(12). An expert meeting was held to discuss the clinical management of CML in Türkiye(13). The experts in this study concluded that the incidence of CML was 0.9 per100,000 adults with a male to female ratio of 1.17 and a mean age at diagnosis of 48.5 years.

Türkiye has a social security based health care system with the Social Security Institution (SSI) covering over 90% of the population. The SSI is the primary purchaser of health care services from both public and private sectors having significant power in determining rules and reimbursement conditions for all health care products and services. These rules and conditions are outlined in the Health Implementation Guide (SUT) published and revised by the SSI. Currently, imatinib, dasatinib, bosutinib and nilotinib are reimbursed by the institution. Ponatinib, although not yet market approved, is reimbursed through the named patient program (Attachment 4/C). Asciminib has market approval but is not currently reimbursed. According to the SSI's reimbursement rules, imatinib is the first line treatment for CP-CML, with bosutinib, dasatinib, and nilotinib as the options in cases of resistance or intolerance to imatinib. Given the extensive coverage of the population and the comprehensive health benefits package of the SSI, there is a growing need for financial information on all diseases. We did not come across any studies about the cost of treating CML in Türkiye from the SSI perspective. This study aims to estimate the financial burden of CP-CML on the SSI of Türkiye.

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MATERIALS AND METHODS

Türkiye has a financial information system (MEDULA) used by the SSI to collect all information about expenditures and utilization of health care services. Since the data collected in this system is not shared with the public, any study aiming to estimate the financial burden of a disease must use alternative methodologies. Expert opinions on the use of health care resources for the diagnosis, treatment and monitoring of a disease are commonly preferred. Reaching a consensus on the use of health care resources can be challenging for researchers. The Delphi Method defined as 'a scientific method to organize and manage structured group communication processes with the aim of generating insights on current or prospective challenges; especially in situations with limited availability of information'(14), is widely used in the healthcare sector including in Türkiye(15–22). In this study we used the Delphi method to identify the type, frequency and duration of health care resources used to treat CP-CML in Türkiye. To reach a consensus we used the Modified Delphi Method which includes a face-to-face meeting with the experts to finalize the consensus-building process(23).

Purposeful sampling(24) was used to identify 6 hematologists as key opinion leaders on the treatment of CML in Türkiye. A Healthcare Resource Use (HRU) form was developed based on the treatment algorithms for CML. The form included questions about the type, patient ratio and frequency of resources used for outpatient, inpatient, intensive care and emergency care. Participants were asked to independently fill out the form. After this initial round, researchers analyzed all responses, calculated averages and created a draft consensus document for discussion during a face-to-face meeting. Healthcare resources were priced according to the SSI's reimbursement rules and guidelines. The unit costs of all tests, procedures and drugs were identified and these unit costs were multiplied by the percentage of patients and frequency of resource use. During the face-to-face meeting all responses were reviewed, and a final consensus was reached. Once the form was finalized, annual per patient costs for CML were calculated. The total cost of CML to the SSI was estimated using epidemiological data provided by the experts.

RESULTS

In the study epidemiological questions were asked first to estimate the number of patients and their disease status for use in the calculations of total expenditures on CP-CML. All the answers presented here are the results of the consensus reached by the experts. The prevalence and incidence of CML were reported as 8 per 100,000 and 1 per 100,000 respectively. The experts indicated that 93% of the patients were in the chronic phase, 5% in the accelerated phase and 1% in the blast phase. Among patients in the chronic phase, 64 % were receiving first line treatment, 24% second line treatment and 12% third line treatment. The majority of the patients were followed on an outpatient basis with a very low rate of hospitalization. Hospitalization rates were 2%, 3% and 11% for patients in the second line, third line treatment and with T315I mutation respectively. Only 1% of the patients in the second line, 2% in the third line and 2 % with T315I mutation required intensive care. Other consensus results related to the general outlook of the disease are presented below:

- Only 2% of patients progress to accelerated or blast phase within the first year.
- Patients typically remain in the chronic phase for an average of 9 years.
- 70% of patients transition from first line to second line due to resistance to current treatment, 25% due to intolerance and 5% due to resistance + intolerance.
- 84% of patients transition from second line to third line and beyond due to resistance to current therapy, 12% due to intolerance and 4% due to resistance + intolerance.
- In cases of failure with first line therapy, in a new TKI is used in 95% of cases while the dose of current

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therapy is increased in 5% of cases.

- 1% of patients have the T315I mutation.

As previously mentioned, experts have reached a consensus on the type, frequency and duration of resources used for CP-CML patients. Based on this information and SSI rules for reimbursement, the cost of treatment per patient is estimated by treatment line and T315I mutation. Table 1 presents the results of this analysis. The cost of diagnosis was estimated as 4,613TRY.

Table 1: Annual Cost per Patient for CP-CML Patients by Treatment Line and T315I Mutation

	Annual Cost per Patient (TRY)	Annual Cost per Patient (€)*
First Line		
Outpatient	99,851.03	2,851
Inpatient	291,81	8.00
Total First Line	**100,142.84**	**2,859**
Second Line		
Outpatient	320,060.12	9,140
Inpatient	331,34	9.50
Intensive Care	98,68	3.00
Total Second Line	**320,490.14**	**9,151**
Third + Line		
Outpatient	357,289.42	10,203
Inpatient	383,23	11.00
Intensive Care	197,35	6.00
Total Third Line	**357,870.00**	**10,219**
Patients with T315I Mutation		
Outpatient	357,289.42	10,204
Inpatient	383,23	11.00
Intensive Care	197,35	6.00
Total	**357,870.00**	**10,219**

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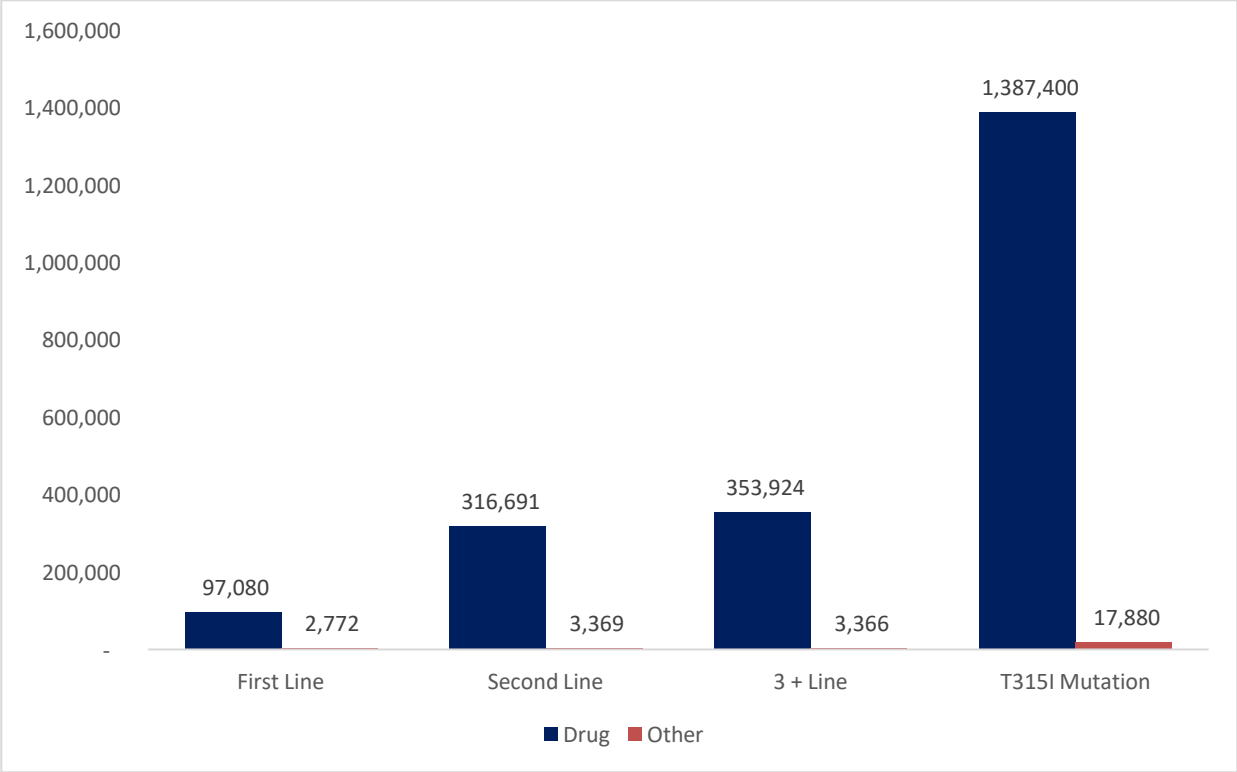
TRY: Turkish Lira, €: Euro

***Turkish Central Bank Exchange rate (20.06.2024): 1€=35.018**

As can be seen from the table the majority of expenditures are for outpatients. Drug expenditures make up the bulk of outpatient costs (Figure 1).

Figure 1: Distribution of CP-CML Outpatient Costs by Treatment Level and T315I Mutation



The annual cost per patient is highest for patients with the T315I mutation primarily due to the use of ponatinib for these patients. After estimating the annual cost per patient for all lines and the T315I mutation, the number of patients within these classifications was calculated based on expert views.

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Table 2: Number of CML Patients by Disease Stage and Treatment Lines

Total Turkish Population (2023)*	86,907,000
CML Prevalence	0.00008
CML Number of Patients	6,953
Distribution of Patients by Phase	
Chronic	6,466
Accelerated	348
Blast	139
Number of CP Patients by Treatment Line	
First Line	4,094
Second Line	1,535
3+ Line	768
Number of Patients with T315I Mutation	70

Table 3 below presents the total annual cost of CP-CML to the SSI based on the estimated annual cost per patient and the number of patients in each line followed by Figure 2.

Table 3: Annual Cost of CP-CML to the Turkish SSI

	Number of Patients	Cost per Patient (TRY)	Total Cost (TRY)	Total Cost (€)*
Diagnosis	869**	4,613	4,008,610	114,472
First Line	4,094	100,142	409,951,456	11,706,577
Second Line	1,535	320,490	491,992,501	14,049,342
3+ Line	768	357,870	274,687,634	7,843,982
T315I Mutation	70	1,475,181	102,562,912	2,928,787
		Total Cost	**1,283,203,113**	**36,643,159**

TRY: Turkish Lira

***Turkish Central Bank Exchange rate (20.06.2024): 1€=35.0189**

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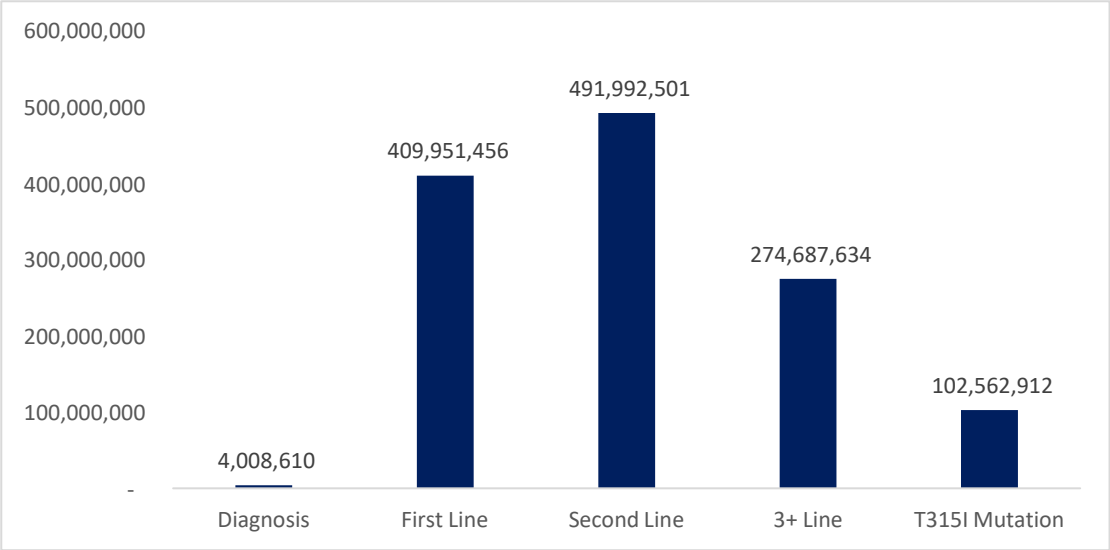
****Based on the incidence (1/100,000)**

Figure 2: Distribution of Annual CP-CML Cost by Treatment Line and T315I Mutation (TRY)



DISCUSSION

The introduction of TKIs for the treatment of CML has improved the expected survival of CML patients with survival rates now similar to the general population(25–27). This has resulted in CML patients receiving treatment for longer periods compared to other types of cancer, using high cost drugs and leading to increased direct health expenditures(28,29). Information on the cost of treating a disease for third-party payer is valuable for policymakers. This study aimed to estimate the cost of CP-CML to the Turkish SSI. The Modified Delphi Method was used to identify the resources used to treat the disease by line of treatment. Information on patients with the T315I mutation was also collected. SSI's reimbursement prices and rules were used to calculate the costs. The annual total cost of CP-CML to SSI was estimated to be 1,283,203,114TRY (€36,643,159). The share of second line treatment in total costs is 38%, for first line 31% and for 3+line 21%.

In terms of annual per patient costs, the highest cost per patient was for those with the T315I mutation (at 1,405,281 TRY, €40,129). The annual cost per patient for first line treatment was 100,142 TRY (€2,859), while for second and third + line treatments the annual costs per patient were 320,490 (€9,151) and 357,870 (€10,219) respectively. Patients received treatment on an outpatient basis with very low costs on hospitalization and intensive care. Within the outpatient costs, drug expenses made up around 98% of the total outpatient costs.

The SSI has spent 553,143,000,000TRY on healthcare services in 2023(30). The share of CP-CML in these expenditures is 0.2%. The drug expenditures of the SSI for the same year were 178,300,000,000TRY. According to our estimations, the annual drug expenditures for CP-CML are 1,252,690,503TRY (€35,700,376) accounting for 0.7% of the SSI's drug expenditures.

This is the first study in Türkiye on estimating the costs of CP-CML to the social security institution. Such studies are also rare in the literature. A real-world study from Italy indicated a heavy economic burden for patients in

the 2nd or ≥ 3rd lines of therapy(25) which aligns with our findings. The high cost of TKIs was also emphasized in a study in Malaysia(31). The benefits and cost-effectiveness of imatinib as the first line treatment for CP-CML have been studied with researchers concluding that imatinib is a cost-effective and safe treatment option(31,32). The introduction of generics for imatinib has made it a preferred option for the first line treatment. Current evidence suggests that the SSI's policy to enforce imatinib as the first line treatment for CP-CML is a good option. The SSI's coverage of TKIs is in line with current scientific evidence.

CONCLUSION

CML is a type of blood cell cancer that originates in the bone marrow. The current treatment for the disease with TKIs has turned it into a chronic condition with patients now reaching survival rates comparable to the normal population. Since TKIs are effective but expensive drugs, it is crucial to consider their use from both the patient's and the payer's perspective. This study aimed to estimate the cost of treating CP-CML from the Turkish payer perspective. Our findings indicate that the total cost of CP-CML within the SSI's health care budget is 0.2%. This suggests that that there is still room to include more recent and effective TKIs on the SSI's reimbursement list.

Conflict of Interest: This study was supported by Novartis Türkiye.

The selected results of this research were presented as a poster at the ISPOR Europe 2024 Congress in Barcelona.

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