Journal of Pharmaceutical Care
jpc.tums.ac.ir

Nilotinib and Imatinib Utilization in Iran over 14 years

Ava Mansouri[1], Kimia Hirbod[1], Maryam Taghizadeh-Ghehi[1*], Aarefeh Jafarzadeh Kohneloo[2], Mohammad Solduzian[3], Molouk Hadjibabaie[1,4]

[1]Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran.
[2]Department of Epidemiology and Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Clinical Pharmacy, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
[4]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

Received: 2020-11-08, Revised: 2020-11-17, Accepted: 2020-11-18, Published: 2020-12-30

ARTICLE INFO

Article type:
Original article

Keywords:
Nilotinib;
Imatinib;
Chronic Myeloid Leukemia;
Insurance Coverage;
Drug Prescriptions;
Drug Utilization Review.

ABSTRACT

Background: Tyrosine Kinase Inhibitors (TKIs) are drugs of choice for Chronic Myeloid Leukemia (CML) treatment. CML healthcare costs greatly exceed of other haematological malignancies treatment mostly due to TKIs. There are several generic and brand preparations of imatinib and nilotinib, the only available TKIs, in Iran with different prices and varied insurance coverage. We have studied TKIs utilization and also investigate the effect of different insurance coverage on TKIs utilization in Iran.

Methods: This was drug utilization study about Imatinib and Nilotinib over 14 years. It was conducted in two phases; data extraction from pharmaceutical wholesale data (2003-2017) for utilization trend assessment and registered data of prescriptions from Sizdah-Aban Pharmacy (2011-2014) for utilization trend and insurance coverage assessment such as; prescriptions frequency, number of TKIs, insurance companies and their cost coverage in each prescription.

Results: Imatinib consumption increased significantly from 2003 to 2013. This trend stopped afterward. Nilotinib consumption had ascending trend. The trend line of years 2014 to 2017 was steeper and statistically significant (β=0.0014, p-value=0.02). The amount of nilotinib cost coverage by insurance companies increased significantly from 2011 to 2014 (p-value=0.04). The coverage of imatinib costs by insurance companies changed slightly during the study period that was not statistically significant. Frequency of prescriptions with full cost coverage doubled for nilotinib, while did not change remarkably for imatinib, from 2011 to 2014. Mean (SD) of imatinib and nilotinib counts per prescription was significantly higher in prescriptions for which 100% of the cost was covered.

Conclusion: We found increasing trend in nilotinib utilization and observed some effects from nilotinib cost coverage by insurance on its consumption. This study made a clear picture for policy makers to monitor imatinib and nilotinib use appropriateness and design the proper cost-effective studies to make evidence-based decisions.

J Pharm Care 2020; 8(4): 170-175.

► Please cite this paper as:

Mnasouri A, Hirbod K, Taghizadeh-Ghehi M, Jafarzadeh Kohneloo A, Solduzian M, Hadjibabaie M. Nilotinib and Imatinib Utilization in Iran over 14 years. J Pharm Care 2020; 8(4): 170-175.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (1). Untreated or symptomatically treated CML is fatal, with a reported median survival of approximately 2–3 years (2). CML accounts for 15-20% of adult leukemias (1, 3, 4) and about 4,600 new cases are reported annually in the United States (4). The usual clinical courses of CML are chronic phase (CP) followed by accelerated phase (AP) and blast phase (BP) or blast crisis (BC) (1). About 90% of patients are diagnosed in the CP which can enter to the AP or BC after a period of 4-6 years without therapeutic interventions (2, 3), with the average survival

*Corresponding Author: Dr Maryam Taghizadeh-Ghehi
Address: Research Center for Rational Use of Drugs, 4th Floor, No. 92, Karimkhan-Zand Ave., Hafte-Tir Sq., Tehran, Iran.Tel/ Fax: +982188814157
Email: taghizadehgm@sina.tums.ac.ir

of 18 weeks (4).

Imatinib mesylate was approved by the FDA in 2001 for the treatment of CML (3). Imatinib has an acceptable safety profile and induces complete recovery in 98% of newly diagnosed patients in CP and complete cytogenic response (CCyR) in 86% of patients (4) results in overall survival (OS) rate of about 85% (3, 5). However, patients in AP and BP and patients with ALL Philadelphia chromosome showed drug resistance over time due to BCR-ABL mutation (3-5). Using higher doses to overcome the resistance increased grade 3 and 4 toxicity in these patients (3).

Nilotinib, as second-generation Tyrosine Kinase Inhibitors (TKIs), initially was approved by FDA for imatinib resistant and/or intolerant patients in 2007 (3, 5). Nilotinib has a greater potency and selectivity than imatinib for binding to ABL kinase (5, 6). Following observed increased response rate and decreased disease progression, FDA approved nilotinib as frontline CML therapy in 2010 (5, 7). Despite the superiority of this new TKI in some aspects, review of the literature indicates that imatinib still has an acceptable efficacy and safety profile in the treatment of CML (8, 9), and the observed differences between these medications were not clinically significant (5). In a systematic review study, it is stated that due to the lack of information, it is difficult to reach any conclusion about the cost-effectiveness of imatinib and nilotinib (7). Therefore, Imatinib and nilotinib are both reasonable choices for starting CML treatment in patients who have not been previously treated and are in CP. In Iran and many other Asian countries imatinib is the first line of CML treatment (10).

Policy-making and management of expensive new anti-cancer drugs has always been one of the most difficult and challenging issues in health system of the countries (11). Iran has a high insurance coverage and great financial support for effective cancer drugs (12), However, the cost-effectiveness of drugs which could be used for treatment of a cancer should be assessed (12, 13). In 2013, a group of more than 100 experts in CML from different countries stated that the cost of drugs used to treat CML was high resulted in limited access and threats to the financial sustainability of health insurance systems (14). Healthcare costs associated with CML treatment which is mostly due to TKIs, greatly exceed those for treatment of other hematological malignancies and increases continually over time (15).

Imatinib entered the Iran's pharmaceutical market in 2003 and its costs were covered by insurance companies since then. Nilotinib cost coverage by insurance companies started on last months of 2013 which was about 2 years after its entrance to Iran's pharmaceutical market in 2011. There are several generic and brand preparations of both imatinib and nilotinib in Iran with different prices and varied insurance coverage (from 30% to 100% of total expenditure). The Iran health system is insurance-based and insurance plays an important role in the healthcare system (16). Insurance coverage for prescription drugs is effective in increasing drug purchases and using more expensive drugs (17, 18). Moreover, there is also a great preference in physicians to prescribe brand drugs (19).

To the extent of our knowledge, utilization of imatinib and nilotinib has not been studied in Iran and no published data is available regarding their amount of use and the effect of insurance plans on their use in the country. Therefore, we aimed to study imatinib and nilotinib utilization in Iran and to investigate different insurance coverage plans with respect to these medications.

Methods

This was a drug utilization study about Imatinib and Nilotinib over 14 years. It was conducted in two phases to investigate utilization of nilotinib and imatinib in Iran.

The trend of imatinib and nilotinib utilization based on pharmaceutical wholesale data was analyzed in this phase. We extracted the consumption data of aforementioned medications since their entrance to our market till 2017 from Iran pharmaceutical wholesale data (Amarnameh). Following data cleaning, we calculated total annual consumption of each medication as average daily doses per 1000 inhabitants per day (AID). Average daily doses for imatinib and nilotinib was defined as 0.6 g and 0.8 g, respectively, considering common maintenance doses of these medications for treatment of CML in our country.

In this phase, we obtained recorded data of prescriptions contained one of the abovementioned medications and had been filled in Sizdah-Aban Pharmacy, during 2011-2014. Sizdah-Aban Pharmacy, a Tehran University of Medical Sciences (TUMS) affiliated referral pharmacy, is one of the main distributors of antineoplastic medication in the capital city of Iran. Data including prescribing frequency, number of dispensed nilotinib or imatinib in each of the prescriptions, insurance companies and cost coverage provided by insurance company in each prescription were extracted.

Quantitative descriptive data have been reported by the frequency (percentage) and mean (SD), respectively. Regression with interaction effect was used to check the effect of insurance on the monthly trend. One-Way ANOVA was used to compare groups. LSD post hoc test was used for pairwise comparisons. For descriptive analysis and analytical data SPSS 24 statistical programs was used. For Joinpoint trend analysis Joinpoint Regression Program, version 4.7.0.0 was used. All program parameters were set to default values.

Results

Imatinib and nilotinib became available in Iran since 2003 and 2011, respectively. Figure 1 shows trend of imatinib consumption (Average daily doses per 1,000 inhabitants per

day (AID)) in Iran from 2003 to 2017. Joinpoint regression analysis showed that the consumption of imatinib increased significantly from 2003 to 2013 which is depicted in two lines with positive slopes (β=0.0014, p-value=0.04 and β=0.0051, p-value<0.001). Imatinib consumption in the last 4 years of the study decreased slightly, which was not statistically significant (β= -0.0016, p-value=0.08).

Figure 2 illustrates the trend of nilotinib consumption (AID) in Iran from 2011 to 2017. Joinpoint regression analysis revealed that nilotinib consumption had ascending trend; however, the trend line of years 2014 to 2017 was steeper and statistically significant (β=0.0014, p-value=0.02).

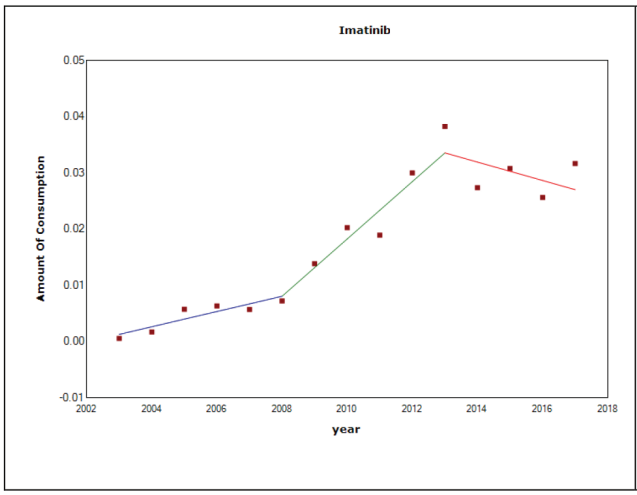

Figure 1. Imatinib consumption trend (AID) in Iran from 2003 to 2017.

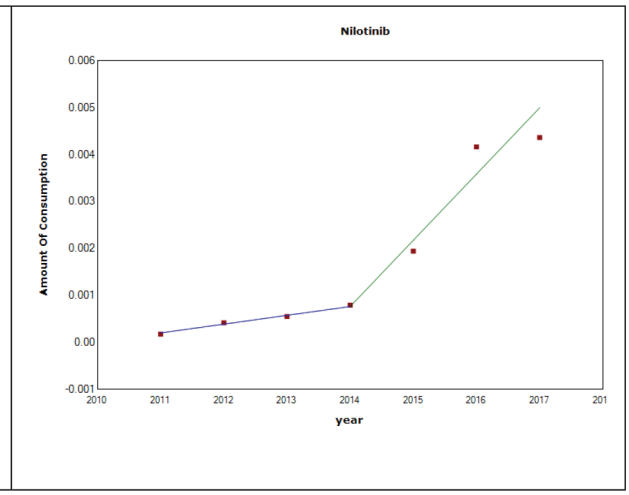

Figure 2. Nilotinib consumption trend (AID) in Iran from 2011 to 2017.

Utilization Based on Prescription Data:

-Consumption

During years 2011 to 2014, 8663 prescriptions including nilotinib or imatinib were filled and registered in Sizdah-Aban Pharmacy. Imatinib and nilotinib were dispensed in 7937 and 726 prescriptions with mean (SD) drug count of 186.7 (91.2) and 93.6 (65.7) per prescription, respectively.

Imatinib and nilotinib consumption rates based on number of medications prescribed and dispensed every month are illustrated in figures 3 and 4, respectively. Time series regression analysis of monthly values revealed that imatinib use did not show a significant trend (p-value = 0.42), while nilotinib use increased significantly (p-value<0.001).

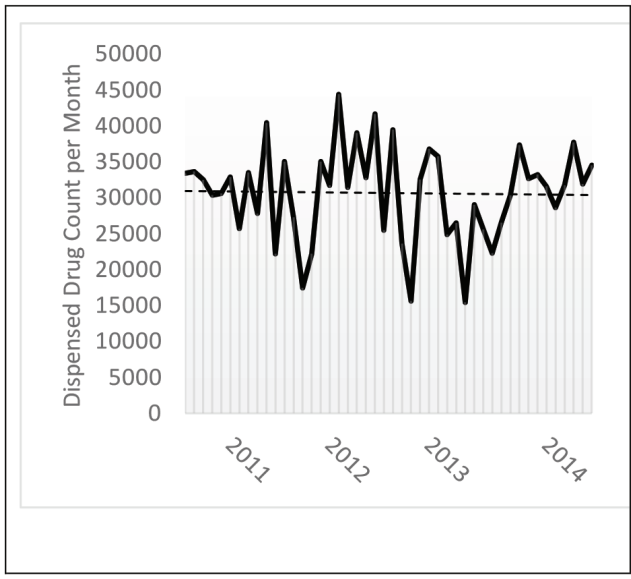

Figure 3. Imatinib monthly use

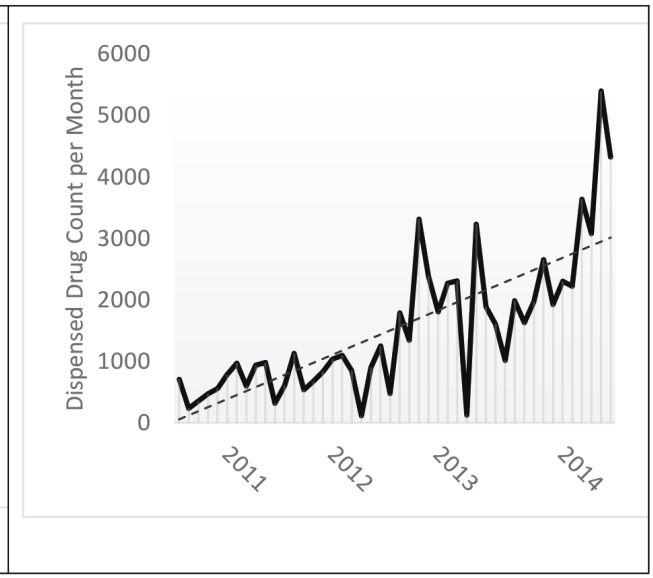

Figure 4. Nilotinib monthly use

Nilotinib has been covered by insurance since 2013/10. The new regression model, which included the different drug insurance coverage, showed that this incremental trend was affected by initiation of insurance coverage of nilotinib costs (p-value=0.006).

-Coverage of Imatinib and nilotinib costs by the insurance companies

Among 8663 studied prescriptions, no cost coverage was provided by insurance companies for 931 (11.7%) and 301 (41.5%) prescriptions contained imatinib and nilotinib, respectively. As it is shown in Figure 5, cost of nilotinib and imatinib was not covered in nearly 85% and 15 % of prescriptions in 2011, respectively. However, 10 % and 5% of imatinib and nilotinib prescriptions, respectively, had no cost coverage in 2014 (Figure 5). Frequency of prescriptions with 100% cost coverage doubled for nilotinib, while, it did not change remarkably for imatinib, from 2011 to 2014 (Figure 5).

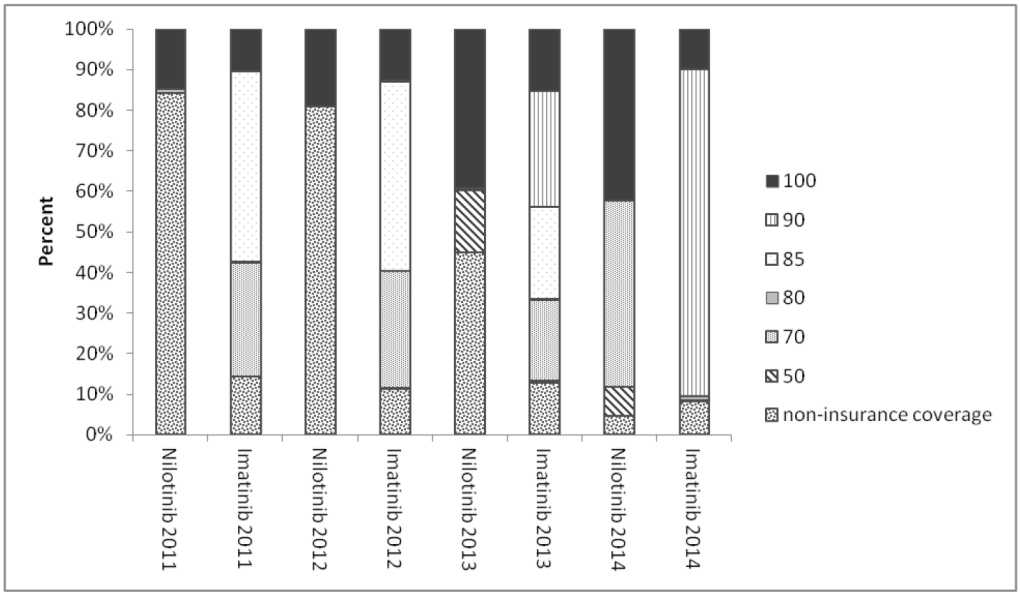

Figure 5. Cost coverage plans provided by insurance companies for imatinib and nilotinib from 2011 to 2014.

The average percent of cost coverage by insurance companies in the imatinib and nilotinib prescriptions filled annually during the study period are depicted in Figure 6. The amount of nilotinib cost coverage by insurance companies increased significantly from 2011 to 2014 (p-value=0.04). The coverage of imatinib costs by insurance companies changed slightly during the study period that was not statistically significant (p=0.06).

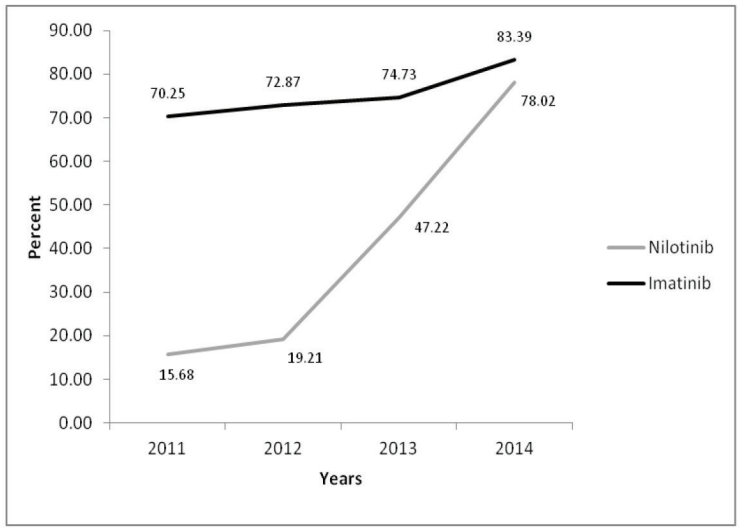

Figure 6. Average percent of cost coverage by insurance companies in the imatinib and nilotinib prescriptions.

Imatinib and Nilotinib counts per prescription (Mean (SD)) was different in prescriptions with various cost coverage (Table 1) (p-value <0.001). Post-Hoc pairwise tests showed that Mean (SD) of imatinib and nilotinib counts per prescription was significantly higher in prescriptions for which 100% of the cost was covered by insurance company (p-value <0.001 for all comparisons,).

Table 1. Imatinib and nilotinib counts per prescription with different cost coverage by insurance companies

Drug counts per prescription	Amount of cost coverage by insurance company			
Mean(SD)	100%	85%	70%	0%
Imatinib	221.71(89.49)	200.35(80.30)	188.73(83.02)	145.38(111.56)
Nilotinib	154.18(61.10)	85.07(41.47)	90.83(46.7)	76.93(59.17)

Discussion

In the present study we assessed the utilization of imatinib and nilotinib in Iran as available drugs of choice for CML treatment. We found that the nilotinib utilization trend was increasing in comparison to imatinib since their entrance to our market.

Generally, consumption amount was higher for imatinib than nilotinib, in the same period, based on both pharmaceutical wholesale data and pharmacy registered prescriptions. This was expected considering similar reports from other countries (20) and the fact that imatinib is still the drug of choice and more cost-effective treatment for CML in Iran and other countries (21, 22).

Imatinib consumption increased significantly during its first 10 years of availability in pharmaceutical market; however, this ascending trend has stopped since 2013. Nilotinib consumption trend was ascending from 2011 till 2017. What we found based on prescription data was in accordance to our finding from wholesale data; increase in nilotinib consumption vs. no significant changes in imatinib consumption.

The observed different pattern in imatinib consumption trend during 2013-2017 could be due to the increase in nilotinib consumption, since nilotinib trend of use became significantly steeper from 2014 to 2017. Increase of nilotinib consumption could be due to its coverage by the insurance companies in late 2013, since insurance coverage is a contributing factor in prescribing the medication by physicians and its use by patients (13, 17).

Nilotinib got cost coverage by insurances when Tasigna©, produced by Novartis Company was the only available preparation of this medication in Iran. In other words, no other brand or generic forms of nilotinib did exist in Iran pharmaceutical market. Whereas, several imported or locally produced imatinib preparations (i.e. Gleevec© by Novartis, and several generic forms from Cipla, Kharazmi, United Biotech and other companies) were available in our country at the same period, it should be noted that Gleevec© costs was not covered by insurances at the time. Therefore, physicians might have preferred to prescribe Tasigna©, that had cost coverage, instead of the available forms of imatinib with insurance coverage and led to increased nilotinib utilization. Studies have shown that physicians prefer to prescribe branded drug preparations (19, 23) because they believe generics may lead to poorer health outcomes; although no evidence supports less efficacy of generic formulations so far (23). On the other hand, prescription drugs cost coverage by insurance is effective in increasing prescribing and purchasing expensive drugs (13, 17, 18).

Our assessments based on prescription extracted data revealed continuous increases in coverage of nilotinib costs by insurance companies and confirmed aforementioned assumptions regarding the relationship between insurance coverage and drug consumption. Nilotinib cost coverage by different insurance companies was significantly increasing (from 15% to 95% of the cost); however, this did not change much for imatinib during the same years (2011-2014). The number of nilotinib prescriptions with 100% coverage of costs by insurance has been tripled. This finding was also associated with the number of drugs per prescription; where we found that counts of nilotinib and imatinib were significantly higher in prescription with 100% cost coverage by insurance.

It has been suggested in previous studies that cost coverage by insurance companies increased patients' demand for prescription drugs (18). It has also been shown that patients with full insurance coverage use more prescribed medications than those who have to pay for a part of the cost (24). Moreover, the majority of oncologists stated that drug costs and patient out-of-pocket costs influence their decisions regarding treatment plan and corresponding recommendations (13).

Considering the observed relationship between insurance coverage and consumption of nilotinib and imatinib, with relatively same effect in specific phase of CML and the reported increasing tendency of physicians to prescribe brand drugs (19), it could be assumed that irrational nilotinib prescribing has occurred in our country during study period, which has imposed remarkable costs to health care system and patients. It should be noted that generic medications are cost savings while prescribing branded medications has led

to a substantial increase in costs for patients and healthcare systems (23).

With rising costs of cancer drugs there is a need to prioritize antineoplastics drugs and make cost-effective drugs available to patients (12). Most oncologists in 35 et al. study in Iran agreed that there is a need to use of cost-effectiveness data for decision-making about cancer drugs cost coverage by insurance companies (13). In the case of CML treatment, there are controversies about the cost-effectiveness of imatinib vs. nilotinib in different countries, e.g. China and Egypt. From the perspective of the Chinese medical system, imatinib seemed to be more cost effective than dasatinib and nilotinib for patients who were first diagnosed with CML-CP (25). However, in Egypt, Nilotinib 300 mg is reasonably priced compared to imatinib 400 mg in patients with newly diagnosed CML from the health insurance perspective (26). Therefore, it is recommended to establish cost-effectiveness studies specifically for Iranian CML patient.

We found increasing trend in nilotinib utilization and observed some effects from nilotinib cost coverage by insurance on its consumption. However, no conclusion could be made regarding the appropriateness and acceptability of the current practice in Iran based on the study findings. This study tried to make a clear picture from imatinib and nilotinib utilization in Iran to trigger future evaluations and shake the bells for policy makers to monitor its appropriateness and design the proper cost-effective studies to make evidence-based decisions.

References

1. Hegde V, Singh S, Sinha P, et al. Flow Cytometry in Chronic Myelogenous Leukemia Blast Crisis. Iranian Journal of Blood and Cancer 2020;12(3):80-83.
2. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM-L. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol 2016;34(24):2851-7.
3. DeRemer DL, Ustun C, Natarajan K. Nilotinib: a second-generation tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia. Clin Ther 2008;30(11):1956-75.
4. Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A, Griffin J. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. Br J Cancer 2006;94(12):1765-9.
5. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362(24):2251-9.
6. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome–positive ALL. N Engl J Med 2006;354(24):2542-51.
7. Rogers G, Hoyle M, Thompson-Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or-intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16(22):1-410
8. Thanopoulou E, Judson I. The safety profile of imatinib in CML and GIST: long-term considerations. Arch Toxicol 2012;86(1):1-12.
9. Zhu Y, Qian S-X. Clinical efficacy and safety of imatinib in the management of Ph+ chronic myeloid or acute lymphoblastic leukemia in Chinese patients. Onco Targets Ther 2014;7:395–404.
10. Daroudi R, Mirzania M, Nikravanfard N, Sadighi S, Sedighi Z, Zendehdel K. Estimation of the prevalence and direct medical costs of chronic myeloid leukemia in the IR of Iran in the era of tyrosine kinase inhibitors. Asia Pac J Clin Oncol 2017;13(5):e416-e422.
11. Rouhollahi MR, Mohammad Nejad S, Harirchi I, et al. Management of Herceptin (Trastuzumab) in Patients with Breast Cancer in Iran: Procurement, Allocation, Patient Eligibility Criteria, Prescription and Financial. Hakim Medical Journal 2012;15(4):270-80.
12. Darrudi A, Daroudi R. High Insurance Coverage and Financial Support for Effective Cancer Drugs in IR Iran. Basic & Clinical Cancer Research 2018;10(3):12-21.
13. Daroudi R, Mirzania M, Zendehdel K. Attitude of Iranian medical oncologists toward economic aspects, and policy-making in relation to new cancer drugs. Int J Health Policy Manag 2015;5(2):99-105.
14. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood 2013;121(22):4439-42.
15. Wilkes J. CML much higher treatment cost than other haematological cancers. Pharmacoeconomics & Outcomes News 2020;861:9-5.
16. Davari M, Haycox A, Walley T. The Iranian health insurance system; past experiences, present challenges and future strategies. Iran J Public Health 2012;41(9):1-9.
17. Stuart B, Briesacher B. Medication decisions—right and wrong. Med Care Res Rev 2002;59(2):123-45.
18. Stuart B, Shea D, Briesacher B. Prescription drug costs for Medicare beneficiaries: coverage and health status matter. Issue Brief (Commonw Fund) 2000;(365):1-9.
19. Flegel K. The adverse effects of brand-name drug prescribing. CMAJ 2012;184(5):616.
20. Bettiol A, Marconi E, Lombardi N, et al. Pattern of use and long-term safety of tyrosine kinase inhibitors: a decade of real-world management of chronic myeloid leukemia. Clin Drug Investig 2018;38(9):837-844.
21. Jame SZB, Sari AA, Majdzadeh R, Rashidian A, Arab M, Rahmani H. The extent of inappropriate use of magnetic resonance imaging in low back pain and its contributory factors. International Journal of Preventive Medicine 2014;5(8):1029-36.

22. Sheng G, Chen S, Dong C, et al. Societal implications of medical insurance coverage for imatinib as first-line treatment of chronic myeloid leukemia in China: a cost-effectiveness analysis. J Med Econ 2017;20(4):371-81.

23. Grant M, Chapman M. The art of prescribing: negotiating the decision of generic or branded medications. Intern Med J 2015;45(7):774-6

24. Harris BL, Stergachis A, Ried LD. The effect of drug co-payments on utilization and cost of pharmaceuticals in a health maintenance organization. Med Care 1990;28(10):907-17.

25. Li N, Zheng B, Cai H-F, et al. Cost effectiveness of imatinib, dasatinib, and nilotinib as first-line treatment for chronic-phase chronic myeloid leukemia in China. Clin Drug Invest 2018;38(1):79-86.

26. Eldessouky R. Cost effectiveness analysis of Nilotinib versus Imatinib in newly diagnosed chronic myeloid leukemia from the health insurance perspective in Egypt. Value in Health 2016;19(7):A735-A736.