Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

Rev Invest Clin. 2024;76(2):91-6 ORIGINAL ARTICLE

Therapeutic Choices in Patients with Ph-Positive Chronic Myelogenous Leukemia In Mexico in the Era of Tyrosine Kinase Inhibitors: Stem Cell Transplantation or Tyrosine Kinase Inhibitors? Fifteen Years Later

Max Robles-Nasta[1,2], Daniela Sánchez-Bonilla[1,2], Moisés M. Gallardo-Pérez[1], Edgar J. Hernández-Flores[1,2], Merittzel A. Montes-Robles[1,3], María de L. Pastelín-Martínez[1,2], Juan C. Olivares-Gazca[1,2], Guillermo J. Ruiz-Delgado[1,2], and Guillermo J. Ruiz-Argüelles[1,2*]

[1]Centro de Hematología y Medicina Interna, Clínica Ruiz, Puebla; [2]Faculty of Medicine, Universidad Popular Autónoma del Estado de Puebla, Puebla; [3]Faculty of Medicine, Universidad Anáhuac Puebla, Puebla, Mexico

ABSTRACT

Background: Chronic myelogenous leukemia is a neoplastic proliferation of the granulocytic series. In Mexico, chronic myelogenous leukemia accounts for approximately 10% of all leukemias. Tyrosine-kinase inhibitors are considered front-line therapy in high-income countries, whereas allogeneic hematopoietic stem cell transplantation is a recognized therapeutic approach, mainly in low- and middle-income countries. **Objective:** To analyze the overall survival of persons with chronic myelogenous leukemia who have received tyrosine-kinase inhibitors or allogeneic hematopoietic stem cell transplantation in a medical center, since 1994, and briefly discuss the current indications of these treatments in the tyrosine-kinase inhibitors era. **Methods:** We retrospectively analyzed all patients with a diagnosis of chronic myelogenous leukemia treated in a medical center between 1994 and 2023; subsets of individuals who received an allogeneic hematopoietic stem cell transplantation or tyrosine-kinase inhibitors therapy as first-line treatment were analyzed. **Results:** 60 persons with chronic myelogenous leukemia were treated with allogeneic hematopoietic stem cell transplantation or tyrosine-kinase inhibitors: 35 received an allogeneic hematopoietic stem cell transplantation, whereas 25 were given tyrosine-kinase inhibitors. All patients who underwent an allogeneic hematopoietic stem cell transplantation engrafted successfully, and the procedure was completed on an outpatient basis in most cases (29/35). The median survival in allogeneic hematopoietic stem cell transplantation was 78.3 months (CI 95%: 0-205.6) and in persons given tyrosine-kinase inhibitors the median was not reached. **Conclusion:** Tyrosine-kinase inhibitors were significantly superior to allogeneic hematopoietic stem cell transplantation in prolonging the overall survival of persons with chronic myelogenous leukemia in our single institution experience. (REV INVEST CLIN. 2024;76(2):91-6)

Keywords: Chronic myelogenous leukemia. Allogeneic hematopoietic stem cell transplantation. Tyrosine kinase inhibitor. Low/middle-income countries. Graft-versus-host disease.

***Corresponding author:**
Guillermo J. Ruiz-Argüelles
E-mail: gruiz1@clinicaruiz.com

Received for publication: 13-12-2023
Approved for publication: 23-01-2024
DOI: 10.24875/RIC.23000274

INTRODUCTION

Chronic myelogenous leukemia (CML) is a neoplastic proliferation of the granulocytic series, predominantly; abnormalities are observed in the red series and platelets, suggesting that the disease originates in stem cells or pluripotent cells. The disease has been classically associated with a chromosomal abnormality known as the Philadelphia chromosome (Ph1). A correct diagnosis requires the demonstration of Ph1 (+) through conventional karyotyping, fluorescent *in situ* hybridization (FISH), or by establishing the presence of the BCR-ABL hybrid gene by polymerase chain reaction (PCR) techniques[1].

CML in Mexico is less frequent than acute leukemia but more common than chronic lymphocytic leukemia[1]. Globally, the incidence of CML is 1-1.5/100,000 inhabitants. Its incidence in the United States is 1-2 cases/100 000 inhabitants/year and it accounts for 15% of all adult leukemias. In Mexico, approximately 10% of all leukemias are CML. The mortality rate of this disease is 3/100,000 inhabitants[1,2], it predominates in adults between the ages of 40-60 years, and it is more frequent in men than in women[1,3].

Before the year 2000, CML treatment was based on the use of busulfan, hydroxyurea, and interferon alpha[4]. The arrival of targeted chronic myelogenous leukemia (CML) therapy in 2001 was revolutionary[5]. Imatinib was the first tyrosine kinase inhibitor (TKI) approved for the management of CML as it significantly increased these patients' overall survival (OS)[6]. However, due to the high costs of TKIs, access to this highly effective therapy with associated stringent monitoring strategies has been limited in low- and middle-income countries (LMIC)[5]. Fifteen years ago, we published that in Mexico, persons with CML were more frequently treated with hematopoietic stem cell transplantation (HSCT) than with TKIs due to the economic burden of long-term TKI administration[7]. Allogeneic HSCT (allo-HSCT) offers the possibility of long-term patient survival, so early consideration of transplantation is crucial based on the individual assessment of the risks and benefits of the potential patient[8]. In LMIC, including Mexico, allo-HSCT is usually preferred over TKIs since the one-time expense proper to transplantation is a superior cost-effective option to the lifelong drug costs[9].

Ten to 20 years ago, the most frequent indication of allo-HSCT throughout the world was CML[10], but the development and approval of TKIs drastically changed the therapeutic scenario. After the first HSCT transplant at the Clínica Ruiz (Puebla, Pue., Mexico) in 1993[11], 1946 HSCTs have been performed as of August 2023; of these, 35 have been conducted in persons with CML. We herein analyze the long-term results of CML treatment with either an allo-HSCT or TKIs at the Clínica Ruiz and briefly discuss the current indications of these therapeutic approaches[12].

MATERIALS AND METHODS

Patients

This research study was conducted retrospectively from data obtained for clinical purposes. All consecutive patients with CML diagnosed and treated at the Centro de Hematología y Medicina Interna de Puebla in Mexico, (CHMI) between 1994 and 2023 were included in the study. Peripheral blood (PB) smears stained with May-Grünwald Giemsa were reviewed and the diagnosis of CML was based on conventional criteria[1]. Cytogenetic markers were assessed and the presence of BCR-ABL1 fusion transcripts was detected by karyotyping, FISH, or multiplex RT-PCR[13,14] after March 1999. Only Philadelphia chromosome (Ph1+) positive patients were included in the study.

All subjects provided written informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Centro de Hematolog.a y Medicina Interna, Clínica Ruiz.

Allografts

The reduced-intensity Mexican method to conduct allogeneic hematopoietic stem cell transplant was employed[7]. Briefly, we administered oral busulfan 4 mg/kg (days −4 and −5), intravenous (IV) cyclophosphamide (350 mg/m^2 days −4, −3, −2 and −1), and IV fludarabine (25 mg/m^2, days −4, −3 and −2) before the transplant. Preventive therapy of graft-versus-host disease (GVHD) included oral cyclosporine (100 mg every 8 h, day −1 until day +180), and IV methotrexate (5 mg/m^2) on days +1, +3, +5, and

+11. Oral cyclosporin A (CyA) was continued through day 180 with the necessary dose adjustments to maintain serum CyA levels between 150-275 ng/ml; it was subsequently tapered over 30-60 days. If GVHD signs or symptoms developed, CyA tapering continued for longer periods. Ondansetron (1 mg IV per hour, for 4 h after IV chemotherapy), oral cotrimoxazole, and an azole were administered to all patients; antibiotics and antimycotics were prescribed until the total granulocyte count increased above 500 granulocytes × 10^9/L. In all instances, the donor was an HLA-identical sibling. Products of the PBSC apheresis were reinfused on Day 0. Patients treated with allo-HSCT were patients who fulfilled the transplant criteria, including patients with no response to TKI treatment.

TKI treatment

All consecutive patients with Ph-positive and/or BCR-ABL1-positive CML in the chronic disease phase that were studied and treated in the *Centro de Hematología y Medicina Interna de Puebla* (CHMI, Puebla, Mexico) were included in the study. All patients were offered imatinib as initial therapy, beginning with a dose of 400 mg/day.

Follow-up

Patients were evaluated clinically every month after the begin of the treatment (TKI or allo-HSCT). The hematological response was evaluated with these criteria: complete hematological response (CHR) was defined as a white blood count of < 10 × 10^9/L, a platelet count of < 450 × 10^9/L, no immature cells (blasts, promyelocytes, and myelocytes) in the peripheral blood, and disappearance of all signs and symptoms related to leukemia (including palpable splenomegaly); partial hematological response (PHR) was defined as the presence of immature cells, platelet count < 50% of the pretreatment count but > 450 × 10^9/L, and persistent splenomegaly but < 50% of the pretreatment spleen size[15].

For cytogenetic response, in our center, we evaluate the positivity or negativity of the Philadelphia (Ph) chromosome by a qualitative analysis, this analysis was repeated every 3 months for the 1st year and every 6 months afterward.

Statistics

The primary endpoint of the analysis was OS, defined as the interval from the start of treatment to death from any cause; it was estimated with Kaplan-Meier survival curves. Statistical analysis was performed with GraphPad Prism 9 (GraphPad Prism version 9 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com).

RESULTS

Patients

After 1994, 60 persons were diagnosed with Ph+ CML at the *Centro de Hematología y Medicina Interna de Puebla;* an allo-HSCT was conducted in 35 subjects, and after 2000, 25 received TKIs. All patients were in the chronic phase. HSCT with an HLA-identical sibling donor was offered to all CML patients; 35 had both a suitable donor and the capability of defraying the cost of the procedure. After 2000, patients who were not HSCT candidates were instructed to use TKIs. The median age was 38.5 (IQR: 27.7-49.2); there were 34 males and 26 females (Table 1). Twenty-one patients harbored the b2a2 transcript, 18 patients had b3a2, and 2 patients had the b2a2/b3a2 variant; the transcript could not be determined in the remaining.

Allografts

The years in which HSCTs were conducted are shown in Fig. 1. Clearly, most transplants were performed between 1999 and 2003. HSCT could be completed on an outpatient basis in 29/35 patients (83%). All patients engrafted successfully. The median time to recovery of > 0.5 × 10^9/L granulocytes was 16 days, whereas the median time to recover a platelet count above 20 × 10^9/L was 20 days. Acute GVHD developed in 12 patients (57%, Grades III/IV), and chronic GVHD developed in 9 (43%) patients. Eighteen (51%) patients have died, all between 11 and 216 months after the transplant. The causes of death are shown in table 2. Eleven of these patients were previously treated with a TKI before allo-HSCT: 6 patients received Imatinib, 4 received Dasatinib, and 1 received Nalotinib. After transplantation 26 patients were Ph negative, only one of these patients was positive

Table 1. Salient features of the patients who received an allo-HSCT or were treated with a TKI

Characteristics	TKI (n = 25)	allo-HSCT (n = 35)	p
Mean age	38.84 ± 20.83	37.80 ± 12.86	0.812a
Female	13	13	0.252b
Male	12	22	
Median survival (months)	Not reached	78.33 (IC 95% 0-205.6)	0.001c

TKI: tyrosine kinase inhibitor; allo-HSCT: allogeneic hematopoietic stem cell transplantation.
[a]p value obtained with Student's t-test.
[b]p value obtained with the Chi-square test.
[c]p value obtained with the log-rank test.

Figure 1. Distribution over time of the 35 allografts conducted in patients with Ph1+ chronic myelogenous leukemia at Centro de Hematología y Medicina Interna de Puebla, Clínica Ruiz.

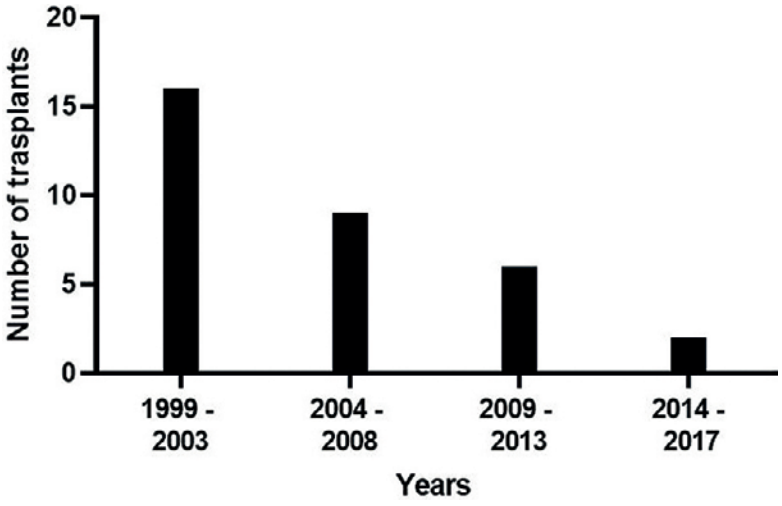

Table 2. Causes of death in all the patients

Cause of death	Number
GVHD	12
Uncontrolled leukemia	3
Graft failure	1
Hemorrhagic dengue	1
Car accident	1

GVHD: graft *versus* host disease.

again after 10 months. At the last evaluation, 10 patients showed a CHR, 25 PHR. The median follow-up was 14 months (IQR: 5.2-122.8 months), the number of patients lost to follow-up was 12, and deaths 17. Median OS was 78.3 months (CI 95%: 0-205.6) (Fig. 2).

Patients treated with TKIs

Twenty-five patients with CML were offered TKIs after 2000: 21 were started on imatinib and 4 on dasatinib. Thirteen required switching to another TKI (3 with dasatinib and 10 with imatinib) due to gastrointestinal intolerance, headache, Sweet's syndrome, or peripheral neuropathy (Table 3). Subsequently, 4 of 13 patients managed with a second TKI received a third TKI (2 imatinib, 1 ponatinib, and 1 nilotinib). Only one patient received a fourth TKI (nilotinib). After the start of treatment with TKI, 14 patients were Ph negative, two patients became positive again: one after 6 years and the other after 6 months. At the last evaluation, 20 patients showed a CHR, 5 PHR. The median follow-up was 34.6 months (IQR: 12.59-60.13 months), the number of patients lost to follow-up was 14, censored 10, and deaths 1. In the TKI cohort, the median OS was not reached, the

Figure 2. Overall survival of the 60 patients with Ph1+ chronic myelogenous leukemia, treated with either tyrosine-kinase inhibitors or allogeneic hematopoietic stem cell transplantation. Differences are statistically significant, p = 0.001.

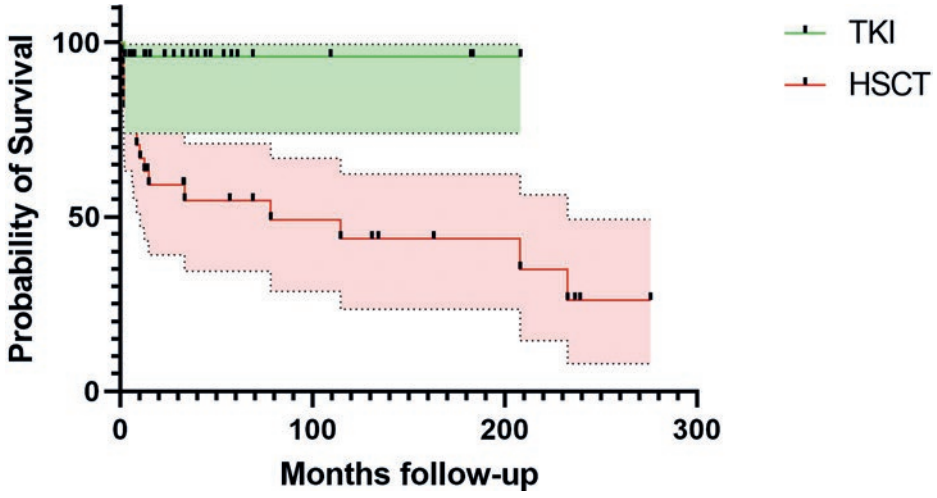

Table 3. Causes of change in the group of persons given tyrosine kinase inhibitor

Causes of change	Number
Gastrointestinal intolerance	10
Headache	1
Sweet's syndrome	1
Peripheral neuropathy	1
Total	13

Kaplan Meier OS curve is depicted in Fig. 2. The differences in OS between persons treated with TKIs or allo-HSCT are statistically different at the p = 0.001 level.

DISCUSSION

In high-income countries, TKIs are currently the first-line therapy of choice in persons with CML[4]. Imatinib is referred to as a first-generation TKI, dasatinib, nilotinib, bosutinib, and radotinib are second-generation, and ponatinib is a third-generation TKI[16]. The introduction of imatinib in 2001 as first-line therapy revolutionized the treatment of CML, transforming this disease from a fatal condition into a manageable chronic ailment. In LMIC, imatinib was initially priced at USD 30,000/patient/year, a cost that further increased over time, thus becoming an instantly inaccessible drug for most of the population around the globe, mainly in LMIC[7]. Nowadays the annual cost of therapy with generic imatinib in Mexico is around $4,500 dollars, however, the annual cost of dasatinib (second-generation TKI) is at least $55,000 dollars. As long as the costs of second-generation TKI's remain significantly higher, imatinib will remain the choice as initial therapy. China, Mexico, Eastern Europe, and other Latin American countries favor allo-HSCT since this is a 'once in a lifetime' procedure and expense, in comparison with lifelong TKI therapy. In Mexico, the cost of an allo-HSCT is substantially lower than a 1-year treatment with the second or higher generation of TKIs[13,14]. The safety and effectiveness of allo-HSCT are continually improving and thus every health-care system must consider it an option in terms of cost-effectiveness when compared with TKI therapy[4,5]. When TKIs were introduced, the number of HSCT in patients with CML decreased substantially[17]; this occurred worldwide and was confirmed by our experience since the greatest number of persons with CML treated with an allo-HSCT in our center peaked between 1999 and 2003 (Fig. 1).

GVHD is an adverse immunological reaction mediated by donor T lymphocytes after allogeneic HSCT. Its incidence is 40-60% and its mortality rate is around 15%[18]. Depending on the time of presentation, this phenomenon is classified as acute (< 100 days post-HSCT) or chronic (> 100 days post-HSCT), and it is graded according to the extension of cutaneous manifestations and involvement of other systems and organs. GVHD significantly compromises the quality of life of persons who receive an allogeneic HSCT[19]. In the group of patients with CML whom we allografted, we found that although the graft prevented leukemic relapses, it compromised

patient OS. GVHD was the most frequent cause of death in this subset of individuals (12/17, 70%).

The main adverse events that develop with TKI administration in patients with CML include abdominal pain, nausea, vomiting, diarrhea, anemia, neutropenia, thrombocytopenia, skin rash, fatigue, myalgia, arthralgia, headache, fluid retention, and among others; not all adverse events are associated with every TKI, and each drug tends to condition the development of drug-specific side effects[9,20].

In our results, we observed that 11 patients did not present a favorable response to treatment with TKI, so these patients were treated with allo-HSCT. In young patients, the alternative to TKI treatment is HSCT, which is maintained as a one-time procedure and is a curative therapy. Since allo-HSCT has become less common in CML, its indications have changed over the past 10 years; it is currently an option if there is intolerance or resistance to TKIs, in a CML blast crisis, and if TKIs are either not available or not affordable to patients[21,22]. Interestingly, one of the indications of allo-HSCT in CML has not changed in the last 10 years: the obstacles imposed by the economic burden of the cost or lack of local availability of TKIs[21,22], circumstances that encompass over 80% of the world's population[9].

As GVHD has become less aggressive and fatal due to preventive and therapeutic measures, the number of allogeneic HSCTs in persons with CML will likely improve, particularly in LMIC.

Fifteen years ago, we reported that over a 70-month observation period, the OS in patients with Ph1+ CML did not differ whether they were managed with TKIs or HSCT; however, cost-benefit analysis favored the use of HSCT. In this paper, by extending the period of observation to 280 months, we have demonstrated that OS is substantially superior among individuals who can afford treatment with TKIs (Fig. 1); however, allo-HSCT is still a valid therapeutic option in persons with CML living in LMIC, and who showed intolerance or resistance to TKIs or cannot afford treatment with TKIs[23].

SUPPLEMENTARY MATERIAL

The data that support the findings of this study are available on request to the corresponding author in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Gómez Almaguer D. Leucemias crónicas. In: Ruiz Argüelles GJ, Ruiz Delgado GJ, editors. Fundamentos de Hematología, 6th ed. México: Editorial Médica Panamericana; 2021. p. 159-68.
2. Daskalakis M, Feller A, Noetzli J, Bonadies N, Arndt V, Baerlocher GM. Potential to improve therapy of chronic myeloid leukemia (Cml), especially for patients with older age: incidence, mortality, and survival rates of patients with cml in Switzerland from 1995 to 2017. Cancers (Basel). 2021;13:6269.
3. Aguayo-González Á, Tuna-Aguilar EJ. Aspectos actuales de la leucemia mieloide crónica. Rev Investig Clín. 2012;64:192-8.
4. Gómez-Almaguer D, Cantú-Rodríguez OG, Gutiérrez-Aguirre CH, Ruiz-Argüelles GJ. The treatment of CML at an environment with limited resources. Hematology. 2016;21:576-82.
5. Gomez-de-León A, Gómez-Almaguer D, Ruiz-Delgado GJ, Ruiz-Arguelles GJ. Insights into the management of chronic myeloid leukemia in resource-poor settings: a Mexican perspective. Expert Rev Hematol. 2017;10:809-19.
6. Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? Nat Rev Clin Oncol. 2017;14:141-54.
7. Ruiz-Argüelles GJ, Tarin-Arzaga LC, Gonzalez-Carrillo ML, Gutierrez-Riveroll KI, Rangel-Malo R, Gutiérrez-Aguirre CH, et al. Therapeutic choices in patients with Ph-positive CML living in Mexico in the tyrosine kinase inhibitor era: SCT or TKIs? Bone Marrow Transplant. 2008;42:23-8.
8. Kulkarni S, Flescher A, Ahmad M, Bayliss G, Bearl D, Biondi L, et al. Ethical analysis examining the prioritisation of living donor transplantation in times of healthcare rationing. J Med Ethics. 2022;49:389-92.
9. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020; 34:966-84.
10. Gratwohl A, Heim D. Current role of stem cell transplantation in chronic myeloid leukaemia. Best Pract Res Clin Haematol. 2009;22:431-43.
11. Murrieta-Álvarez I, Olivares-Gazca JC, León-Peña A, Pérez-López R, Vallejo-Villalobos MF, Ruiz-Delgado GJ, et al. El programa de trasplantes de la clínica ruiz de puebla: a 25 años de su creación. Rev Hematol. 2018;19:141-52.
12. Niederwieser C, Kröger N. Transplantation in CML in the TKI era: who, when, and how ? Hematol Am Soc Hematal Educ Program. 2022;2022:114-22.
13. Ruiz-Argüelles GJ, López-Martínez B, Ramírez-Cabrera JM, Reyes-Nuñez V, Rodríguez-Cedeño H, Garcés-Eisele J. Molecular monitoring of the treatment of patients with BCR/ABL (+) chronic myelogenous leukemia. Rev Invest Clín Méx. 2001;53:235-9.
14. Ruiz-Argüelles GJ, Garcés-Eisele J, Reyes-Núñez V, Pérez-Romano B, Ruiz-Argüelles A, Ramírez-Cisneros F, et al. Assessment of residual disease in acute leukemia by means of polymerase chain reaction: a prospective study in a single institution. Rev Invest Clin Mex. 2000;52:118-24.
15. Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med. 1999; 131:207-19.
16. Osman AE, Deininger MW. Chronic myeloid leukemia: modern therapies, current challenges and future directions. Blood Rev. 2021;49:100825.
17. Champlin R, Jabbour E, Kebriaei P, Anderlini P, Andersson B, De Lima M. Allogeneic stem cell transplantation for chronic myeloid leukemia resistant to tyrosine kinase inhibitors. Clin Lymphoma Myeloma Leuk. 2011;11:S96-100.
18. Ramachandran V, Kolli SS, Strowd LC. Review of graft-versus-host disease. Dermatol Clin. 2019;37:569-82.
19. De Vere Hunt I, Kilgour JM, Danby R, Peniket A, Matin RN. "Is this the GVHD?" A qualitative exploration of quality of life issues in individuals with graft-versus-host disease following allogeneic stem cell transplant and their experiences of a specialist multidisciplinary bone marrow transplant service. Health Qual Life Outcomes. 2021;19:11.
20. Senapati J, Sasaki K, Issa GC, Lipton JH, Radich JP, Jabbour E, et al. Management of chronic myeloid leukemia in 2023-common ground and common sense. Blood Cancer J. 2023;13:58.
21. Radich J. Allogeneic transplantation for chronic myeloid leukemia: i'm not dead yet! Am J Hematol. 2023;98:4-5.
22. Gale RP, Goldman JM. Treating chronic myeloid leukemia in the era of tyrosine kinase inhibitors. Acta Haematol. 2013;130:192-95.
23. Ruiz-Argüelles GJ, Gomez-Almaguer D. Perspectives in diagnosis and therapeutics in hematology. Rev Investig Clín. 2021;73:306-9.