ZITA MEDICAL MANAGEMENT

www.hsmc.gr/en/pharmakeftiki-journal/

Drug-drug interactions between tyrosine kinase inhibitors and concomitant medications: drug safety in chronic myeloid leukemia treatment.

Dr. Alberto Frutos Pérez-Surio[1,2,*], Dr. Roberto Lozano Ortiz[3], Dr. Alejandro Martínez Crespo[1,4]

[1]*Clinical Pharmacy Service. Hospital Clínico Universitario Lozano Blesa. Zaragoza, Spain*

[2]*Unit of Preventive Medicine and Public Health. Universidad de Zaragoza. Zaragoza, Spain*

[3]*Clinical Pharmacy Service. Hospital Real Nuestra Señora de Gracia. Zaragoza, Spain*

[4]*Clinical Pharmacy Service. Centro de Rehabilitación Psicosocial Nuestra Señora del Pilar, Zaragoza, Spain*

KEYWORDS:
Drug-drug interaction; Tyrosine kinase inhibitor; Chronic myeloid leukemia

SUMMARY

Background: Clinical Pharmacist should be aware of hematologic toxicities from tyrosine kinase inhibitors (TKI) used to treat chronic myelogenous leukemia (CML). Drug-drug interactions (DDI) may be problematic.
Objective: To analyze DDI between TKI and the concomitant medication.
Setting: Retrospective observational study carried in a tertiary hospital of Spain.
Method: A bibliographic search was made on the UpToDate®, Lexicomp® and Micromedex® software platforms to search for evidence on DDI between TKI and the concomitant medication.
Main outcome measure: Number of interactions with respect to sex, to number of concomitant drugs, and to TKI used.
Results: A total of 28 patients were analyzed. 78.6% of patients had medication associated with the TKI. There was a total of 50 significant DDI, out of a total of 128 drugs, so the risk of having interaction in the study population was 39.1%. Regarding the management of the interactions by the hematologist and the acceptance of the pharmaceutical intervention: 10 patients experienced 14 high-level interactions. Of these the doctor knew 50% and had performed intervention in all cases: modify the treatment in 28.6%, consulted with service responsible for treatment in 42.8% and spaced the intake of drugs in 28.6%. It is important to periodically review concomitant medication and to have a strategy to manage interactions. The role of the clinical pharmacist is essential in communication with the patient, assessment of treatments, detecting potential interactions and disseminating information among the multidisciplinary team.

Corresponding author
Prof. Dr. Alberto Frutos Pérez-Surio
Email: ajfrutos@salud.aragon.es, ajfrutos@unizar.es
Avda San Juan Bosco 15, 50009 Zaragoza Spain

Conclusion: All patients who are prescribed oral antineoplastic drugs are provided patient education materials about TKI, which include possible interactions. Any changes in the patient's medications prompt a review for DDI.

Introduction

In recent years, advances in the treatment of cancer have led to the emergence of numerous oral antineoplastic drugs. The oral route is consolidated in the first-line treatments of some carcinomas, as it has been shown that the disease-free survival and overall survival, as well as the toxicity profiles, are not different from those of the parenteral route[1]. However, drug interactions are common and may be problematic. Concomitant use with moderate CYP3A inhibitors, strong or moderate CYP3A inducers, glycoprotein-P (P-gp) inhibitors, or narrow therapeutic index P-gp substrates should be avoided. Therefore, the pharmacodynamic characteristics of drugs do not vary over time, but plasma and tissue concentrations, as well as efficacy may be influenced as a result of concomitant treatments or specific eating habits[2, 3].

In this scenario, new challenges have been posed for the clinical pharmacist, specialized in the area of oncological consultation, and in charge of the care of these patients such as the monitoring of therapeutic adherence, and management of adverse effects and interactions or safe handling of toxic waste at home. The onco-hematological patient is especially susceptible to drug interactions, as he often receives one or more antineoplastic agents, along with concomitant medications, to alleviate the pain or adverse effects of the chemotherapy itself. In addition, there are several factors derived from the disease that predispose patients to interactions, such as poor absorption, malnutrition, liver or kidney damage[4].

The most concerning interactions are those whose consequences are detrimental for the patient exposure to the drug, either because it is increased causing adverse effects, or because exposure is diminished causing an inadequate therapeutic response[5]. In the case of antineoplastic drugs, this can lead to treatment failure or loss of scarce therapeutic options available[6], thus compromising patient's safety[7].

Riechelmann et al. concluded that 67% of hospitalized cancer patients were at risk of experiencing a drug interaction[8]. The factors that predispose them to this include the number of drugs involved in their treatment[9], frequent use of alternative medicines, comorbidities, organic deterioration that affects the processes of metabolization and excretion of the drugs, and finally, the fact that a large number of the recently commercialized cytostatics have not undergone extensive premarketing studies that allow proper drug interactions analysis[10].

This study expresses oral cytostatics involved in the treatment of chronic myeloid leukemia (CML). The introduction of tyrosine kinase inhibitors (TKIs) revolutionized the management of CML[11, 12], improving the 10-year overall survival from ~20% to 80-90%. In some patients, expected survival is indistinguishable from that of the general population [13]. These are the first drugs with a specific therapeutic target: the BCR-ABL fusion gene. The first TKI to appear was Imatinib. Despite the good results of studies with this drug, there is a group of patients in whom it is not possible to use Imatinib, either due to intolerance, adverse reactions, suboptimal effects or resistance to the drug. The options available after Imatinib resistance at maximum doses are the second-generation TKIs include Dasatinib and Nilotinib.

It is important to consider potential drug-drug interactions between TKIs and substrates, inhibitors or inducers of the CYP3A4 isoform and the P-gp. Recent studies revealed that concomitant prescription of drugs that can inhibit the effectiveness of protein

kinase inhibitors can vary between 23 and 57%, and drugs that can increase their toxicity between 25 and 74%[10, 14, 15].

Patients with CML usually take several medications simultaneously with their oncological therapy therefore, taking into account the risks of polypharmacy, it is possible that there are potential pharmacological interactions between their oncological treatment and the rest of medications. To assess the impact of these interactions, we intend to carry out a study in patients treated with TKIs in a third level clinical university hospital.

The aim of this study was to analyze the presence of pharmacological interactions between TKIs and the concomitant medications used in patients with CML, and to investigate the influence of clinical pharmacist's interventions.

Material and methods

A retrospective observational study in which 28 adult patients diagnosed with CML and treated with TKI were selected who attended the Clinical Pharmacy Service of a tertiary level Clinical University Hospital from October 1, 2016 to October 1, 2017. The data on the treatment were obtained retrospectively from the individual dispensing module of the Dominion Farmatools® program. The following variables related to the patients were collected: age, sex, type and dose of antineoplastic drug, characteristics and number of concomitant non-antineoplastic medications and number, level and type of drug-drug interactions noted. The collected information included additional medication patients could be taking for other indications such us medications prescribed by the GP/other Doctors/specialists. To detect the possible interactions between their regular mediations and oncological therapy, a bibliographic search was carried out on the UpToDate® (and Lexicomp® to detect DDIs) and Micromedex® computer platforms and the information obtained with the technical data sheets of the drugs was completed. The interactions were classified according to their severity, following the classification of Lexicomp® database (LexiComp, Inc, Hudson, Ohio, 2010) and DRUG-REAX System® (Thomson Reuters, Greenwood Village, Colo, USA, 2010). Each drug-drug interaction is assigned a risk rating of A, B, C, D, or X. Monographs rated X, D or C indicate situations that will likely demand a clinician's attention.

- Level of interaction X: significant interaction, avoid combination. The risks associated with the concomitant use of these two drugs normally outweigh the benefits. It is a contraindicated drug combination.

- Level of interaction D: significant interaction, consider therapy modification. A patient-specific evaluation should be conducted to determine if the benefits of such treatment outweigh the risks. Actions such as exhaustive monitoring, dose changes or use of alternative drugs should be carried out to obtain benefits or decrease the toxicity resulting from the concomitant use of said drugs.

- Level of interaction C: significant interaction, monitor therapy. Normally, the benefits of the concomitant use of these drugs outweigh the risks. In any case, a monitoring plan must be carried out to detect potential adverse events. Dose adjustments may be necessary in one or both drugs in a minority of patients.

Potential interactions were identified, as well as their prevalence and the risk that this could pose to the patient. They were also classified according to the type of interaction in pharmacokinetics, pharmacodynamics or others and within each of them an increase or decrease in dose was expected.

Once all the information was collected, the specialist responsible for the patients was informed about the most relevant interactions. A detailed review was done for each patient, jointly between the hematologist and the pharmacist using the clinical history, evolution of the analytical data, and medication changes, in order to design a clinical decision for each type of interaction in each patient. The clinical significance of these interactions was recorded by the hematologist and the acceptance and utility of the pharmaceutical intervention performed was evaluated.

The quantitative variables were summarized with mean and standard deviation or median and range,

and the qualitative variables with percentages. Statistical analysis was performed in the group of patients who were prescribed concomitant treatment, and the patients were grouped according to whether they had relevant interactions between the antineoplastic drugs and their concomitant drugs. Differences in sex, concomitant treatment (greater or lesser than 5 drugs) and TKI used were evaluated using the chi-square test (χ^2). Statistical analysis was carried out with the statistical package SPSS 21.0 for Windows (License of the University of Zaragoza).

Ethics approval: A study with initial protocol was prepared to submit to explore confirmation by the Clinical Research Ethics Committee. Enrollment, medical, and drug files were linkable based on an encrypted patient identification number. The use and analysis of de-identified administrative claims or limited data sets; was considered exempt from review by an Institutional Review Board (IRB), as de-identified information requires personal health information (PHI) waiver of authorization.

Results

A total of 28 patients with CML treated with a TKI were analyzed. 60.7% were males with an average age of 56.5 ± 14.2 years, and only 42.8% of the patients were older than 60 years. 39.3% of patients were treated with a first-generation TKI (Imatinib), while 39.3% were being treated with Dasatinib, and 21.4% of patients with Nilotinib.

78.6% of the patients had concomitant medications that included analgesics / opioids, anxiolytics / hypnotics / sedatives and antihypertensives, followed by proton pump inhibitors (PPIs). Table 1 describes the frequencies of prescribed non-antineoplastic drugs.

The median of concomitant drugs prescribed was 4 (range 0 to 16). 21.4% of patients did not take any additional drugs, 39.3% had 1 to 5 concomitant drugs and 39.3% had ≥5 prescribed non-antineoplastic drugs.

A total of 50 TKI- no TKI interactions were recorded. These interactions occurred in 20 patients out of 28, who took a total of 128 drugs, so the risk of interactions in the study population was 39.1%. Of the total interactions detected, 72.6% were potential interactions (level C) in which a dose adjustment is not necessary but precaution and monitoring of adverse events is recommended, 15.1% were level D, in which the modification of the therapy is recommended, while the amount of contraindicated interactions (level X) was 12.2%, in which it was recommended to avoid this combination of drugs. The median of interactions was 1 (0-5). Interactions almost entirely were of pharmacokinetic nature (90.7%), of these 87.4% involved a possible increase in concomitant drug concentrations, due to the inhibitory nature of TKI and only 12.6% a possible decrease in the concentration of TKI due to interference in absorption (antacids and PPIs). The drugs with the highest number of interactions were analgesic / opioid, antihypertensive and antipsychotic potential (Table 2).

In patients treated with Imatinib, 34.2% of the concomitant treatment could result in an interaction. Of these interactions, 84.6% were of level C, due to the moderate inhibition of cytochromes CYP3A4 (31.8%) and CYP2D6 (27.3%) and of the P-gp (4.5%). 3.8% were level D, and 11.6% were level X. In this last group, interaction with Metamizole (dipyrone) stands out, as it can increase adverse reactions such as agranulocytosis and pancytopenia.

In case of Dasatinib, 48.0% of concomitant drugs had the possibility of interacting with TKIs. Of these interactions, 75.0% were level C, due mainly to the inhibition of cytochrome CYP3A4 (44.4%) and the increase in the antiplatelet effect (33.3%). 8.3% were level D and 16.7% level X, highlighting the interaction with PPIs, which significantly reduce the absorption of Dasatinib, thus reducing its plasma concentration.

Finally, amongst the patients on Nilotinib, 44.4% of concomitant drugs had some type of interaction. 58.3% of the interactions were of level C, 33.3% were of level D, due to their interaction with antacids and divalent ions (66.7%) and 8.4% of level X, due to the high risk of prolongation of the QT segment on ECG and risk of developing cardiac toxicity, as with Quetiapine.

In the overall statistical analysis, there were no significant differences in the number of interactions with respect to sex (p = 0.386). There were also no significant differences in the frequency of relevant interactions between patients who had less than 5 concomitant drugs and more than 5 drugs (p = 0.603). As for the TKI used, no significant differences were found in patients who used first generation (Imatinib) or second generation TKI (Dasatinib / Nilotinib) (p = 0.174) although there is a tendency to have more interactions with the second generation TKIs.

Regarding the management of the interactions by the hematologist and the acceptance of the pharmaceutical intervention: 10 patients experienced 14 high-level interactions (D or X). Of these the doctor managed 50% of the interactions and had made intervention in all cases: modify the treatment in 28.6%, interconsultation with service responsible for treatment in 42.8% and space the taking of drugs in 28.6 %. With the other 50% of the interactions an individualized pharmaceutical intervention was carried out and recommendations included interconsultation to the service responsible for the treatment (14.3%), space the taking of the drugs (42.8%), monitor possible adverse effects due to the interaction (14.3%) and modify / reduce treatment (28.6%). All the proposals were accepted by the responsible physician.

Discussion

In the present study, the estimation of the risk of presenting with clinically relevant interactions between TKI and non-TKI drugs was lower than that described in the literature[8,9]. The percentage of interactions that increase concomitant drug concentrations was higher than that of a study presented in the USA by Bowlin et al. in 2013[16], while the percentage of interactions that decrease the concentration of TKI and thus its effectiveness, was lower than that of Browlin study. The cause of these differences may be the limited sample of patients and the fact that the study has been done only for the TKIs that treat CML. Other studies confirm that greater the number of concomitant drugs in patients diagnosed with CML on TKIs, greater the risk of interactions [5,6], On the other hand, in the current study no significant differences were observed regarding the frequency of relevant interactions between patients who had less than 5 concomitant drugs and more than 5 drugs. This is because the interactions between non-antineoplastic drugs have not been included. No differences were observed in interactions when administering first generation or second generation TKI, since pharmacologically no metabolic profile more is susceptible to suffering interactions than another.

The analgesic and sedative drugs together with the antihypertensive drugs were the most frequently prescribed in the patients included in the study. Pain, insomnia and depression were one of the most frequent comorbidities in the cancer population and, therefore, analgesic and psychiatric drugs are the most frequently prescribed drugs. The concomitant drugs involved in the interactions were analgesics, antihypertensives and antipsychotics, followed very closely by anxiolytic drugs, PPIs and blood glucose lowering drugs.

Regarding the joint assessment with the responsible physician, the professionals' concern about the interactions of this group of drugs was demonstrated and, due to the lack of time in the consultation or the limitation in access to search tools and databases, cannot be properly addressed by the hematologist. The intervention of the clinical pharmacist both at the beginning of the treatment and in successive reviews of medication could help avoid adverse events and even avoid the change to second generation TKIs, which sometimes occurs due to intolerances or adverse events of unknown origin, thus improving adherence. With this intervention, the real need of another drug, molecular response of the patient, clinical situation and, in some cases, the plasma levels of TKI, would help to predict the result of the interaction. Thus, the personalized pharmacotherapeutic follow-up of the hematological patient should lead to collaboration with the hematologist and other health professionals forming part of a multidisciplinary team.

Table 1. Frequencies of prescribed non-antineoplastic drugs

PRESCRIBED NON-ANTINEOPLASTIC DRUGS	DRUGS (N=128) % (N)
ANALGESICS / OPIOIDS	14.8 % (19)
ANXIOLYTICS / HYPNOTICS / SEDATIVES	12.5 % (16)
ANTIHYPERTENSIVES	10.1 % (13)
PROTON PUMP INHIBITORS	9.4 % (12)
ANTIDEPRESSIVES	7.8 % (10)
LIPID MODIFYING AGENTS	7.0 % (9)
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	6.2 % (8)
ANTIPSYCHOTICS / NEUROLEPTICS	6.2 % (8)
STEROIDS	5.5 % (7)
ANTICOAGULANTS	5.5 % (7)
ANTIHISTAMINES FOR SYSTEMIC USE	4.7 % (6)
ANTIBACTERIALS	3.1 % (4)
DIURETICS	2.3 % (3)
ANTICONVULSIVANTS	1.6 % (2)
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	1.6 % (2)
ANTIVIRALS	0.8 % (1)
ANTIPARKINSONIANS	0.8 % (1)

In the present study, most of the interactions were pharmacokinetic, due to substrates, inhibitors or inducers of the CYP3A4, CYP2D6 and P-gp isoforms, confirming the information published in a review carried out in 2014[6].

The work carried out presents a series of perfectly defined limitations. Firstly, the sample size is limited; resulting directly from the population of adult patients with treated CML in the geographic area of study. Secondly, as it is a retrospective analysis, there may be loss of information in the variables collected from the computerized medical record, since it is possible that the concomitant treatment in progress was not updated correctly in some cases. As the study was retrospective, there is also potential that the patient is no longer taking the interacting medication. Thirdly, interaction data was not always available in the databases for the different drug combinations. Fourthly, the study has been carried out for the TKIs that treat CML, there are other TKIs with other indications and most of the studies consulted analyze all the TKIs, so they cannot be compared directly. Finally, the interaction rates have been underestimated since the interactions between the antineoplastic drugs themselves or among the non-antineoplastic drugs have not been included. To sum up, this is a small study which does provide evidence of the benefit of pharmacist role in reviewing pa-

Table 2. No tyrosine kinase inhibitors (TKI) implicated in interactions

NON-ANTINEOPLASTIC DRUGS	INTERACTIONS (N=50) % (N)
ANALGESICS / OPIOIDS	20 % (10)
ANTIHYPERTENSIVES	16 % (8)
ANTIPSYCHOTICS / NEUROLEPTICS	16 % (8)
ANXIOLYTICS / HYPNOTICS / SEDATIVES	10 % (5)
PROTON PUMP INHIBITORS	8 % (4)
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	8 % (4)
ANTICOAGULANTS	6 % (3)
ANTIACIDS	6 % (3)
STEROIDS	4 % (2)
ANTIBACTERIALS	2 % (1)
LIPID MODIFYING AGENTS	2 % (1)
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	2 % (1)

tients who are taking TKIs for CML

This study demonstrates that oral antineoplastics require pharmaceutical interventions aimed at preventing and / or minimizing the risk of toxicity or decreased efficacy due to interactions with other medications. Many of the drug interactions in oncology are not recognized as such since they are masked by some symptoms of the pathology itself and are even confused with the toxicity inherent to the use of antineoplastic drugs. Therefore, before introducing a new drug in onco-hematological patient therapy, it is important to question the real need for it, assessing possible safer alternatives.

The Clinical Pharmacy Services have shown that by means of the pharmaceutical intervention, the risk of an adverse event caused by a pharmacological DDI can be reduced by 25.9 %[17]. This context makes the act of the pharmaceutical interview a valuable tool to detect and manage interactions involving oral antineoplastic drugs[18]. Therefore, patients with complex treatments and a high risk of potential pharmacotherapeutic problems (that may compromise the effectiveness and safety of the treatment) may benefit from this Service. In this context, clinical pharmacists have played a fundamental role in pharmacotherapeutic care and monitoring of the external onco-hematological patient.

This work could be used in the future for developments of the Clinical Pharmacy Service. Another possible future guideline with these drugs, given the wide possibility of pharmacological interaction, would be their pharmacokinetic monitoring in routine clinical practice, since target concentrations are available in terms of efficacy, and target concentrations to ensure the safety of the treatment[19, 20].

With this study we conclude that administration of concomitant drugs causes a potential risk of experiencing DDIs. In addition, it is important to periodically review the concomitant medication and have a strategy to manage those interactions and avoid them. And that the role of the pharmacist is fundamental in the communication with the patient, assessment of their treatment, and detection

of potential interactions and the dissemination of medication information among the multidisciplinary team.

Conclusions

All patients who are prescribed oral antineoplastic drugs should be provided written or electronic patient education materials about their treatment before or at the time of prescription. Patient education includes: the preparation, administration, and disposal of their antineoplastic drug; concurrent cancer treatment and supportive care medications/ measures (when applicable); possible drug/drug and drug/food interactions; and the plan for missed doses. At each clinical encounter, staff must review the patient's current medications including over the counter medications and complementary and alternative therapies. Any changes in the patient's medications prompt, should review for drug-drug interactions, as well as communication the prescribing physicians. □

Funding
This study did not receive special funding.

Conflicts of interest
All the authors declare that they have no conflict of interest.

REFERENCES

1. Caldemeyer L., Dugan M., Edwards J., Akard L. Long-term side effects of tyrosine kinase inhibitors in chronic myeloid leukemia. *Curr. Hematol. Malig. Rep. 11*, 71-9, 2016.
2. Ruggiero A., Cefalo M.G., Coccia P., Mastrangelo S., Maurizi P., Riccardi R. The role of diet on the clinical pharmacology of oral antineoplastic agents. *Eur. J. Clin. Pharmacol*. 68,115–22, 2012.
3. Stuurman F.E., Nuijen B., Beijnen J.H., Schellens J.H.M. Oral Anticancer Drugs: Mechanisms of low bioavailability and strategies for improvement. Clin. Pharmacokinet. 52, 399-414, 2013.
4. Riechelmann R.P., Tannock I.F., Wang L., Saad E.D., Taback N.A., Krzyzanowska M.K. Potential drug interactions and duplicate prescriptions among cancer patients. *J. Natl. Cancer Inst.* 99, 592-600, 2007.
5. Rang H. P., Dale M.M., Ritter J., Flower R., Henderson G. (2012) Rang and Dale's Pharmacology. 7th ed. Edinburgh, Elsevier Churchill Livingstone.
6. Agu K.A., Oqua D., Agada P., Ohiaeri S.I., Adesina A., Abdulkareem M.H., King R.C., Wutoh A.K. Assessment of satisfaction with pharmaceutical services in patients receiving antiretroviral therapy in outpatient HIV treatment setting. Int. *J. Clin. Pharm.* 36,636-47, 2014.
7. ISMP Medication Safety Alert, Institute for Safe Medication Practices, Huntingdon Valley, PA, 11, 2-3, 2006.
8. Riechelmann R., Saad E. A Systematic Review on Drug Interactions in Oncology. Cancer Investig. 24,704-12, 2006.
9. Haouala A., Widmer N., Duchosal M.A., Montemurro M., Buclin T., Decosterd L.A. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. Blood. 117 : e75-87, 2011.
10. Kheshti R., Aalipour M., Namazi S. A comparison of five common drug–drug interaction software programs regarding accuracy and comprehensiveness. *J.R.P.P.* 5, 257-63, 2016.
11. American Cancer Society: Cancer Facts and Figures 2014. Atlanta, Ga: American Cancer Society, 2014.
12. Hoffmann V.S., Baccarani M., Hasford J., Lindoerfer D., Burgstaller S., Sertic D., et al. The EUTOS population-based registry: incidence and

clinical characteristics of 2904 CML patients in 20 European Countries. *Leukemia*. 29,1336-43, 2015.

13. Björkholm M., Ohm L., Eloranta S., Derolf A., Hultcrantz M., Sjöberg J., Andersson T., Höglund M., Richter J., Landgren O., Kristinsson S.Y., Dickman P.W. Success story of targeted therapy in chronic myeloid leukemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008. *J. Clin. Oncol*. 29, 2514-20, 2011.
14. Teo Y.L., Ho H.K., Chan A. Metabolism-related pharmacokinetic drug-drug interactions with tyrosine kinase inhibitors: current understanding, challenges and recommendations. *Br. J. Clin. Pharmacol.* 79, 241-53, 2015.
15. Shao J., Markowitz J.S., Bei D., An G. Enzyme- and transporter-mediated drug interactions with small molecule tyrosine kinase inhibitors. *J. Pharm. Sci.* 103 , 3810-33, 2014.
16. Bowlin S.J., Xia F., Wang W., Robinson K.D., Stanek E.J. Twelve-month frequency of drug-metabolizing enzyme and transporter-based drug-drug interaction potential in patients receiving oral enzyme-targeted kinase inhibitor antineoplastic agents. *Mayo Clin. Proc*. 88,139-48, 2013.
17. Holland R., Desborough J., Goodyer L., Hall S., Wright D., Loke Y.K. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br. J. Clin. Pharmacol.* 65,303–16,. 2007.
18. Garrido P., Aldaz A., Vera R., Calleja M.A., de Álava E., Martín M., Matías-Guiu X., Palacios J. Proposal for the creation of a national strategy for precision medicine in cancer: a position statement of SEOM, SEAP, and SEFH. *Clin. Transl. Oncol*. 20,443-447, 2018.
19. Guilhot F., Hughes T.P., Cortes J., Druker B.J., Baccarani M., Gathmann I., Hayes M., Granvil C., Wang Y. Plasma exposure of imatinib and its correlation with clinical response in the Tyrosine Kinase Inhibitor Optimization and Selectivity Trial. *Haematologica*. 97,731-8, 2012.
20. Larson R.A., Yin O.Q., Hochhaus A., Saglio G., Clark R.E., Nakamae H., Gallagher N.J., Demirhan E., Hughes T.P., Kantarjian H.M., le Coutre P.D. Population pharmacokinetic and exposure-response analysis of nilotinib in patients with newly diagnosed Ph+ chronic myeloid leukemia in chronic phase. *Eur. J. Clin. Pharmacol*. 68,723-33, 2012.