Complications of Tyrosine Kinase Inhibitors Therapy in Chronic Myeloid Leukemia - Chronic Phase

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Chronic myeloid leukaemia is a malignant tumor of pluripotent haemopoetic stem cell, characterized by increase granulocytes with left shift and the presence of the Ph chromosome. Treatment of chronic phase is made with tyrosine kinase inhibitors administered orally and can have secondary effects: haematological and non-haematological. The purpose of this paper is to assess complications of tyrosine kinase inhibitor therapy in chronic phase of chronic myeloid leukemia and establishing correlations with the type of inhibitor used. The study was performed on a total of 140 patients diagnosed with chronic phase CML in the Hematology Department of the City Clinical Emergency Hospital Timisoara between January 2006 - January 2016. The lot proposed has been studied in terms of anthropometric parameters and also the haematological and biochemical. It showed complications after initiation of therapy with tyrosine kinase inhibitors and also the correlations statistically significant between complications and type of inhibitor used. The study reveals that regardless the type of inhibitor used both haematological complications arise and non haematological. The most common are: neutropenia, thrombocytopenia, anemia, fluid retention, muscle and joint pain. Less common are nausea, diarrhea, abdominal pain, increased liver enzymes. Despite complications of occurring, these modern therapies significantly improve both survival and quality of life of patients.

Keywords: chronic myeloid leukemia, tyrosine kinase inhibitors, treatment, complications

Chronic myeloid leukemia was treated throughout its history with Busulfan or Hydroxyurea and presented a poor prognosis. These agents have controlled hematologic manifestations but have not delayed disease progression. Imatinib, a small molecule tyrosine kinase inhibitor, was first generation of drugs that target BCR-ABL and became the standard first-line therapy in chronic phase of CML.

Subsequently emerged second generation molecules, following the strategies used to overcome resistance to Imatinib. These include new drugs, more powerful like Dasatinib and Nilotinib. These three molecules being used.

This paper aims to assess complications of therapy with tyrosine kinase inhibitors in chronic phase of chronic myeloid leukemia and establishing correlations with the type of inhibitor used.

Experimental part

Material and methods

The study was performed on a total of 140 patients diagnosed with chronic phase CML in the Hematology Department of the City Clinical Emergency Hospital Timisoara between January 2006 - January 2016. The database includes anthropometric data and results of laboratory investigations, types of inhibitors used and complications occurred after their administration. Data presented in percentage and comparisons between groups were made Oneway Anova [3-5].

Results and discussions

The group included a total of 140 patients, of which 57 (40.72%) were female and 83 (59.28%) were males. The ratio B / F is 1.45 for male. The age was between 23 and 82 years. The average age was 52.16 years. The patients were divided into three age groups, namely : 20-30 years, 31-50 years and over 50 years. The distribution of patients by age is shown in Table 1. We can see that in the age group 20 to 30 entered a total of 7 patients (5%), of which...
3 were women and 4 men, in the group 31 - 50 years we have 44 patients (31.43%) of which 15 women and 29 men, and 50 years group, 89 patients (63.57%) of which 39 were women and 50 were men.

Female gender in the age group over 50 years of age has a number of premenopausal, menopausal disorders that alter daily activities. The increased incidence of malignant pathology in the genital area (uterine cancer, breast) at this age, as well as cardiovascular pathology are more and more common clinical diagnoses [6-15].

There were analyzed few important parameters in clinical and laboratory diagnosis of chronic phase in chronic myeloid leukemia. All the data are shown in Table 2. The distribution of patients according to the type of tyrosine kinase inhibitors used in the treatment of the patients in our study group is shown in Table 3.

The most common complications of patients treated with tyrosine kinase inhibitors were: neutropenia (24%), anemia (16%), thrombocytopenia (10%), fluid retention (9%), rash (7%). Less frequent were: kidney failure (4%), joint pain (2.5%), muscle cramps (2%), bleeding syndrome (1%). Distribution of complications in patients diagnosed with chronic myelogenous leukemia-chronic phase is shown in Figure 1. Depending on the type of tyrosine kinase inhibitors use, modify complications occur, therefore in the following we present our lot comparative study on those complication [16,17].

To assess complications presented in the Table 4 were performed for all patients complete and extensive biochemical tests, ECG, cardiac ultrasound, and very thorough case history.

| Parameter                      | Values        | No. of patients | Percentage |
|-------------------------------|---------------|-----------------|------------|
| Splenomegaly                  | <5 cm         | 65              | 45.43      |
|                              | 5-10 cm       | 47              | 33.57      |
|                              | >10 cm        | 28              | 20         |
| Leukocytes (mmc)              | <50,000/mmc   | 22.14%          | 31         |
|                              | 50-100,000/mmc| 29.29%          | 41         |
|                              | >100,000/mmc  | 48.17%          | 68         |
| Hb(g/dL)                      | <12g/dL       | 48              | 34.29      |
|                              | 6-10 g/dL     | 85              | 60.71      |
|                              | <6 g/dL       | 7               | 5          |
| Left shift deviation          | Mbl + Pr. < 20% | 133            | 95         |
|                              | Mbl + Pr. > 20%| 7              | 5          |
| Platelets (mmc)               | Normal value  | 89              | 63.57      |
|                              | Decrease      | 6               | 4.29       |
|                              | Increase but ≤80,000/mmc | 29         | 20.71      |
|                              | Increase > 80,000/mmc  | 7              | 5          |
|                              | Increase ≥100,000/mmc | 9          | 6.43       |
| Basophils in P.B.             | <10%          | 107             | 75.42      |
|                              | 10%-20%       | 29              | 20.72      |
|                              | >20%          | 4               | 2.86       |
| Basophils in D.M.             | <3%           | 91              | 63         |
|                              | 3%-10%        | 40              | 28.37      |
|                              | >10%          | 5               | 6.43       |
| Mbl-Promide in B.M.           | <10%          | 102             | 72.86      |
|                              | 10%-15%       | 22              | 15.71      |
|                              | 15%-20%       | 10              | 7.14       |
|                              | >20%          | 6               | 4.29       |
| Cr. Ph                        | Present       | 120             | 85.71      |
|                              | Absent        | 20              | 14.29      |
| BCR - ABL                     | Present       | 140             | 100        |
|                              | Absent        | 0               | 0          |

Table 1 DISTRIBUTION OF THE LOT BY AGE AND GENDER

Table 2 CLINICAL AND LABORATORY PARAMETERS

Table 3 DISTRIBUTION OF PATIENTS BY TYPE OF TREATMENT
Regarding patients treated with Nilotinib complications most often occurred were neutropenia, thrombocytopenia, increase of serum transaminases and lipase.

Conclusions
Patients with chronic myeloid leukemia develop numerous complications that differ depending on the type of tyrosine kinase inhibitor used. What is important to note is that all types of inhibitors occur in a higher percentage of haematological complications as seen in Table 4: Anemia, neutropenia, thrombocytopenia. The importance of these complications has been studied in many clinical trials both in the United States and the UK, and is mainly related to the need to discontinue treatment until normalization of hemogram values [18-20].

This study reveals that depending on the type of tyrosine kinase inhibitors, the most frequently occurring complications vary but there are some haematological changes that persist in a large number of patients regardless of the inhibitor used.

The most common complications of patients with tyrosine kinase inhibitors were: neutropenia (24%), anemia (16%), thrombocytopenia (10%), fluid retention (9%), rash (7%).

Despite these inconveniences, modern ITK therapy significantly improves both survival and quality of life for patients.

Table 4
THE FREQUENCY OF COMPLICATIONS ACCORDING TO THE TYROSINE KINASE INHIBITOR

| Parameters          | IMATINIB (118) | DASATINIB (10) | NILOTINIB (12) |
|---------------------|----------------|---------------|----------------|
| Neutropenia         | 26(22.03%)     | 4(40%)        | 4(33.33%)      |
| Anemia              | 18(15.25%)     | 2(20%)        | 3(25%)         |
| Thrombocytopenia    | 8(6.78%)       | 2(20%)        | 4(33.33%)      |
| Fluid retention     | 1(0.85%)       | 6(60%)        | 2(16.66%)      |
| Infections          | 3(2.54%)       | 2(20%)        | 3(25%)         |
| Bleeding            | 1(0.85%)       | 1(10%)        | 0              |
| Rash                | 5(4.24%)       | 2(20%)        | 3(25%)         |
| Chest pain          | 3(2.43%)       | 8(80%)        | 1(8.33%)       |
| Heart problems      | 2(1.69%)       | 7(70%)        | 0              |
| Pulmonary arterial hypertension | 0 | 7(70%) | 1(8.33%) |
| Kidney failure      | 1(0.85%)       | 2(20%)        | 2(16.66%)      |
| Increased levels of serum lipase | 1(0.85%) | 1(10%) | 4(33.33%) |
| High levels of liver transaminases | 1(0.85%) | 1(10%) | 4(33.33%) |
| High levels of glycemia | 3(2.54%) | 1(10%) | 1(8.33%) |
| QT prolongation     | 1(0.85%)       | 0             | 0              |
| Joint pain          | 1(0.85%)       | 0             | 0              |
| Muscle cramps       | 1(0.85%)       | 0             | 0              |

References
1. IONITA H., Clinical Hematology , Editura Victor Babes , Timisoara, 2015, p.243 - 261.
2. HOFFBRAND A.V. - P.H.A. Moss, Essential Haematology, 6th edition , 2011, p.191-200.
3. CORTES J., DEININGER M.- Chronic myeloid leukemia, CRC press,2006, p.27- 45.
4. HUGHES T.P., ROSS D.M. and MELO J.V. - Handbook of Chronic Myeloid Leukemia , Springer International 2016, p. 53 - 51.
5. WILLIAMS HEMATOLOGY, 9th Ed, Ed. Mc Graw - Hill Education USA, 2016, p. 1331-1381.
6. PANTEA S., CRAINA M., CHIRIAC V.D., MOLERIU R.D., BOGLUT A., BACEAN MILOICOV O.C., PETRE I., Anatomiopathological and Histopathological Aspects of Malignant Tumors of the Uterus. The 13th Conference of the Romanian-German Society of Obstetrics and Gynecology,Timișoara, Romania, 14-16 September 2017, pag 147 - 150, Ed. Filodiritto Editore Proceeding, ISBN 978-88-95922-95-9
7. FURAU C., FURAU Gh, TATARU A.L., CRAINA M, PANTEA S., ILYES S.G., BOGLUT A., MOLERIU L.C., PETRE I., Pathology of Postmenopause in Women’s Range Arad County, The 13th Conference of the Romanian-German Society of Obstetrics and Gynecology,Timisoara, Romania, 14-16 Sept. 2017, pag 177 - 183, Ed. Filodiritto Editore Proceeding, ISBN 978-88-95922-95-9
8. PANTEA S., DUTA C., SARGAN I., LAZĂR F. PAPURICA F.M., BALASA-GURAGATA C., BORDOS D. - Histerectomy totală vaginală asistată laparoscopic cu evidare ganglionară pentru cancer de col incipient - tehnică operatorie. Chirurgia, (2011) 106: 365-368, Nr. 3, Mai - Iunie, ISSN 1221-9118, ISSN on line 184
9. BORDIANU A., FLORESCU I. P., MURESAN A., SARGAN I., The squamous cell carcinoma at the level of the cephalic extremity: epidemiological, clinical and histopathological aspects Romanian Journal Of Morphology And Embryology Volume: 54 Issue: 3 Supplement: Pages: 901-904 Published: 2013
10. BORDIANU A., FLORESCU I. P., MURESAN A., SARGAN I., Anato-moclinical aspects of the basal cell carcinoma at the level of the cephalic end, Romanian Journal Of Morphology And Embryology Volume: 106 Issue: 3 Pages: 609-612 Published: 2011
11. BENJULIŚECU I., PANTEA S., PANTEA C., SARGAN I, et al. New minimally invasive surgical technique in varicoce disease - endovenous laser therapy, European Journal of Medical Research Volume: 15 Supplement: 1 Pages: 228-228 Published: OCT 13, 2010
12. SALAPA M, POPA Z, MARGAN M, CRAINA M, PANTEA S, ILYES SG, BOGLUT A, PETRE I, False Positive Results in Breast Elastography. A Retrospective Analysis, The 13th Conference of the Romanian-German Society of Obstetrics and Gynecology, Timișoara, Romania, 14-16 September 2017, pag 154-156, Ed. Filodirtto Editore Proceeding, ISBN 978-88-95922-959

13. MURESAN A., LAZAR E., DEMA A., SARGAN I et al. The antigen Ki-67: marker of the tumoral proliferation in the invasive mammary cancer and the connection with the classical prognostic factors, Virchows Archiv Volume: 457 Issue: 2 Pages: 168-168 Published: Aug 2010

14. MURESAN A. M., LAZAR E., RAICA M., SARGAN I. et al., HER2 immunoexpression in invasive breast cancer: morpho-clinic and prognostic correlations, Virchows Archiv Volume: 455 Pages: 193 - 193 Published: Aug 2010

15. MURESAN A. M., LAZAR E., RAICA M., SARGAN I. et al., The study of an immunohistochemical aggressivity marker in mammary carcinomas, Virchows Archiv Volume: 455 Pages: 194 - 194 Published: Aug 2010

16. ***WINTROBE’S CLINICAL HEMATOLOGY, Thirteenth Edition, Ed.Lippincott Williams & Wilkins 2014, p.2011 – 2031.

17. BOYADZIS M., FRAME J., KOHLER D.R., FOJO T. Hematology-Oncology Therapy Second Edition, Ed. McGraw Hill Education 2015.p.551-607.

18. KESKIN D., ESKAZAN A.E. - The Treatment of Chronic Myeloid Leukaemia (CML) in the Era of Tyrosine Kinase Inhibitors - What is New in the Battle of CML European Oncology & Haematology, 2015:11(1):30-1.

19. CARELLA A.M., DELLEPIANE C., LOVERA D., IBATICI A., GHIGGI C., CARELLA A., BELTRAMI G., Chronic Myeloid Leukaemia - The Choice of Therapy and Future Perspective European Oncology & Haematology, 2015:11(1):25-9.

20. CALAMAR POPOVICI, D., IONITA, I., IONITA, C., MARINITA, A., MOLERIU, R.D., IONITA, H., IACOB, D., CHIRIAC, V.D., PETRE, I., - Statistical Hierarchy of Diagnostic Criteria for Chronic Myeloid Leukemia, Rev.Chim.(Bucharest), 68, no.10, 2017, p.2463 - 2466,

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