Statistical analysis of chronic myeloid leukemia patients in Albania

Gledjan Caka
Department of Biotechnology
University of Tirana, Faculty of Natural Sciences
Tirana, Albania
gledjan.caka@fshn.edu.al

Helidon Nina
Department of Surgery
University of Medicine Tirana, Faculty of Medicine
Tirana, Albania
ninahelios@yahoo.com

Abstract— **Leukemia, also known as blood cancer, is a hematological disease that affects the normal function and development of white blood cells in the vascular system or bone marrow. Chronic myeloid leukemia is hematological disorder affecting the myeloid lineage and usually is found in people 60 years or older. It is expanding in Albania, and the number of cases in the recent years has been on the rise, both in new cases and relapsing patients.**

In our study we examined 497 cases of chronic myeloid patients, ranging from different age groups and both genders. Data was taken from hospitalized patients at the University Hospital "Nënë Tereza" in Tirana. Data shows that both gender and age are significant factors in the development of this disease with a p-value ≤ 0.05 and 0.001 respectively.

Keywords— chronic myeloid leukemia, age, gender, statistics.

I. INTRODUCTION

Chronic myeloid leukemia (CML) is a hematological disease that affects the cells of the myeloid lineage by producing an excessive amount of white blood cells and disrupting normal function and development of blood forming cells in the bone marrow [1]. It is a clonal disorder that affects the hematopoietic stem cells and is characterized by the reciprocal translocation in the Philadelphia chromosome between chromosomes 9 and 22 [2,3]. This translocation gives birth to fusion oncogene BCR-ABL [4]. This translocation adds a 3' segment of the ABL gene to the 5' site of the BCR gene [5]. This new fusion is a distinct characteristic of CML and is found in more than 95 percent of affected people and sometimes in up to 30% of adults with other types of leukemia [6].

The disease is comprised of three unique phases: chronic, accelerated and blast phases, which leads to a loss in the ability of the clone to differentiate and leading to the proliferation of malignant myeloid cells [1, 4].

CML has an incidence rate of 0.7 to 1 cases per 100000 persons each year and it comprises of 10-15% of all leukemia types [7].

Abnormal function of the fused gene BCR-ABL shows a deregulated tyrosine kinase activity [8]. As a result this leads to a higher and continuous phosphorylation of other signaling proteins. The functions that the mutated BCR-ABL plays in CML patients include and are not limited to increased malignant cell proliferation, inhibition of apoptosis and increased cell survival [9, 10]. Figure 1 shows how the BCR-ABL gene promotes leukemogenesis.
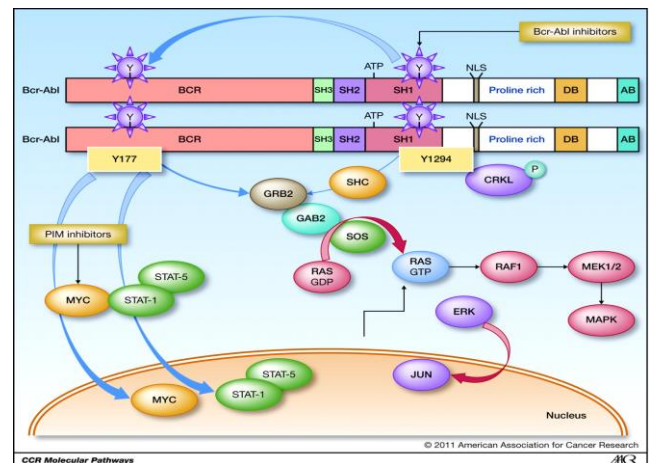

Figure 1: Molecular pathway of BCR-ABL gene [11]

BCR-ABL is phosphorylated by tyrosine kinase protein Tyr177 and is essential for leukemogenesis [12] and binds to the GRB2 adaptor protein. The BCR-ABL/GRB2 complex recruits the Son of Sevenless (SOS). This new formation leads to an activation of the inactive Ras protein, resulting in the phosphorylation of the MAPKinase downstream signaling that promotes abnormal cell proliferation [13]. On the other hand the BCR-ABL/GRB2/SOS complex activates the PI3K/AKT pathway which leads to increased leukemia cell survival by suppressing the activity of the FOXO gene responsible for promoting apoptosis [14].

Material and methods.

497 patient cases were taken into consideration in this study. The patients have all been hospitalized and treated at the University Hospital "Nënë Tereza", Tirana, Albania. Double cases were removed from the analysis and only new patients or recurring ones were taken into consideration. A number of factors were used when patients were hospitalized. Age, gender, place of residence, family history and in the relapsing

cases, the treatment that was previously used on them. Age, gender and place of residency were the primary factors that were analyzed in this study, whereas data for the other factor are not shown here. The data was shown to be significant with a P-value <0.05 and they were analyzed with the Graph Pad Prism software. We conducted a 2 way ANOVA test to determine the effects of two variables.

Results and Discussion

The number of patients analyzed was 497. Age varied from 2 – 80 years old with a mean age of 52.4±15.6 years. The ratio of males to females was 1.44 to 1. The number of females comprised 40.85 percent of the total cases (203) with a mean age of 49.5±15.11 years and the males comprised the rest of the population with 294 cases and an average age of 54.4±15.6 years.
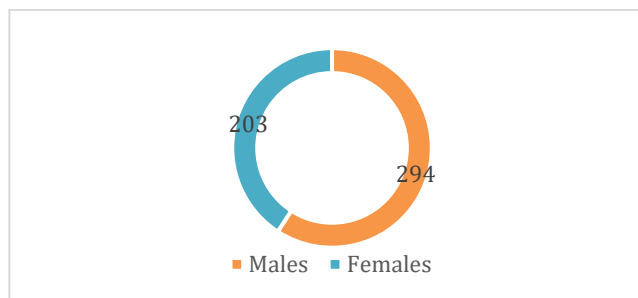

Figure 2: Number of female and male reported cases

From our analysis we could determine that the number of people affected by chronic myeloid leukemia until the age of 50 was nearly equal for both genders with a ration of nearly 1:1, but there is a sharp increase in the number of male leukemia patients after the age of 50. The percentage of hospitalized male patients was 65 (n=194), whereas females comprised 35% of the cases (n=105). This is supported by other studies than males are more affected than women [15]. Until the age of 25 data shows that females are more affected by CML than males as shown in figure 3.
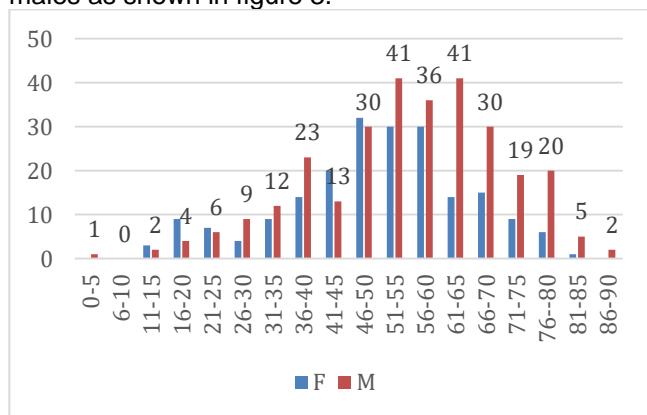

Figure 3: Number of cases by age groups.

Data shows that gender appears to be a factor when talking about chronic myeloid leukemia with a p-value 0.0189. On the other hand, when discussing about group ages it distinctly shows a very high significance

and p-value of 0.0001, as also stated in other studies [16, 17]. People of ages 55 and older are more high risk and have a higher morbidity rate. Preexisting conditions could also serve as a stepping stone for the formation of abnormal white cells. In some rare cases chronic leukemia can also lead to rapid transformation of acute leukemia [18].
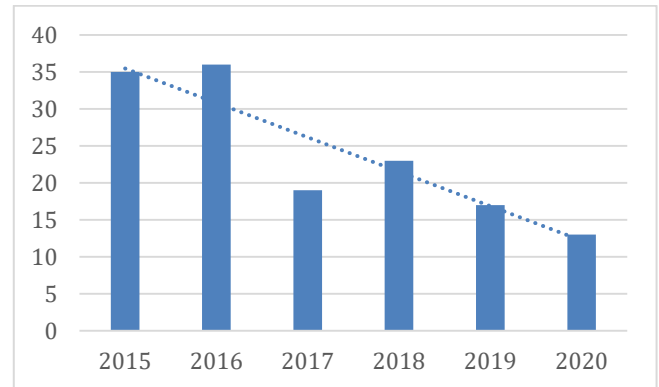

Figure 4: Number of cases for the period 2015-2020

Figure 4 shows the number of leukemia cases from 2015 until 2020. It is shown that there is a receding trend in the number of cases reported for chronic myeloid leukemia patients. According to the Oncology department at the University Hospital this is expected because people may not be rightfully diagnosed or they could not be part of the leukemia database because they could be treated for another existing condition and leukemia appeared latter. Another indication as to why this trend is decreasing is in relation to the fact that there are a large number of people living in rural or urban areas that never go the hospital for a checkup. Whereas for the year 2020, the lockdown in Albania for an extended period of time minimized the contact of people with the hospital unless it was for Covid-19 related health issues which lead to a decrease in both treatment or diagnose of old or new patients.

Another factor we took in consideration was the place of residence. Demographic data was suspected to show a trend in patients affected by CML, but data showed that was not the case.
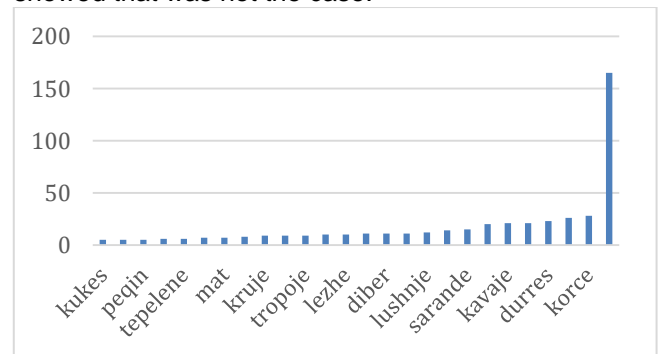

Figure 5: Number of cases related to place of residency

According to figure 5 the number with the highest cases is the city of Tirana, which is also the capital of Albania and has the highest population. Except for Tirana which was expected to be the leader of CML

cases, all the other cities have a deviation in correlation to the number of inhabitants and the number of cases present with CML according to the data from the hospital. In this graph cities with less than 5 CML cases were not included. There is significance regarding habitation since patients showed up randomly to be treated for their existing condition. One factor that could affect the total number of existing cases is the fact that not all leukemia patients are treated at the University Hospital but opt for other alternatives, such as the private sector or going abroad. Another factor that could be seen as important is the environment surrounding the different cities. Cities that are mostly dependent on heavy or chemical industry are more prone to be affected by genetic defects which could lead to dysregulation of normal blood and bone marrow functions.

Conclusions

Leukemia is a very complex disease with ever increasing numbers that affects all ages and genders. The more high risk patients of older ages show a high mortality rate because data showed that not all of them make it during the 3-5 year period when they are affected by CML. One of the big challenges we face is the large amount of data at our disposal, which needs to be carefully selected because of many cases of mislabeling or double cases which throws off the trend of the disease and also increases the amount of misinformation that is reported. Our results have shown that a more accurate classification is needed in order to better differentiate among the different age groups that are living with CML. But despite the bumps in the road, our study is in accordance with other studies from the EU or USA stating that individuals 60+ years old are definitely a very high risk group.

REFERENCES

[1] B. Druker, M. Talpaz, D. Resta, B. Ping, Efficacy and safety of a specific inhibitor of the bcr-abl tyrosine kinase in chronic myeloid leukemia, N Engl J Med, Vol. 344, No. 14 · April 5, 2001

[2] Rowley, JD. A new consistent abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and giemsa staining. *Nature* 1973. **243**:290-293

[3] Pophali PA, Patnaik MM. The Role of New Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. *Cancer J.* 2016;22(1):40-50. doi:10.1097/PPO.0000000000000165

[4] K. stam, N. Heisterkamp, Evidence that the phl Gene Encodes a 160,000-Dalton Phosphoprotein with Associated Kinase Activity, Molecular and Cellular Biology, May 1987, p. 1955-1960

[5] Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164-172

[6] Cortes J. E., Talpaz M., Beran M., O'Brien S. M., Rios M. B., Stass S., Kantarjian H. M. Philadelphia chromosome-negative chronic myelogenous leukemia with rearrangement of the breakpoint cluster region. Long-term follow-up results. *Cancer*, **75**: 464-470, 1995

[7] Höglund M, Sandin F, Simonsson B. Epidemiology of chronic myeloid leukaemia: an update. Ann Hematol. 2015 Apr;94 Suppl 2:S241-7. doi: 10.1007/s00277-015-2314-2. Epub 2015 Mar 27. PMID: 25814090.

[8] Tang, Z., Toruner, G.A., Tang, G. *et al.* Chronic myeloid leukemia with insertion-derived *BCR–ABL1* fusion: redefining complex chromosomal abnormalities by correlation of FISH and karyotype predicts prognosis. *Mod Pathol* **33**, 2035–2045 (2020). https://doi.org/10. 1038/s41379-020-0564-6

[9] Ross TS, Mgbemena VE. Re-evaluating the role of BCR/ABL in chronic myelogenous leukemia. *Mol Cell Oncol.* 2014;1(3):e963450. Published 2014 Oct 29. doi:10.4161/23723548.2014.963450

[10] Soverini, S., Mancini, M., Bavaro, L. *et al.* Chronic myeloid leukemia: the paradigm of targeting oncogenic tyrosine kinase signaling and counteracting resistance for successful cancer therapy. *Mol Cancer* 17, 49 (2018). https://doi.org/10.1186/s12943-018-0780-6

[11] Daniela Cilloni and Giuseppe Saglio, Molecular Pathways: BCR-ABL, Clinical Cancer Research, DOI: 10.1158/1078-0432.CCR-10-1613 Published February 2012

[12] Zhang X, Subrahmanyam R, Wong R, Gross AW, Ren R. The NH(2)-terminal coiled-coil domain and tyrosine 177 play important roles in induction of a myeloproliferative disease in mice by Bcr-Abl. Mol Cell Biol 2001;**21**:840–53.

[13] Suzuki M, Abe A, Imagama S, Nomura Y, Tanizaki R, Minami Y, Hayakawa F, Ito Y, Katsumi A, Yamamoto K, Emi N, Kiyoi H, Naoe T. BCR-ABL-independent and RAS / MAPK pathway-dependent form of imatinib resistance in Ph-positive acute lymphoblastic leukemia cell line with activation of EphB4. Eur J Haematol. 2010 Mar;84(3):229-38. doi: 10.1111/j.1600-0609.2009.01387.x. Epub 2009 Nov 28. PMID: 20002159.

[14] Pellicano F, Scott MT, Helgason GV, et al. The antiproliferative activity of kinase inhibitors in chronic myeloid leukemia cells is mediated by FOXO transcription factors. *Stem Cells.* 2014;32(9):2324-2337. doi:10.1002/stem.1748

[15] Tomas Radivoyevitch, Gradimir M Jankovic, Ramon Tiu, Sex differences in the incidence of chronic myeloid leukemia, Radiation and

Environmental Biophysics 53(1), December 2013, DOI: 10.1007/s00411-013-0507-4

[16] Berger, U., Maywald, O., Pfirrmann, M. *et al.* Gender aspects in chronic myeloid leukemia: long-term results from randomized studies. *Leukemia* **19,** 984–989 (2005). https://doi.org/10.1038/sj.leu.2403756

[17] Nguyen, L.T., Guo, M., Naugler, C. *et al.* Incidence of chronic myeloid leukemia in Calgary, Alberta, Canada. *BMC Res Notes* **11,** 780 (2018). https://doi.org/10.1186/s13104-018-3890-8

[18] Kaur M, Nibhoria S, Tiwana K, Bajaj A, Chhabra S. Rapid transformation of chronic lymphocytic leukemia to acute lymphoblastic leukemia: A rare case report. *J Basic Clin Pharm.* 2016;7(2):60-63. doi:10.4103/0976-0105.177702