Commentary

Imatinib improved the overall survival of chronic myeloid leukemia patients in low- and middle-income countries: A therapeutic goal has been reached

Massimo Breccia*

Hematology, Department of Translational and Precision Medicine, Sapienza University, Azienda Polyclinico Umberto 1, Rome, Italy

The management of patients with chronic myeloid leukemia (CML) has drastically changed following the introduction of different tyrosine kinase inhibitors (TKIs). In particular, long-term results obtained with imatinib, the first generation TKI, demonstrates that patients who achieved at least a complete cytogenetic response or better, a deep molecular response, have a survival similar to that of matched (age and gender) normal controls [1]. Unfortunately, the cost of therapy remained elevated with limitation of use in low and middle-income countries [2]. A global program, namely the Glivec International Patients Assistance Program (GIPAP), was created by Novartis in 2001 and provide imatinib without any cost to patients affected by CML or gastrointestinal stromal tumor (GIST). From the partnership Max Foundation database, long-term survival analysis was recently published by Chukwuemeka and colleagues [3], covering a period of 13 years: 63 000 patients received imatinib in 93 countries, the majority of them (85%) affected by CML in different stages of disease. Seven-year survival was estimated to be 87.7% for CML patients and 78.6% for GIST patients. For CML patients, survival rate of different stage of disease was also reported and although the brilliant results achieved with imatinib, the 7-year survival of accelerated and blast phase patients was 77.5% and 53%, respectively. The risk of death was higher in male patients (7% higher), in non-CML patients (24.6% higher), in older patients (increases of 1.7% for each year increase in age at enrollment), for each year increase between diagnosis and enrollment (0.4%, with increased survival in the late years of enrollment into the program). More than 17 000 patients were estimated to be saved by GIPAP program. To maintain sustainability, Novartis Pharma Industry collaborated and supported foundations and translate the GIPAP program into CMLPath to Care model, providing imatinib in 65 countries. Similar to Novartis, other Pharma industries started similar collaborations and 25 countries have now the possibility to prescribe available TKIs for the cure of this disease.

Contrasting results were reported for life expectancy of CML patients treated with imatinib: the Swedish Cancer registry reported 2662 CML patients diagnosed over a period of 40 years, showing a survival improvement, in particular in youngest ages. For younger patients, an increase in life expectancy was seen after 1990 and continued until 2013, with a largest increase seen between 1990 and 2000 and a more steady increase after 2000 [4]. Long-term follow-up of the first international trial that compared frontline imatinib versus best available therapy, namely the IRIS study, showed that 10-year estimated overall survival of patients who achieved a complete cytogenetic response was 83.3% [5].

Surveillance, Epidemiology and End Results (SEER)-Medicare database analysis was recently reported: 805 CML patients followed for 5 years were matched with non-cancer beneficiary sample. An improved survival (79%) was described only for patients with more than 85% compliance similar to that of non-cancer beneficiaries (76%), compared indeed to 62% in patients with less than 85% compliance. Decreased survival could be related to reduced access to TKIs probably insurance-related [6].

Indeed, a recent analysis of US SEER dataset using SEERaBomb software highlighted controversies on the survival topic of CML patients treated with TKIs. From a statistical analysis that showed the relative risk of death, it seems that CML patients in the US have a 2.38-fold higher risk of death than controls, completely in contrast with information reported by registries or clinical trials. Possible explanation for discordant data reported since now could be related to the access and availability of drugs, healthcare system and the unavailability of molecular monitoring [7]. In line with this analysis, Jiang and colleagues reported the impact of socio-demographics features on survival of adult Chinese CML patients: male patients with a low level of education and rural residence, with low probability of continuous molecular monitoring have a worse outcome compared with controls [8]. Some authors suggested caution in the interpretation of survival data extrapolated from clinical trials and registries [7]. Indeed, the survival analysis by Chukwuemeka et al [3] estimated the number of lives saved by the introduction of imatinib as optimal treatment. Even if this analysis has the limitation based on the absence of some prognostic features at baseline, such as the Sokal...
stratification, the median age at presentation was 41 years, much lower than in the high-income countries. Several studies have demonstrated that in younger patients, poor adherence and inadequate drug dosing are associated with increased relapse and decreased survival [9]. Despite the possible low compliance to treatment and appropriate molecular monitoring in low- and middle-income countries, the GIPAP program reached a therapeutic goal with a real survival increase.

Declaration of competing interest

MB received honoraria by Pfizer, Incyte, Novartis.

References

[1] Gambacorti-Passerini C, Antolini L, Mahon FX, Guilhot F, Deininger M, Fava C, Nagler A, Della Casa CM, Morra E, Abruzzese E, D’Emilio A, Stagno F, le Coutre P, Hurtado-Monroy R, Santini V, Martino B, Pane F, Piccin A, Giraldo P, Assouline S, Durosinmi MA, Leeksma O, Pogliani EM, Puttini M, D’Emilio A, Stagno F, le Coutre P, Hurtado-Monroy R, Santini V, Martino B, Pane F, Piccin A, Giraldo P, Assouline S, Durosinmi MA, Leeksma O, Pogliani EM, Puttini M, Jang E, Reiffers J, Piazza R. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. J Natl Cancer Inst 2011;103:553–61.

[2] Experts in chronic myeloid leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices for cancer drugs: from the perspective of a large group of CML experts. Blood. 2013;121(22):4439–42.

[3] Chukwuuemeka AT, Garcia-Gonzalez F, Tremblay D, Laing R. The survival of patients enrolled in a global direct-to-patient cancer medicine donation program: the Gleevec International Patient Assistance Program (GIPAP). E Clin Med 2019. doi:10.1016/j.eclinm.2020.100257.

[4] Bower H, Bjorkholm M, Dickman PW, Högland M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol 2016;34(24):2851–7.

[5] Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, Baccarani M, Deininger MW, Cervantes F, Fujihara S, Ortmann CE, Menssen HD, Kantarjian H, O’Brien SG, Druker BJ. Investigators IRIS. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017;376(10):917–27.

[6] Kenzik KM, Bhatia R, Williams GR, Bhatta S. Medicare and patient spending among beneficiaries diagnosed with chronic myelogenous leukemia. Cancer. 2019;125(15):2570–8.

[7] Radivoyevitch T, Weaver D, Hobbs B, Maciejewski JP, Hehlmann R, Jiang Q, Hochhaus A, Gale RP. Do persons with chronic myeloid leukemia have normal or near normal survival? Leukemia. 2019 Dec 20 [Epub ahead of print]. doi:10.1038/s41375-019-0699-y.

[8] Jiang Q, Yu L, Dou X. Impact of socio-demographics on disease phase and risk, drug choice, and treatment outcomes in adults with newly diagnosed chronic myeloid leukemia. In: Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy; 2019.

[9] Pemmaraju N, Kantarjian H, Shan J, Jabbar E, Quintas-Cardama A, Verstovsek S, Ravandi F, Wierda W, O’Brien S, Cortes J. Analysis of outcomes in adolescents and young adults with chronic myelogenous leukemia treated with upfront tyrosine kinase inhibitor therapy. Haematologica. 2012;97(7):1029–35.