Imatinib in Chronic myeloid leukemia in Albanian patients, overview

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Abstract

Imatinib was the first signal transduction inhibitor used in a clinical practice. Imatinib prevents the BCR-ABL protein from playing its role in the oncogenic pathway in chronic myeloid leukemia (CML). Imatinib directly inhibits tyrosine kinase activity. Imatinib binds to BCR-ABL kinase domain. As a result, the transmission of proliferative signals to the nucleus is blocked and leukemic cell apoptosis is induced. The FDA has approved imatinib as first-line treatment for newly diagnosed CML in December 2002 following an International Randomized Study (IRIS), who started in June 2000(1).Results from this study show the effectiveness of imatinib and its superiority with respect to the rates of complete hematological response (CHR), major and complete cytogenetic response (MCyR, CCyR). Patients randomized to imatinib arm at 8 – year data cut off continue to have a durable hematologic and cytogenetic responses, low progression to AP or BC, and remarkable survival outcomes. An overall survival (OS) rate is 85% for patients receiving imatinib (93% when only CML-related deaths and those prior to stem cell transplantation are considered).The very first patient treated with Imatinib for the first time was in 2002 in a 69 years old patient which is still alive and well today .

Introduction

Chronic myeloid leukemia accounts for 15% of all leukemia in adults. The incidence of this type of leukemia in adults in Albania is 0.6-1.1/100 000. On figure 3 we have a picture of the incidence of CML in Albania according to the cities.

Imatinib was the first signal transduction inhibitor (STI), used in a clinical practice. It prevents a BCR-ABL protein from playing its role in the oncogenic pathway in chronic myeloid leukemia (CML). Imatinib directly inhibits the tyrosine kinase activity, which results in the modification of the function of various genes involved in the control of the cell cycle, cell adhesion, cytoskeleton organization and finally in the apoptotic death of Ph(+) cells(2).

Imatinib binds to BCR-ABL kinase domain, which is in an inactive conformation in a pocket reserved for the ATP binding site, thus preventing the transfer of a phosphate group to tyrosine on the protein substrate and the subsequent activation of phosphorylated protein. As the result, the transmission of proliferative signals to the nucleus is blocked and leukemic cell apoptosis is induced (3). Imatinib exhibits high level of selectivity.

Imatinib in clinicals trials

The first phase I trial was initiated in June 1998 and enrolled patients diagnosed with CML in chronic phase (CP) who were resistant to or intolerant of interferon alpha (IFN alpha). Almost all patients (98%) treated with at least 300 mg imatinib per day achieved complete hematological response (CHR)(4).

All this results, made it possible to start phase two trial just one year later, three international multicenter phase II trials were initiated in 1999(5). The study population included patients with CML in myeloid BC, relapsed Ph+ALL, CML in AP, and patients who were resistant to IFN alpha. Ninety five percent of all patients achieved CHR; CCyR and MCyR were seen in 41% and 60% of patients respectively, and the progression-free survival rate at 18 months was 89%.

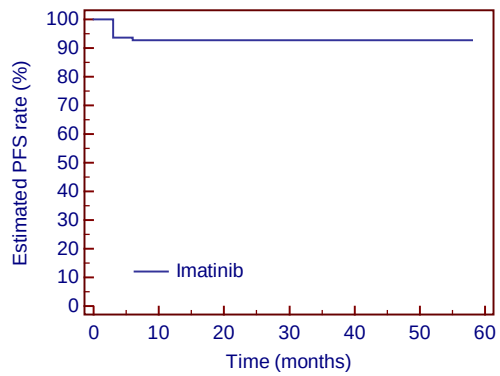
An International Randomized Study of Interferon and STI571 (IRIS) comparing imatinib at a single daily dose 400 mg to IFN alpha plus cytarabine in newly diagnosed patients with CML in CP was initiated in June 2000(6). Results from this study show the effectiveness of imatinib and its superiority with respect to the rates of CHR, MCyR and CCyR. Based on these results, the FDA has approved imatinib as first-line treatment for newly diagnosed CML in December 2002. The achievement of an MMR continued to be associated with an improved outcome at 5-year, with estimated rates without progression to AP/BC of 100%, 98%, and

87% for patients achieving CCyR and MMR, CCyR without MMR, and no CCyR, respectively. The best observed MMR rate with the 8-year follow-up of IRIS trial is 86%. The results of imatinib first line based on analysis of data derived from clinical trials and registries have been reported in the last three years by several groups (PETHEMA, SPIRIT, GIMEMA, CAMELIA, German Study Group IV, and others.). The rates of CCyR achieved after one year of therapy with imatinib at standard dose ranged from 49% to 77%, and the proportion of patients who achieved MMR after one year ranged between 18% and 58%.

Following this we made a retrospective study in our Albanian patients diagnosed with Chronic myeloid leukemia in chronic phase CP treated with Imatinib on first line (7).This is a comprehensive retrospective analysis of first-line CP CML pts treated with IM first-line 400 mg daily since diagnosis and followed in the Hematology clinic at the University Hospital Center 'Mother Teresa' between 2003 and 2008 a time that all our CML patients were introduced to Imatinib as the first line therapy. All the patients who are alive have given their agreement for participation in this retrospective analysis. Pts have been analyzed in intention-to-treat, CML was defined according to ELN criteria [CP, accelerated phase (AP) and blast crises (BC)], Sokal, Euro and EUTOS scores have been calculated at the diagnosis. Cytogenetic and molecular responses could not be monitored in our patients back at that time. Overall survival (OS) was calculated from the date of IM initiation until death at any time and for any reason; until progression to AP or BC at any time for progression-free survival (PFS); and until death, progression to AP or BC, failure on IM or IM treatment discontinuation for any cause including treatment-free remission (TFR).

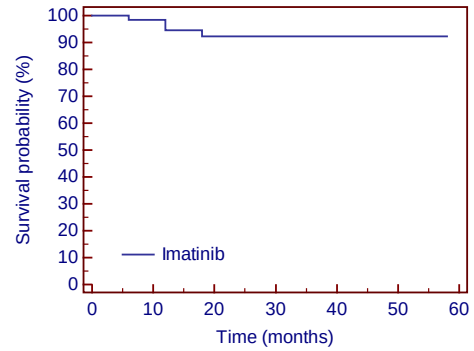
At time of analysis, 120 pts could be analyzed, with a median follow-up of 50 months (1-60) months, 70 (58%) were males, with a median age of 53 (11-85) at IM initiation. Eutos, Euro and Sokal scores had no impact on OS, PFS. The estimated PFS rate of patients treated with Imatinib is 92.8%. The overall survival OS of patients treated with Imatinib is 92.1%

FIG 1. PFS of patients treated with Imatinib



The estimated PFS rate of patients treated with Imatinib is 92.8%

FIG 2. Survival of patients treated with Imatinib



The survival of patients treated with Imatinib is 92.1%

FIG 3.

Conclusions

The usage of target therapy in this type of leukemia has made a lot of progress. Today, we have other kind of TKI like nilotinib, dasatinib, bosutinib some of which were better as far as molecular remission. Imatinib is still a good choice in the first line of therapy in patients with Chronic myeloid leukemia in chronic phase CP.

After a very long median follow-up of more than 60 months in our patients, imatinib still consistently provides high rates of remission and survival, without disease progression and severe long-term toxicities. In addition, this is the first data on our Albanian patients diagnosed with Chronic myeloid leukemia in chronic phase CP treated with Imatinib as first line therapy.

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The role of the private sector in developing the health system in Albania and governance

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Abstract

The private sector plays an increasingly important role in health systems in the countries with low and medium incomes. "Private health sector" includes a large variety of actors, including providers, financiers and physical and knowledge suppliers for the health sector. Boundaries between the public and private sector are often unclear, as many private actors act outside the framework health sector regulator on the basis of informality. Public sector institutions often have limited experience of engaging with the private sector due to lack of communication, concerns about sustainability, and complexity. This paper presents an analytical framework for conceptualizing the functioning of health care system governance and the role of government in the context of expanding private and public services its financing. Governance is increasingly recognized by the World Health Organization and other national and