THE EFFICIENCY OF THE TYROSINE KINASE INHIBITORS IN THE CHRONIC PHASE OF THE CHRONIC MYELOID LEUKAEMIA

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Abstract: *The treatment of the chronic myeloid leukaemia (CML) was revolutionized when the tyrosine-kinase inhibitors were discovered, with imatinib 400mg/day po succeeding to keep under control the disease for many years. In the case of patients with suboptimal or no response, the increase in the imatinib dose to 600mg/day or 800mg/day can still be efficient or other options could be taken into consideration, such as the use of the second generation of tyrosine-kinase inhibitors (dasatinib, nilotinib, etc) or the stem cell transplant.*

Keywords: *chronic myeloid leukaemia, cytogenetic response, molecular response, tyrosine-kinase inhibitors*

Rezumat: *Tratamentul leucemiei mieloide cornice (LMC) a fost revoluţionat prin descoperirea inhibitorilor tirozinkinazici, imatinibul 400mg/zi po realizând controlul bolii pentru mulţi ani. Pentru pacienţii cu răspuns suboptimal sau fara răspuns, creşterea dozei de imatinib la 600mg/zi sau 800mg/zi poate avea inca eficienta sau se poate opta pentru a doua generaţie de inhibitori tirozinkinazici (dasatinib, nilotinib, etc) sau transplant de celule stem hematopoietice.*

Cuvinte cheie: *leucemie mieloida cronica, răspuns citogenetic, raspuns molecular, inhibitori tirozin kinazici*

INTRODUCTION

The treatment of patients with chronic phase chronic myeloid leukaemia (chronic phase CML) registered a significant modification once with the discovery of imatinib mesylate (STI571, glivec) a 2-*phenylaminopyrimidine* with affinity and selectivity for the ABL gene. Imatinib acts by a competitive antagonist of the ATP binding site located in the tyrosine-kinase P-loop of BCR-ABL, gene, blocking the transduction signal of cell growing. The imatinib connects to the inactive form of ABL gene, with a particular structure different from the active conformation. When it was introduced in the clinic in 1998, imatinib was used only as second line therapy, being reserved to cases without response to rIFN α or with an progression of the disease (accelerated phase or blast crisis). With a CCR of 41% observed in the I and II phase studies, the imatinib 400mg/day has proved its superiority towards the rIFN α + ARA-C.(1,2) The results of the ***randomized*** phase III clinical ***trial IRIS*** showed a complete hematologic response (RHC) of 95% with imatinib towards the 55% with rIFN α **,** while the CCR rate was of 76% versus 15%. The major molecular response rate (RMM) after 12 months was significantly better to patients treated with imatinib - 40% - compared to the 2% for the patients treated with rIFN α.(3)

According to the IRIS trial, with the administration as a first line therapy in the early stage chronic myeloid leukaemia (during the first 12 months), after 72 months of surveillance the global survival is of 88%.(4) The annual rate of disease progression to an accelerated stage or blastic phase was relatively constant for the first 4 years, varying between 1,5% and 0,9%, with a decrease during the fifth year to 0,5%.(5,6,7). Patients with a sustained CCysR for a period of 4 years have zero risk to head towards an accelerated stage or blastic phase.(4). In late chronic phase, defined by the resistance (no response) or intolerance to rIFN α, the treatment with imatinib determined a CCR (RCC) between 41% and 64%, with a disease-free survival after 5 years in a percentage of 69%. A particular aspect observed during the studies was that, despite no effects on CCyR, imatinib prolongs survival, even if lately administered in the progression of the disease.(7). The high rates of CCR generated by imatinib requested the need to identify the level of the BCR-ABL transcript, as a way to quantify the minimal residual disease. From the 70% of patients that reached a CCR with administration of imatinib in early chronic phase, 50% of them presented MMR. The complete molecular response (CMR), presuming the absence of BCR-ABL transcript, varies between 4-34%, being more and more difficult to attain as the imatinib is administered in an advancing phase disease.(7,8)

At the moment, the imatinib in 400mg/day dose, is the standard treatment in the first line therapy for chronic phase CML, the dose being approved based on studies that demonstrated the direct correlation between the cell destruction in vitro and the inhibitory activity of tyrosine-kinase. The start of therapy with low doses of 100mg/day or 200mg/day must be avoided, as favourites the development of resistance.(9,10,11)

Monitoring the response to treatment is made with the complete blood count made every 2 weeks until the CHR is attained, with a cytogenetic study every 6 months until the CCR is reached and then on an annual basis, and with molecular biology (RQ-PCR) every 3 months on undetermined term.(12)

Table no. 2 – Definition of hematologic, cytogenetic and molecular responses After Michael W.D. Deininger, ASH, 2005 (6)

HAEMATOLOGICAL RESPONSE	CYTOGENETIC RESPONSE	MOLECULAR RESPONSE
COMPLETE HEMATOLOGIC RESPONSE (CHR) Absence of B phenomena (nonpalpable spleen) Normal HLG with FL Platelets < 450 x 109/l Leucocytes < 10 x 109/l ***immature granulocytes*** + basofile < 5% Absence of extramedullary tumours PARTIAL HEMATOLOGIC RESPONSE (PHR) Decrease of leucocytes and platelets, e, and splenomegaly with 50%	MINIMAL CYTOGENETIC RESPONSE → 66-95% Ph positive metaphase MINOR CYTOGENETIC RESPONSE (mCR) → 36-65% Ph positive metaphase PARTIAL CYTOGENETIC RESPONSE (PCR) → 1-35% Ph positive metaphase MAJOR CYTOGENETIC RESPONSE (MCR) → 0-35% Ph positive metaphase COMPLETE CYTOGENETIC RESPONSE (CCR) → 0% Ph positive metaphase	MAJOR MOLECULAR RESPONSE (MMR) : Decrease with > 3 log in BCR-ABL level The BCR-ABL/ABL level < 0,05% COMPLETE MOLECULAR RESPONSE (CMR) Negative RT-PCR

The patients that do not meet one or other criteria of response in an established time interval are considered non-responsive. In case of an optimal response, imatinib in dose of 400mg/day must be administered continuously on an indefinite period, at these patients the resistance to imatinib being rare, and the response to stable treatment on 5-6 years. Suboptimal response presupposes the continuance of imatinib treatment but in higher dose, the 400mg/day dose not having long term benefits. Lack of any response (failure) requires the stop of imatinib and tackling another therapy.(7)

Imatinib resistance. Despite the impressive efficiency of imatinib treatment, the results of IRIS trial point out that after 72 months of observance, 20-30% from the patients do not have any response to imatinib, requiring alternative therapies.(4) The regression rate observed in the same trial was of 17%, 7% from the patients presented a progression of the disease, (7) while at 5 years of observance, 25% stopped the treatment because of the lack of any response.(4)

The definitions of optimal response, suboptimal response and failure or warnings are the ones set by European LeukemiaNet.(7)

Primary resistance is defined by lack of any response from the start of the therapy, while the **secondary resistance** is when patients presented initially responses but subsequently they did not presented any response or the disease progress. If in case of primary resistance, the mechanisms of activation are not clear, in case of secondary resistance they are grouped into BCR-ABL dependent and BCR-ABL independent mechanisms.(13)

According to the mechanisms of resistance, the options of current therapies are: increase in the imatinib dose, second generation tyrosine-kinase inhibitors, allogeneic haematopoietic stem cell transplantation (HSCT) or experimental therapies.

The BCR-ABL mutations with partial resistance to the standard dose of imatinib, BCR-ABL gene amplification and overexpression, are indicators to increase the dose to 600mg/zi or 800mg/zi.(14) With these doses cytogenetic responses were obtained at 56% from the patients with previous partial resistance or with regression in disease under the standard dose.

Current therapeutic guidelines recommend the increase in the imatinib dosage to 600mg/day or 800mg/day according to tolerance, if after 6 months at least a mCR and after 12 months the PCR were not obtained. (10) It is not recommended to continue the therapy with imatinib over 12 months to patients presenting a mCR only in order to maintain the hematologic response.(7)

The second generation tirozin kinase inhibitors

The second generation tyrosine-kinase inhibitors used at the moment comprises two categories: nilotinib and INNO-406 which have at their basis an improved structure of imatinib, respectively the dasatinib and bosutinib with dual action mechanism, which are BCR-ABL gene and SRC kinases inhibitors.(14,15)

As a dual BCR-ABL and SRC inhibitor, **dasatinib** is 300 times more efficient than imatinib, binding to both active and inactive conformation of the BCR-ABL, with proved efficiency against all the mutations resistant to imatinib, except T315I.mutation. Dasatinib is an efficient inhibitor for c-Kit kinase, the ***platelet***-derived growth ***factor*** receptor (PDGFR-β) and receptor A for epinephrine, pathogenic cells responsible for the progression of the disease.(17)

In chronic phase CML, on a lot of 387 intolerant/ resistant to imatinib patients, dasatinib had a CHR of 91%, a MCR of 59% from which 49% CCR, with a percentage of 88% of disease-free survival. (14) From cases with MCR, we mention that 42% of cases are from those who with previous treatment with imatinib had no cytogenetic response, and 57% of the patients had BCR-ABL mutations.(14)

The compared study between dasatinib 70mgX2/day with imatinib 800mg/day demonstrated the superiority of dasatinib on an average surveillance period of 21 months, although the frequency of BCR-ABL mutations was double in this lot of patients (45% vv 22%). The MCR was of 52% to patients treated with dasatinib versus 33% in case of patients treated with imatinib, the CCR being of 40% compared to 16%, with a survival rate after 15 months significantly better for patients treated with dasatinib: 90% compared to 50%.(14)

Table no. 3 – Definitions of ELN (7)

TIME INTERVAL	FAILURE	SUBOPTIMAL RESPONSE	WARNING	OPTIMAL RESPONSE
When diagnosed	Nonapplicable	Nonapplicable	High risk, del9q+, Additional cr. anomalies in Ph+ cells	Nonapplicable
3 months from diagnosis	No hematologic response (stable disease or in progression)	Less than CHR	Nonapplicable	CHR
6 months from diagnosis	Less than CHR No Ph+ cytogenetic response (>95%)	Less than PCR (Ph+>35%)	Nonapplicable	At least PCR Ph+<35%
12 months from diagnosis	Less than PCR	Less than PCR CCR	Less than MMR	CCR
18 months from diagnosis	Less than CCR	Less than MMR	Nonapplicable	MMR
At any time interval from diagnosis	Loss of CHR, CCR, occurrence of new mutations	Additional cr. anomalies, new mutations, loss of MMR	Any increase in the BCR-ABL transcript, any chromosomal anomaly in Ph- cells	Nonapplicable

From frequently met secondary reactions we mention: ***myelosuppression***, mild to moderate gastrointestinal disturbances, liquid retention and pleurisy. Maximal therapeutic efficiency with minimal secondary reactions in chronic phase CML was obtained with 100mg/day, this being the recommended dose at the moment.(7,10,15) Due to its complex mechanism of action, dasatinib is now a line II therapy in chronic myeloid leukemia, after failure of imatinib.

Nilotinib is an analog to imatinib, with 20-50 times higher affinity for inactive conformation of BCR-ABL, active against the ABL mutations resistant to imatinib, except T315I. As a line II therapy, the recommended nilotinib dose is of 400mg X2/day.(14,17)

As an **experimental therapy**, it is effective against T315I, MK-0457 being used until now with a very limited number of patients.

CONCLUSIONS

If in the past, CML was considered a disease with reserved prognosis, with a survival of 5-6 years, currently with all the new therapies in line, the disease has a relatively idle evolution with a survival rate of 88% after 72 months.

REFERENCES

1. Kantarjian H, Sawyers C, Hochhaus A et al. Hematologyc and cytogenetic responses to imatinib mesylate in chronic myeloid leukemia. N Engl J Med 2002;346:645-652.
2. Kantarjian HM, Talpaz M, O'Brien S et al. Imatinib mesylate for Ph chromosome positive chronic phase myeloid leukemia after failure of imterferon alpha: follow up results.Clin Cancer Res 2002;8:2177-2187.
3. Colita D, Colita A. The place of imatinib in the treatment of chronic myeloid leukemia at five years follow up by the IRIS programme:benefits, limits and their management. Documenta Haematologica 2006, vol.XIV,1-2:5-9.
4. Deininger M. Milestones and monitoring in patients with CML treated with imatinib. ASH2008, Educational program book, 419-426.
5. Guilhot F, Roy L, Millot F. Update of first line imatinib therapy in chronic myeloid leukemia. Hematology 2006;293-297.
6. Deininger MWN. Management of early stage disease. ASH 2005, Educational program: 174-181.
7. Baccarani M, Saglio G, Goldman J, Hochhaus A et al. Evolving concepts in the management of chronic myeloid leukaemia: recommendations from an expert panel on behalf of the European LuekemiaNet. Blood, 15sept.2006, vol.108, nr.6
8. Marin D, Marktel S, Bua M et al. Prognostic factor for patients with chronic myeloid leukemia in chronic phase treated with imatinib mesylate after failure of interferon alpha. Leukemia 2003;17:1448.
9. Lupu A. Leucemia mieloida cronica–Protocol terapeutic actualizare.Documenta Haematologica, suplim.2006:24-27.
10. Lupu A. Managementul pacientilor cu leucemie mieloida cronica cu rezistenta sau intoleranta la imatinib. Documenta Haematologica 2007, vol.XVIII, NR.1-2:14-19.
11. Baccarani M, Palandri F, Castagnetti F, Pusiol A. Decision making at diagnosis in chonic myeloid leukemia. Education program for the 12-th congress of the EHA, 2007:225-229.
12. Hughes T, Branford S. Molecular monitoring of chronic myeloid leukemia. Semin Hematol 2003;40:65-68.
13. Melo J. Chuan C. Molecular basis of resistance to imatinib. Education program for the 11-th congress of the EHA, 2006;2:86-92.
14. Kujawski L & Talpaz M. Strategies for overcoming imatinib resistance in chronic myeloid leukemia. Leukemia&Lymphoma December, 2007;48(12):2310-2322.
15. Deininger M. The role of new agents in the management of chronic myeloid leukaemia. The education program for the annual congress of the European Haematology Association 2008;2:8-13-19.
16. Cortes J. Natural history and staging of chronic myelogenous leukaemia. Hematol Oncol Clin N Am, 18(2004),569-584.
17. Olavarria E, Apperley J. Management of patients with imatinib resistance. Education program for the 12-th congress of the EHA, 2007;230-238.