PROCEEDINGS ARTICLE

Second-generation TKIs: which and when?

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Impressive response rates and good tolerability have led imatinib 400 mg once a day to become the standard frontline therapy for chronic myeloid leukemia (CML) patients. However, approximately one-third of the treated patients do not respond in an optimal manner to this drug, and the appropriate type and rhythm of CML monitoring, as well as the correct action to be undertaken in case of failure or suboptimal responses to imatinib therapy have been published in specific recommendations by European Leukemia Net and National Comprehensive Cancer Network. Failure and also cytogenetic suboptimal responses strongly demand for a change in treatment and for a switch from imatinib to one of the two second-generation tyrosine kinase inhibitors (TKIs) so far registered, dasatinib and nilotinib, for which efficacy as second-line therapy in imatinib-resistant or intolerant cases has been clearly demonstrated in phase II studies, and for which 4-year updates are now available. Other TKIs, at the moment, still under clinical investigation for imatinib-resistant patients include bosutinib and the next-generation TKI ponatinib. Different efficacy and safety criteria characterize each of the mentioned compounds and may help to decide on the one to be preferably used in individual patients.

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BACKGROUND

It is well known that the degree of reduction of the leukemic Philadelphia (Ph)-chromosome clone in response to therapy, assessable by conventional cytogenetic analysis, is the most important prognostic factor for the long-term outcome of chronic myeloid leukemia (CML) patients, and in recent years, the impressive complete cytogenetic response (CCyR) rates and the good tolerability led imatinib to become the standard frontline therapy for CML patients in early chronic phase.^{1,2} Indeed, the 8-year follow-up of the IRIS study (International Randomized Study of Interferon vs STI571) shows the achievement of CCyR in 83% of the patients and a projected overall survival (OS) of 85%.³ Optimal response to imatinib therapy is considered to reach at least CCyR within 12 months from the start of therapy,⁴ as this target has been demonstrated to be sufficient to have the highest probability of long-term survival.⁵ In the IRIS trial, however, 31% of the patients did not achieve CCyR within 1 year, 17% of patients never achieved CCyR, 15% achieved CCyR but eventually lost it, and approximately 5% were intolerant to imatinib.³ As also confirmed by other studies,⁶ the outcome for patients who fail first-line imatinib therapy is not as favorable as for those who respond to the therapy. In this context, the availability of two tyrosine kinase inhibitors (TKIs) of second generation, dasatinib⁷ and nilotinib,⁸ both endowed with a higher potency in suppressing the Bcr-Abl tyrosine kinase activity and the ability to inhibit most of the BCR-ABL mutants whose presence characterizes the Ph-positive clones resistant to imatinib, has certainly contributed to greatly improve the therapeutic perspectives in these patients. On the basis of the results of a number of Phase II clinical trials,^{9–11} both drugs have been registered as second-line therapy for CML patients resistant or intolerant to imatinib in most countries of the world; however, the correct timing and the specific choice of one or the

other drug have been the subject of an intense debate in the past few years.

APPROPRIATE TIMING OF SWITCHING

For CML patients in therapy with imatinib 400 mg once a day, the last term to achieve CCyR has been established at 18 months, and the residual probability of attaining this goal is greatly reduced for those who do not present at least complete hematological response by 3 months or any CyR by 6 months, or major CyR (Ph-positive metaphases <35%) by 12 months.^{4,12} These conditions are considered treatment failures, and a change in therapy is highly recommended.^{4,12} Of course, also the confirmed loss of any previously achieved degree of hematological or cytogenetic response in patients initially responding to therapy is also considered a failure that calls for a change in therapy.^{4,12} Finally, there are intermediate degrees of cytogenetic response in which, although not totally compromised, the possibilities of achieving CCyR later on are decreased. These intermediate situations have been termed 'suboptimal responses'.⁴ The therapeutic options to be followed in these situations (i.e., continuing the same therapy, increasing the dosage of imatinib or switching to second-generation TKIs) have not been clearly established at the moment, but a recent review of the data derived from these categories of patients suggests that at least for cytogenetic suboptimal responders, the final outcome in terms of progression-free survival and OS is so inferior to that of those who respond optimally that, even in absence of evidence from clinical trials, an attempt to improve the therapeutic efficacy by switching to second-generation TKIs appears justified.¹³ In contrast, although the achievement of major molecular response (MMR) in addition to CCyR is associated with a significant decrease of the risk of losing CCyR¹⁴ and to a more stable response,¹⁵ the present data do not support

the notion that achieving MMR may improve OS relative to achieving CCyR without MMR,⁵ and therefore, the European Leukemia Net recommendations consider no achievement of MMR or loss of MMR without the loss of CCyR as a suboptimal response only, which does not require a change in therapy unless they are associated with the presence of mutations poorly sensitive to imatinib, such as the T315I, E255K/V or Y253H. These situations are considered failures and should therefore prompt appropriate changes in therapy.⁴ Indeed, the European Leukemia Net recommends mutational analysis not only in all instances of failure, but also in cases of suboptimal response.⁴ The reason for this is that it is progressively becoming clear that in these situations the presence of BCR-ABL-mutated clones represents an element endorsing the presence of true resistance that could more likely urge a change in treatment rather than an imatinib dose increase.¹⁶ Furthermore, mutational analysis could also drive the more appropriate therapeutic choice, including the second-generation TKIs to be used in specific cases, as well as the indication for stem cell transplantation.^{17–19}

ELEMENTS INFLUENCING THE CHOICE OF THE SECOND-GENERATION TKIS

Second-line TKI options include dasatinib and nilotinib, and both these two agents, tested in the context of patients resistant or intolerant to imatinib in patients in all stages of the disease, have resulted in hematological and CyRs in a large proportion of cases, particularly in chronic phase, stable in time as confirmed by follow-up results.^{11,20} Although both are potent BCR-ABL TKIs, dasatinib and nilotinib exhibit different characteristics. In addition to BCR-ABL, dasatinib inhibits a number of other tyrosine kinases, including the Src kinases, whereas similar to imatinib, the spectrum of the tyrosine kinase inhibited by nilotinib is limited to ABL, KIT and the platelet-derived growth factor receptor- α and - β .^{7,8} Dasatinib and nilotinib, as compared with imatinib, have also the capacity to inhibit the majority of the clinically relevant and imatinib-insensitive BCR-ABL mutants, with the notable exception of the T315I.²¹ *In vitro* data and clinical trials, however, suggest that mutations affecting three residues, E255K/V, Y253H and F359C/V, are less sensitive to nilotinib, whereas V299L, F317L, E255K/V and Q252H appear to be less sensitive to dasatinib.^{22,23} If patients have one of these mutations, they should be treated with the drug that is known to be active against the specific mutation. Unfortunately, none of the two approved second-generation TKIs appear active against T315I-positive clones, and also patients with mutation E255K/V, in addition to being unresponsive to nilotinib, do not appear to be very responsive to dasatinib.²⁴ Other criteria that should drive the choice between the two second-generation TKIs currently registered as second-line therapy are based on the patients' clinical profile.²⁴ Indeed, although both show in general a good tolerability, nilotinib and dasatinib present distinct adverse-event (AE) profiles. In general, nilotinib shows a lower incidence of hematological toxicity (neutropenia in particular) with respect to other TKIs, and the most frequent non-hematological AEs of any grade reported in patients with CML receiving nilotinib are rash, headache and pruritus, but nilotinib shows lower rates of gastrointestinal and fluid retention-related AEs compared with imatinib.²⁵ In addition, in dasatinib-treated patients, fluid retention, nausea, vomiting, myalgia and rash appear less frequent than in imatinib-treated patients, but pleural effusion and myelosuppression (particularly thrombocytopenia) are more common.²⁶ The percentage of patients receiving dasatinib and developing pleural effusion ranges approximately between 10 and 40%, and age, hypertension and twice-daily dosage have been found to be associated with a higher risk of developing pleural effusion.²⁷ In nilotinib-treated patients, a greater incidence of laboratory abnormalities including lipase level elevation, hyperbilirubinemia, elevated levels of alanine and aspartate aminotransferases, and

hyperglycemia have been reported, although in the majority of the cases these abnormalities are not clinically relevant and transient.²⁸ In contrast to imatinib and dasatinib, nilotinib has been shown to cause hyperglycemia. However, in patients with preexisting type 2 diabetes treated with nilotinib, hyperglycemic events are generally mild and easily manageable, and the majority of them do not require a change in diabetes treatment.²⁹ The rates of response in this populations are comparable to those obtained in the overall population.³⁰

CONCLUSIONS

At the moment, the short-term toxicity profiles characteristic of each second-generation TKI, together with the evaluation of the presence of specific mutations, are the major factors that should drive the choice of one agent with respect to the other. In the future, however, other elements concerning the long-term toxicity profile of second-generation TKIs will also have to be taken into consideration, as the patients who respond to therapy after switching, as well as those who are switching because of intolerance to imatinib, are supposed to remain indefinitely in treatment with the second-line drug. For them, as well as for those who are now directly starting nilotinib or dasatinib as first-line therapy, also the presence of risk factors potentially associated with the occurrence of long-term toxicity events, as peripheral arterial obstructive disease reported for nilotinib³¹ and pulmonary hypertension³² reported for dasatinib. To optimize therapeutic benefit, clinicians should select treatment based on each patient's probability of response, AE tolerance and risk factors.

CONFLICT OF INTEREST

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