PROCEEDINGS ARTICLE

Initial treatment for patients with chronic myeloid leukemia

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The first-line treatment of chronic myeloid leukemia is based on the three currently available tyrosine kinase inhibitors (TKIs), namely imatinib, nilotinib and dasatinib. Nilotinib and dasatinib are more potent, and it is predicted that, in comparison with imatinib, they can reduce the risk of progression and increase the number of the patients who can discontinue the treatment without relapsing. Other TKIs are still being developed and may help to improve treatment options further on. Hydroxyurea has no longer a role. Allogeneic stem cell transplantation is the treatment of choice for the advanced phases, and in case of resistance to at least two TKIs.

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The initial treatment of Philadelphia-positive (Ph⁺), BCR-ABL + chronic myeloid leukemia (CML) is based on tyrosine kinase inhibitors (TKI), a class of small molecules that can inhibit the phosphorylative function of the proteins that are coded by the BCR-ABL fusion gene on chromosome 22q.^{1–4} These proteins are located in the cytoplasm, where they activate a number of downstream signals of proliferation and survival, resulting in the transformation of normal hematopoietic stem cells to leukemic cells. The Ph⁺ leukemic stem and progenitor cells on one hand proliferate and mature, expanding the myeloid tissue in the bone marrow and in the spleen, and causing leukocytosis, whereas on the other hand, they are genetically unstable and develop a number of secondary genomic lesions, leading to the progression from chronic to accelerated and blastic phase.^{1–4} Therefore, the first goal of treatment is to prevent progression, and the second one is to eliminate the leukemic clone. Achieving the first goal may be sufficient to ensure a normal survival. Achieving the second goal may be necessary to cure the disease and discontinue the treatment safely. Both goals can be achieved with TKIs, although achieving the second goal may require other agents.

TYROSINE KINASE INHIBITORS

The TKIs are a class of small molecules that have been designed with the purpose of inhibiting the phosphorylative activity of the TK. Several TKIs are able to inhibit the BCR-ABL proteins, although none is truly specific, because they inhibit other TKs as well. The TKIs that have been selected and registered so far for their activity on BCR-ABL, then for the treatment of CML, both first-line and second-line treatment, are as follows:

- Imatinib (Glivec or Gleevec, Novartis Pharma)^{2,5}
- Nilotinib (Tasigna, Novartis Pharma)^{2,6}
- Dasatinib (Sprycel, Bristol-Myers Squibb)^{2,7}

Another compound (Bosutinib, Pfizer) has already been tested in first-line and second-line treatment.⁸ A fifth compound (Ponatinib, Ariad) has been tested in second-line and third-line treatment.⁹

Imatinib, first of the class, was introduced more than 10 years ago. With imatinib, the complete hematologic response rate is

close to 100%, the complete cytogenetic response (CCgR) rate ranges between 65 and 80%, the major molecular response (or BCR-ABL $\leq 0.1\%$ on the International Scale) rate ranges between 40 and 60%, and the complete molecular response (or BCR-ABL $\leq 0.01\%$ on the International Scale) rate ranges between 15 and 30%.^{5,10–14} About 20% of patients are or become resistant, about 15% of patients discontinue imatinib because of side effects, but progression-free survival and overall survival at 8–10 years are in the order of 80–85%.^{10–14} The major side effects are fatigue, myalgia and fluid retention.

Nilotinib is a derivative of imatinib, which was designed to target BCR-ABL more specifically. It is a more potent inhibitor of BCR-ABL, both the unmutated and most mutated forms, with the exceptions of some P-loop mutations and the T315I mutation, that are resistant to Imatinib.¹⁵ When nilotinib was used as a second-line treatment, in patients resistant to imatinib, the CCgR rate was around 50% and the major molecular response rate was around 25%.⁶ The secondary responses are stable over time.⁶ When nilotinib was tested, first-line treatment compared with imatinib, all the responses were faster and superior, and the molecular response was also deeper.^{16–18} The follow-up of the patients treated with nilotinib first-line is still short, less than 3 years. The major side effects of nilotinib are skin rash, hyperglycemia, elevated bilirubin, aspartate and alanine aminotransferase, elevated lipase and peripheral arterial obliterative disease.

Dasatinib was designed as a inhibitor of the Src kinase, but it is also active on BCR-ABL. Therefore, it is called a dual inhibitor, but also inhibits many other TKIs.^{2,7} It is a more potent inhibitor of BCR-ABL, both the unmutated and most mutated forms, with the exception of some mutations and of the T315I mutation, which are resistant to dasatinib.¹⁵ When dasatinib was used as a second-line treatment, in patients resistant to imatinib, the CCgR rate was around 50% and the major molecular response rate around 25%.⁷ These secondary responses are stable over time.⁷ When dasatinib was tested, first-line treatment compared with imatinib, the responses were faster and superior, and the molecular response was also deeper.^{19,20} The follow-up of the patients treated first line with dasatinib is still short, less than 3 years. The major side effects of dasatinib are leucopenia, thrombocytopenia, pleural effusion and pulmonary complications.

Bosutinib is also a dual inhibitor that is active on wild-type BCR-ABL and most mutated forms, with the exception of the T315I mutation.⁸ The results of bosutinib treatment, second-line and first-line, are similar to those of nilotinib and dasatinib, although the differences in comparison with imatinib are less significant, because of the side effect of the drug, mainly diarrhea and increase of aspartate and alanine aminotransferase.

Ponatinib is a third-generation TKI that binds to BCR-ABL at a different position, so that it can inhibit all mutated forms, including the T315I one. It inhibits also several other TKIs, and its safety profile is not yet fully understood. When it was used as the third-line treatment, more than 50% of the patients who were resistant to two or three TKIs achieved a CCgR.⁹

WHICH OPTIONS ARE AVAILABLE FOR THE TREATMENT OF CML?

- (1) Cytotoxic drugs (conventional chemotherapy): many drugs are effective, but all are palliative. Currently, only hydroxyurea is still used.
- (2) Interferon (IFN)- α : there are two preparations, α 2a (Roferon-A, Roche) and α 2b (Intron, MSD). There are also pegylated preparations that have been tested in first-line treatment in combination with imatinib, but are not registered for CML.
- (3) Allogeneic hematopoietic stem cell transplantation.

WHICH IS THE BEST FIRST-LINE OPTION FOR THE AVERAGE PATIENT?

Hydroxyurea can be used to contain a high white blood cell or a high platelet count, when one is waiting for a more precise diagnosis, but it is not more rapid or more convenient than TKI. Apart from that, hydroxyurea is never a valid option, even in very old patients; maybe only in the rare patients with a documented prolongation of QTc, more than 500 ms, or with a very severe cardiovascular disease.

The best first option for the average patient is one of the three currently available TKIs, namely imatinib at doses of 400–800 mg daily, nilotinib at doses of 300 mg twice daily, or dasatinib at doses of 100 mg daily. This applies also to the few patients who present already in accelerated or blast phase. Both nilotinib and dasatinib are superior to imatinib in terms of early surrogate markers of the outcome, that is to say in terms of CCgR and in terms of major molecular response and complete molecular response during the first 12–24 months of treatment. With either drugs, the rate of early progression to accelerated phase and blastic phase is likely to be slightly lower. These early responses predict an improvement on the progression-free survival and overall survival, which may be significant.^{16–20} However, the magnitude and importance of the differences are not yet assessable.

Still in favor of imatinib may be the length of the observation time, concerning the durability of the response on one side, and the lack of late, off-label, adverse events, as well as the cost, on the other side.

ARE THERE DISEASE-RELATED FACTORS THAT MAY INFLUENCE THE CHOICE OF FIRST-LINE TKIS?

Several reports agree that the outcome of imatinib treatment is related to risk,^{21–23} because high-risk patients respond less well and less rapidly, and may progress to accelerated phase or blastic phase more than non-high-risk ones. On the basis of these findings, the use of a more potent and a faster second-generation TKI may be more appealing in high-risk patients. However, there is no evidence that the benefit is limited to high-risk patients, and is not extended to all patients irrespective of risk.^{16–20}

ARE THERE PATIENT-RELATED FACTORS THAT MAY INFLUENCE THE CHOICE OF FIRST-LINE TKIS?

Age should have no influence. TKIs are first-line treatment in children as well as in very old patients. Severe cardiovascular comorbidities, including a QTc over 500 ms, are a contraindication for all TKI at the standard recommended doses; but also in these cases, TKI can be tested and used at lower doses. Some comorbidities may warn against nilotinib (active liver or pancreas diseases, poorly controlled or complicated diabetes mellitus, peripheral arterial obstructive disease) or dasatinib (pleural effusion, pulmonary chronic disease, autoimmune disease), but there is no evidence, as yet, that these comorbidities may compromise the therapy and results of the therapy.

What is the impact of the choice of first-line TKI on the outcome?

Based on the limited available knowledge,^{16–20} it is expected that the short range outcome will be affected significantly by the choice of first-line TKI, imatinib versus second-generation agents, in favor of the latter. However, it is difficult to predict what it will be the benefit for the long-term outcome, as it is expected that about 50% of the patients who fail on imatinib can be rescued to an optimal response with a second-generation TKI second-line. A careful consideration of the side effects, and a careful monitoring of the response, can be determinant for a proper and timely switch from one TKI to another, and may be as important as the initial choice, as it concerns overall survival and life quality.

Is there a place for TKI-based combinations?

The only combination that has been tested successfully so far, is that of imatinib and the pegylated preparations of IFN α 2a (Pegasys, Roche) or IFN α 2b (Peg-Intron, MSD).^{24,25} The early responses, cytogenetic and molecular, were deeper and faster, but the effect on progression-free survival cannot yet be determined. The underlying problems are as follows: (1) IFN α has unpleasant side-effects (50% of patients in those trials discontinued IFN within 1 year);^{24,25} (2) the pegylated forms of IFN α have not been approved for the treatment of CML and are prepared in vials containing much more IFN than required; (3) another study¹⁴ did not confirm the superiority of the combination; and (4) it is unknown how the combination of IFN α and imatinib would compare with a second-generation TKI alone. Therefore, the place for a combination of TKI and IFN α is still in the investigational setting. Combinations of TKI and other agents, such as the so-called stem cell agents, are an interesting area of investigation, aiming at the eradication of all residual Ph⁺ stem cells, but their use in the first-line setting cannot be allowed until more information will be available on these agents, on their side effects and on their safety.

Is there a place for allogeneic hematopoietic stem cell transplantation?

Allogeneic hematopoietic stem cell transplantation is never the treatment of choice in the first-line setting. It is indicated in all the patients who are in accelerated phase or blastic phase, even if they are responsive to TKI, because in most of these patients, the response is not durable. It is indicated in all the patients who are in CP and are resistant to two TKIs.^{10,11,28}

What is the goal of treatment?

The goal of treatment is dual: first, to ensure a normal survival; and second, to eradicate the leukemic cell clone, or to control the leukemic stem cell clone to an extent that treatment can be discontinued without relapse. The first goal can be achieved with all the available TKIs in at least 65% of patients, probably slightly more with second-generation TKIs than with imatinib. The second goal can be achieved in less patients, very few with imatinib,²⁹

probably more with second-generation TKIs, because with second-generation TKIs, the molecular response is deeper.^{16–20}

The incidence of CML is low, around $10/10^6$ per year, and the median age at presentation is about 60 years. For elderly patients, a chronic treatment with a good quality of life may be an acceptable goal. However, for young people, a path to treatment discontinuation and to cure should be marked. The rate and the degree of cytogenetic and of molecular responses are important and useful early surrogate markers of the outcome,^{10,11,28} but the very measure of the outcome are progression-free survivals, and the proportion of the patients who will discontinue treatment without relapsing.

CONFLICT OF INTEREST

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