Is Imatinib Still an Acceptable First-Line Treatment for CML in Chronic Phase?

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Is it reasonable to start all new CML patients on treatment with imatinib alone and continue the drug indefinitely in those who fare well, or should one start treatment with one of the newer agents or possibly with imatinib in combination with another anti-CML agent in order to secure the best possible outcome for an individual patient?

Introduction

The management of patients with newly diagnosed chronic myeloid leukemia (CML) in chronic phase (CML-CP) has changed very fundamentally over the past 10 years. Until 1998 there was little dispute that a new patient should be offered treatment by allogeneic stem cell transplantation (allo-SCT) if he or she was relatively young and had a suitable human leukocyte antigen (HLA)-matched sibling donor. If there were no sibling donors, then efforts were made to identify an HLA-matched family member or an unrelated volunteer from the general public. Patients not eligible for treatment by allo-SCT usually received interferon alfa or hydroxyurea, but the median expectation of life ranged between 3 and 6 years. In the 1990s, Druker, working in conjunction with Ciba-Geigy (now Novartis) in Switzerland, developed the 2-phenylaminopyrimidine derivative tyrosine kinase inhibitor (TKI) imatinib mesylate (Gleevec), now referred to just as imatinib, which specifically targeted the BCR-ABL1 oncprotein characteristic of CML and selectively killed CML cells in vitro.[1,2] Imatinib was first used in the clinic in 1998, and it soon became clear that this agent produced impressive cytogenetic responses in patients with interferon-resistant CML.[3] This led rapidly to the initiation in 2000 of the International Randomized Study of Interferon vs STI571 (IRIS study), in which 1,106 CML-CP patients from 15 countries were recruited over a 6-month period and randomly assigned to receive either imatinib or interferon alfa + cytarabine in a 1:1 ratio. The early results of this study were reported first in 2003[4] and have been updated at intervals since then.[5,6] They showed that imatinib produced an extremely high cumulative incidence of complete cytogenetic responses, and the patients who experienced a complete response had a mortality at 8 years of 16%. The crossover or drop-out of patients from the interferon/cytarabine arm was so great that the comparison component of the study rapidly became inevaluable, but the long-term survival of patients treated in the imatinib arm was of course substantially better than would have been expected based on treatment with interferon in an earlier era.

In the past decade, the notion of treating CML by targeting the BCR-ABL1 oncprotein has been developed further. Four new TKIs, namely dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), and ponatinib, have been introduced; all have demonstrable efficacy in treating patients whose leukemia has proved resistant to imatinib. The first three agents, dasatinib, nilotinib, and bosutinib, have been compared prospectively with imatinib in newly diagnosed patients, and all clearly produced more rapid responses than imatinib at the dose levels employed.[7-9] A phase III study of ponatinib compared with imatinib is just starting, and the same may prove to be true for ponatinib. The newer TKIs are, however, generally more expensive than imatinib, and when the patents on imatinib expire and generic versions become available, the difference in cost may increase still further. The critical question is therefore: Is it reasonable to start all new CML patients on treatment with imatinib alone and continue the drug indefinitely in those who fare well, or should one start treatment with one of the newer agents or possibly with imatinib in combination with another anti-CML agent in order to secure the best possible outcome for an individual patient?

TKIs: Side-Effect Overview

TABLE 1
Comparison of Efficacy, Adverse Events, and Laboratory Abnormalities Associated With the Four TKIs Used as Initial Therapy for Patients With CML-CP

Side effects differ from drug to drug, but for TKIs it is possible to define a drug class side-effect profile; this includes myelosuppression (the main side effect), fatigue, fluid retention, hepatotoxicity, gastrointestinal disturbances, myalgias, arthralgias, rashes, prolongation of the QTc interval, hypocalcemia, hypophosphatemia, and increases in amylase and lipase levels. All four TKIs can cause these effects, but their relative frequencies differ: for example, facial edema is very common with imatinib but rare with dasatinib, whereas rashes are relatively common with nilotinib but less prominent with dasatinib (Table 1).

**Imatinib**

Imatinib was the first TKI. Typically it is given once a day at a standardized dose of 400 mg, although the maximum tolerated dose was never formally established. Some studies have tested higher doses—e.g., 600 or 800 mg daily.[10,11-13] Imatinib is normally given with food to prevent or minimize nausea.

**Side effects**

We have more than 14 years of experience with imatinib, and 12 years of experience with imatinib as first-line therapy for CML. The drug is safe. It has been taken by many thousands of patients, and the side-effect profile is well established. Nausea, myalgia, arthralgia, and fluid retention are seen far more frequently in patients receiving imatinib than in those treated with other TKIs. Nausea and fluid retention can be easily managed, but arthralgia and myalgia may persist as late side effects in a minority of patients despite optimal support.

**Efficacy**

Approximately 70% of patients who receive imatinib as first-line therapy achieve a complete cytogenetic response (CCyR) by 12 months, and 80% do so by 5 years.[5] In a series of 282 patients treated at Hammersmith Hospital in London, the 8-year probability of overall survival on an intention-to-treat basis was 84%, the 8-year probability of being alive and in CCyR was 77%, and the 8-year probability of imatinib failure-free survival was 50%,[14] indicating that although the majority of patients who begin imatinib therapy fare well, a significant proportion need a change of therapy on account of unsatisfactory response or side effects.

Attempts have been made to start treatment for CML-CP by combining imatinib with other agents, notably with interferon alfa. In two studies, this combination yielded better short-term results than the use of imatinib alone, but there was no difference in progression-free or overall survival.[13,15] In one study, there was no demonstrable difference between the regimen that included interferon and the regimen that did not include it.[16] Thus, the suggestion that interferon together with imatinib might be the best initial therapy for CML is so far unproved.

**Summary**

The obvious advantages of imatinib are that it is the only drug with which we have long-term (>10 years) experience, its side-effect profile is well known, and in most countries it is the least expensive of the available TKIs. Conversely, imatinib probably induces a higher proportion of insidious
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low-grade side effects (eg, muscle cramps) than nilotinib or dasatinib. At a standard dosage, the proportion of patients who achieve CCyR by 1 year is lower with imatinib than with nilotinib or dasatinib.

**Nilotinib**

Nilotinib is a BCR-ABL1 inhibitor that was rationally designed to be more potent and more selective than imatinib. Until recently it had been used, for the most part quite successfully, as a second-line agent; it is now approved for first-line use at a dosage of 300 mg bid.

**Efficacy**

A number of studies report the use of nilotinib in patients deemed to be either refractory to or intolerant of imatinib (or both).[17-19] The 2-year incidence of CCyR in such patients has been on the order of 40%, which is generally consistent with the conclusion that nilotinib can “rescue” a proportion of the patients who fail imatinib. This initial experience with the use of nilotinib led to the design of a prospective study, the Evaluating Nilotinib Efficacy and Safety in clinical Trials of newly diagnosed (Philadelphia chromosome [Ph]+ CML) patients (ENESTnd) trial, in which 846 previously untreated patients were randomly assigned to receive imatinib, 400 mg once daily; nilotinib, 300 mg twice daily; or nilotinib, 400 mg twice daily.[7] As a consequence of this study, the recommended dosage for newly diagnosed patients was specified as 300 mg twice daily. Perhaps the most important result has been that by 1 year the cumulative incidence of CCyR was 15% higher in the patients receiving nilotinib than in imatinib controls. Furthermore, patients receiving nilotinib had a much higher probability of achieving major molecular response (MMR). However, these superior response rates have not yet translated into any improvement in progression-free or overall survival.

**Side effects**

Nilotinib is well tolerated; it causes less nausea, and fewer patients develop myalgias, arthralgias, or fluid retention than do patients receiving imatinib. It does produce rash or pruritus in the majority of patients; however, in most cases, these symptoms can be easily controlled with antihistamines or topical corticosteroids. Nilotinib is the most hepatotoxic of the four TKIs, although this hepatotoxicity is usually limited to a mild increase in transaminase levels that does not require action. Severe toxic hepatitis is rare. Nilotinib has been associated with progressive peripheral arterial occlusive disease, but this seems to be rare.[20] Nilotinib causes an increase in the bilirubin level in the majority of patients, but this seldom requires any action.

**Summary**

Nilotinib is thus preferable to imatinib, since a higher proportion of patients achieve CCyR by 1 year. It is well tolerated and indeed has a better side-effect profile than imatinib if one excludes the rash. However, the posology is quite complicated because the drug has a short half-life. It is given every 12 hours, and patients have to fast for 2 hours before taking it and for 1 hour afterwards. In the majority of countries, nilotinib is significantly more expensive than imatinib.

**Dasatinib**

Dasatinib is a multi-target kinase inhibitor that, based on in vitro studies, is more than 300 times more potent than imatinib in inhibiting the BCR-ABL1 oncprotein.

**Efficacy**

As with nilotinib, most of the experience to date with dasatinib has been in patients who have failed imatinib. The results are similar to those achievable with nilotinib in this setting; about 40% of patients who fail imatinib may achieve worthwhile responses to dasatinib.[17,21,22] It is worth noting parenthetically that these responses to second-generation TKIs in patients who fail imatinib can be predicted with some reliability soon after starting the second-line treatment—or in some cases, even before this is started.[17,23,24]

Again, most of the information on first-line use comes from a single multi-center industry-sponsored study by the manufacturers, the Dasatinib vs Imatinib Study in Treatment-Naive CML-CP Patients (Dasision trial), in which 519 CML patients were randomly assigned to receive either dasatinib, 100 mg daily, or imatinib, 400 mg daily, as initial therapy.[25] Briefly, dasatinib induced a higher rate of CCyR at 12 months (12 percentage points higher than imatinib). However the difference had
disappeared by 24 months; this may have little practical consequence, though, since most physicians will consider that a patient who is not in CCyR by 12 months needs to change therapy. Like nilotinib, dasatinib induces molecular responses in a considerably higher proportion of patients than does imatinib.

**Side effects**

Dasatinib is well tolerated; it has a lower incidence of insidious low-grade side effects than imatinib. Pleural effusions are the main complication of dasatinib therapy, but the reported incidence varies among the different series. Most studies report incidences below 20%, although cumulative incidences as high as 54% have been reported.[25-29] Because pleural effusions can occur some time after the start of treatment, the proportion of patients who will eventually be affected is not known. Pleural effusions are easy to manage. Diagnostic thoracocentesis is not usually required, and the effusion almost always resolves on discontinuation of the drug, without the need for any invasive procedure. The practice at the Hammersmith Hospital is to confirm the suspected diagnosis of pleural effusion with a chest x-ray, interrupt the dasatinib, and treat the patient with 0.5 mg/kg of prednisolone for 1 or 2 weeks. Pleural effusions may recur in spite of dose reduction.

**Summary**

Dasatinib is now approved for advanced-phase disease. In chronic-phase CML, a higher proportion of patients achieve CCyR by 1 year with dasatinib than with imatinib. Dasatinib is well tolerated (better than imatinib, if one excludes the pleural effusions). It is given once a day and can be taken with food or fasting (unlike imatinib and nilotinib). Conversely, dasatinib is associated with a relatively high incidence of pleural effusions. The side-effect profile is not yet fully understood, and dasatinib has been associated with pulmonary arterial hypertension.[30] The incidence of this complication, although low, is not clearly established; nonetheless, it seems to be reversible on the discontinuation of the drug. Myelosuppression may be more of a problem than with imatinib or nilotinib, but the anemia may respond to administration of erythropoietin, and the neutropenia may respond to granulocyte colony-stimulating factor. As in the case of nilotinib, in most countries dasatinib is significantly more expensive than imatinib.

**Bosutinib**

Bosutinib is a dual inhibitor of the SRC and ABL tyrosine kinases that is not currently approved for first-line use. A large phase III clinical trial, the Bosutinib Efficacy and safety in chronic myeloid Leukemia (BELA) trial, has recently been completed,[9] and the drug has very recently been approved by the US Food and Drug Administration (FDA) for second-line use. In the BELA study, 502 patients were randomly assigned to receive 500 mg daily of bosutinib or 400 mg daily of imatinib. At 1 year the cumulative incidence of the CCyR rate was similar for the two drugs, but bosutinib induced a higher proportion of molecular responses.

**Side effects**

Bosutinib is well tolerated. Its main side effect is diarrhea, which in our experience can easily be managed symptomatically. However, diarrhea is frequent, even though it is usually self-limited or responds to simple measures. The posology of bosutinib is easy, and the drug is probably less toxic than imatinib.

**Imatinib Failure**

Patients who start treatment with imatinib may fail at any time as a result of resistance or intolerance. Resistance may be primary, meaning that the patient never achieves any useful level of cytogenetic response, or it may be secondary, in which case the patient may have achieved a CCyR but then lost it despite continuing imatinib at the same dose. A small proportion of patients progress to advanced-phase disease after starting imatinib, but such progression is rare after the first 1 or 2 years of treatment. If one could reliably predict which patients are destined to become resistant to imatinib, one could make a good case for starting such patients on a second-generation TKI and starting all the remaining patients on imatinib at 400 mg daily.

A number of efforts have been made to predict response to imatinib. It is interesting to note that the Sokal score developed in the 1980s and based on patients treated with busulfan or hydroxyurea[31] still has some predictive value in the era of TKIs. Because imatinib is transported into cells by human
organic cation transporter 1 (hOCT1), some investigators have studied hOCT1 expression by
leukemia cells and concluded that low endogenous hOCT1 levels predict poorer responses to
imatinib.[32-34] The notion that the speed of response to imatinib, measured either as the speed
with which a patient achieves a given level of cytogenetic response or a given level of reduction of
BCR-ABL1 transcripts in the peripheral blood, seems now to be emerging as the best single
prognostic marker.

TABLE 2

Relative Risk for OS, PFS, and EFS at 8 Years, and Cumulative Incidences of CC yR, MMR, and CMR
According to the Transcript Level at 3 Months in Patients Receiving Imatinib (Gleevec) as First-Line
Therapy

In 2003, the Liverpool group proposed that patients whose transcript number fails to fall to below
10% by 3 months have overall prognoses poorer than those with lower transcript numbers.[35] We
at the Hammersmith have recently reported the use of receiver operating characteristic analysis to
study 282 patients who started treatment with imatinib.[14] We showed that using a cut-off of 9.8%
discriminated very significantly between patients with relatively good and those with relatively poor
subsequent survival. The same technique—but with different cut-offs at 3 months—could be used to
predict progression-free survival and indeed the achievement of a complete molecular response
(Table 2). Others have reported similar findings using a 10% cut-off at 3 months. Thus it now seems
that the speed in achieving transcript levels below 9.8% or 10% could be the single prognostic
criterion necessary to identify the good imatinib responder.

Cure of CML

Investigators in France have recently reported the results of stopping imatinib in select patients.
They collected data on 100 CML patients from throughout France who had started treatment with
imatinib and had achieved complete molecular responses that had been maintained on treatment for
a further 2 or more years.[36] These patients then stopped the imatinib and were monitored closely
at the molecular level. Relapse was defined as recurrence of detectable transcripts in the blood. The
actuarial risk of relapse at 18 months was 61%, and almost all the patients who did relapse did so
within the first 6 months of stopping therapy. The authors concluded that at least some of the
patients who had not relapsed might prove to have been “cured” of their leukemia. This of course
raises the question of how best to define cure, but for practical purposes one could say that a patient
who survives for an appreciable number of years without detectable evidence of leukemia in his or
her body has at least achieved an “operational” cure.[37] Similar data have been published in a
smaller number of patients from Australia.[38] If some patients treated with imatinib can achieve an
operational cure, the number treated with one or another of the second generation of TKIs might be
greater,[39] and such a finding could in due course become an important factor in determining which
TKI is best for long-term treatment.

Conclusions

For the present, it seems impossible to make a firm recommendation that would apply to all new
CML-CP patients scheduled to start therapy with a TKI. Instead there are two contrasting options.
1. The clinician could argue that he or she has considerable experience with imatinib and less
experience with the newer agents. If 50% or more of patients do well with imatinib, would this not be
an argument for starting all on imatinib and only changing to another agent if necessary? This
argument gains traction if one can indeed identify early on those patients destined to fare badly. It gains further support from the expectation that the cost of imatinib may fall precipitously within the next few years. Also, one could perhaps increase the short-term efficacy of imatinib by increasing the starting dosage to 600 or even 800 mg daily or by combining it with interferon alfa.

2. Conversely, the clinician could argue that the second-generation TKIs undoubtedly act more rapidly to reduce the leukemia cell burden and may thus protect patients from progression in the first year or two after the start of treatment. They are also useful in managing some imatinib-refractory patients, and it might therefore be better to start all new patients on a second-generation TKI in the expectation that the overall incidence of resistance would be lower than with imatinib. It also seems likely that the cost of these agents will fall in the foreseeable future as the various TKIs become more readily available. Between nilotinib and dasatinib there is little reason to choose one over the other on the basis of differential efficacy. For an individual patient, the choice may depend on how he or she perceives the risks or harm associated with the side effects of the two agents.

It is quite likely that the choice between initial treatment with imatinib or with a second-generation TKI will become much clearer in the next few years.

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References:


38. Ross DM, Hughes TP, Melo JV. Do we have to kill the last CML cell? Leukemia. 2011;25:193-200


Links: