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The use of imatinib (STI571) in chronic myeloid leukemia: some practical considerations

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Background and Objectives. The new Abl tyrosine kinase inhibitor imatinib (imatinib mesylate, STI571) is very effective in the treatment of patients with chronic myeloid leukemia (CML). It induces complete hematologic control in >90% of patients with CML in chronic phase and preliminary data suggest that the incidence of complete cytogenetic remission may exceed 60% in previously untreated patients, though its capacity to prolong life in comparison with other agents has not yet been clearly established. It is also active in the management of patients in advanced phases of CML.

Information sources. We present here provisional indications for the use of imatinib in CML patients and give details of the dosage regimens we have used and side-effects we have encountered.

State of the Art and Perspectives. It is likely that the optimal usage of this important new agent will become better defined as more experience is gained.

Key words: CML, STI571.

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The treatment of patients with Ph-positive (or BCR-ABL-positive) chronic myeloid leukemia (CML) did not improve very greatly in the 1990s. It is now widely accepted that patients treated by allogeneic stem cell transplantation (SCT) may be cured but only a minority of CML patients are eligible for this procedure and the risks of morbidity and mortality directly attributable to the procedure remain appreciable.[1] The majority of patients have hitherto been treated with hydroxyurea, interferon-α or interferon-α plus cytarabine; with these approaches the median survival is between 5 and 8 years and none can be regarded as curative.[1,2] The recent introduction of imatinib (imatinib mesylate, STI571, Glivec®) appears to be a major advance in the treatment of CML[3-5] and this paper summarizes some practical aspects of its use at the Hammersmith Hospital in London during the last two years. We have not attempted to address the issue of whether imatinib should displace allogeneic stem cell transplantation as primary treatment for newly diagnosed patients, which is considered elsewhere,[6] nor the question of its cost-effectiveness.

Imatinib was first administered to patients with CML in June 1998 in the USA and further clinical trials recruited patients rapidly. Internationally there is experience now with the treatment of more than 10,000 patients. The drug is given orally, is well tolerated, and has a manageable side-effect profile. Results from phase II/III trials suggest that complete cytogenetic remissions (CCR, defined in Table 1) can be obtained in some patients in all phases of the disease.[3,4]

Imatinib occupies the ATP-binding site of the ABL tyrosine kinase component of the BCR-ABL oncoprotein and maintains it an inactive conformation.[7] It inhibits the kinase action of normal Abl and at least two other tyrosine kinases, c-kit and platelet derived growth factor receptor β (PDGFRB).[8,9] Although *in vitro* studies have demonstrated selective killing of CML hematopoietic cells,[10,11] presumably resulting from BCR-ABL kinase inhibition, its precise mechanism of action *in vivo* is still unclear.

Indications

CML in chronic phase

To date the major experience with use of imatinib has been gained in patients classified as intolerant of or refractory to interferon-α. Both in our series of 145 patients and the multinational phase II trial with 454 patients[3,5] the incidence of complete hematologic remission exceeds 95% and about 30% of these patients achieve CCR after 9-12 months of imatinib therapy but there are as yet no long-term survival data. Experience with the use of imatinib in previously untreated patients is still limited but it appears that the incidence of CCR at 6 months will be of the order of 50-60%.[12]

For the present we recommend treating with imatinib any patient who cannot tolerate interferon α and any patient not in major cytogenetic remission after treatment with interferon-α for 12 months or longer. Patients who have achieved a CCR and who tolerate the drug well should continue on interferon-α as long as the response is sustained. For newly diagnosed patients, the high incidence of cytogenetic remissions, the relative lack of toxicity and the fact that the drug can be given orally all suggest, but do not prove, that imatinib should already be regarded as the drug of choice for first-line treatment. However, if an allogeneic SCT is definitely planned, it may be wise to avoid use of imatinib, since possible adverse effects on the outcome of allogeneic SCT are not yet excluded. In cases in which the indications for allogeneic SCT are less clear, a therapeutic trial of imatinib may be undertaken; patients who have achieved a CCR by 6 or 9 months may be advised to continue treatment with imatinib while those not in CCR may be considered for allogeneic SCT.[6]

CML in blastic phase

At present the clinical value of imatinib for patients with advanced phase disease (accelerated phase or blastic transformation) is still not clear. Many patients treated in blast crisis will achieve a short-lived hematologic remission and some cytogenetic remissions have been seen.[4,13] Remissions were less durable in patients with lymphoid than in those with myeloid blastic transformation.[4] However, in a recent analysis of results of treating blastic phase patients at the Hammersmith Hospital since 1995, those who received imatinib in combination with other agents had a similar outcome to those patients treated without imatinib.[14] Currently we consider that for patients in blastic transformation imatinib is best considered as part of a treatment strategy that also incorporates conventional cytotoxic drugs and/or allogeneic or autologous SCT.

Table 1. Conventional definitions of cytogenetic responses to treatment for chronic myeloid leukemia.

Ph-positive marrow metaphases (%)	*Designation*
0	Complete cytogenetic response (CCR)
1-35	Partial cytogenetic response (PCR)
36-95	Minor cytogenetic response
>95	None

Percentages cited above are based on a minimum of 20 analyzable metaphases. Complete and partial responses are often grouped together as 'Major cytogenetic responses' (MCR).[35]

CML in accelerated phase

The responses of patients in accelerated phase to imatinib vary according to the definition of acceleration (Table 2 and Figure 1). In our series of 106 patients in accelerated phase defined according to the World Health Organization criteria,[15] the actuarial survival and progression-free survivals at 18 months were 73% and 37%, respectively. Eighteen percent of patients achieved CCR and 25% MCR although in many cases these responses were not sustained. In a multinational phase II trial of imatinib in 181 patients in accelerated phase according to criteria defined by Kantarjian[16] the 12-month survival was estimated to be 74%;[13] 17% of patients achieved CCR and 24% MCR. The proportion of responders was similar for the two dose levels (400mg daily in 62 and 600mg daily in 119 patients) but a dose of 600mg daily and a hemoglobin >10 g/dL were important prognostic factors for improved progression-free survival. In our series patients with more than 15% blasts in peripheral blood or bone marrow, or with two or more of the following criteria: hemoglobin <10 g/dL, clonal cytogenetic abnormalities in addition to the Philadelphia one or hematologic resistance to interferon had a significantly increased risk of mortality (Figure 2). The median survival of patients without these risk factors (n = 54) was 93% at 18 months compared to 48% in the 46 patients with these risk factors ($p = 0.0001$) (*unpublished data*). We recommend treatment with imatinib for all patients in the low risk group. Patients in the high risk group may benefit from similar strategies to those for blastic transformation.

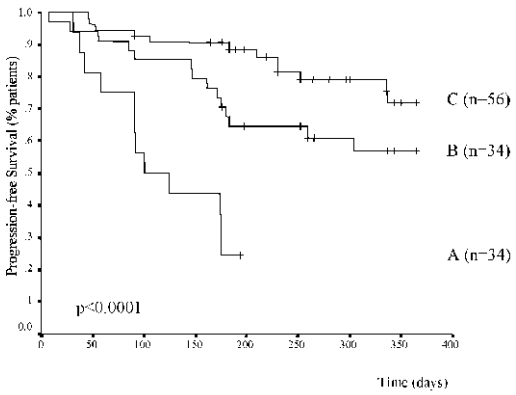

Figure 1. Progression-free survival according to different criteria of acceleration. A. Patients with more than 15% blasts in peripheral blood or bone marrow. B. Patients with additional cytogenetic abnormalities excluding extra Ph chromosome as the only criterion of acceleration. C. Patients with either (1) blasts plus promyelocytes > 30% in peripheral blood or bone marrow, (2) splenomegaly, (3) grade III-IV bone marrow fibrosis, (4) platelet count < 100 × 10⁹/L unrelated to therapy, (5) platelet count >1,000 × 10⁹/L unresponsive to therapy, or (6) basophil count >20% in peripheral blood or BM.

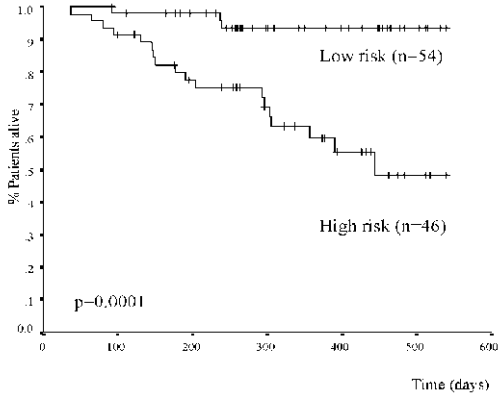

Figure 2. Survival of the Hammersmith patients with accelerated phase disease according to risk group (defined in text).

Relapse after allogeneic SCT

The majority of patients in early relapse and 50% of patients in hematologic relapse after allogeneic SCT achieve a sustained molecular remission with donor lymphocyte infusions (DLI).[17] The main complications after DLI include graft-versus-host disease (GvHD) and myelosuppression, both of which can be prevented to some degree by the use of escalating doses of donor lymphocytes.[18,19] The use of imatinib after allogeneic SCT could offer advantages. It could induce remission without GvHD and could be effective when DLI has failed.[20] It could also be used in combination with lower doses of DLI to prevent GvHD.

A number of groups have now used imatinib in the management of patients relapsing after allogeneic SCT.[21-23] Most of these patients were treated for relapse into advanced phase disease, since DLI are of limited value in this situation. Other patients were treated for cytogenetic relapse or hematologic relapse into chronic phase, often in the presence of on-going immunosuppression for GvHD and/or after failure or lack of availability of DLI.[20] Some hematologic, cytogenetic and molecular remissions have been achieved although the durability of these responses is as yet unknown.

Table 2. Definitions of chronic, accelerated and blastic phase.

1. Kantarjian criteria (Kantarjian *et al.*)[16]

Chronic phase (all of the following)
- Blasts in peripheral blood or bone marrow <15%
- Blasts plus promyelocytes in peripheral blood or bone marrow <30%
- Basophils in peripheral blood or bone marrow <20%
- Platelet count >100 × 10⁹/L

Accelerated phase (one of the following)
- 15-29% blasts in peripheral blood or bone marrow
- >30% blasts plus promyelocytes in peripheral blood or bone marrow
- >20% basophils in peripheral blood or bone marrow
- Platelets < 100 × 10⁹/L unrelated to therapy

Blastic phase (one of the following)
- Blasts in peripheral blood or bone marrow ≥30%
- Presence of extramedullary blastic disease

2. WHO criteria (Jaffe *et al.*)[15]

Accelerated phase
- Blasts 10-19% in bone marrow or peripheral blood
- Peripheral blood basophils ≥ 20%
- Persistent thrombocytopenia (<100 × 10⁹/L) unrelated to therapy, or persistent thrombocytosis (>1,000 × 10⁹/L) unresponsive to therapy
- Increasing WBC count unresponsive to therapy
- Cytogenetic evidence of clonal evolution
- Severe bone marrow fibrosis

Blastic phase
- Blasts in peripheral blood or bone marrow ≥20%
- Presence of extramedullary blastic disease
- Large foci or clusters of blasts in the bone marrow biopsy

Some of these patients received imatinib relatively soon after DLI and responses could have been the result of the DLI. In our standard practice, imatinib is used as a second-line therapy for relapse.

Pharmacokinetics and drug interactions

Imatinib has very good oral absorption - its oral bioavailability is close to 100% and absorption is not impaired by food.[24] The half-life of imatinib after a once daily dose of 400 mg is 13 to 16 hours. The mean maximal concentration is 4.6 μM, reaching 1.46 μM 24 hours after administration.[25]

This amount exceeds the concentration required for inhibition of cellular phosphorylation by BCR-ABL[10] and is sufficient to cause killing of BCR-ABL-positive cell lines *in vitro*.[11] From pharmacokinetic studies, there is no evidence that the body mass of the patient has any impact on the plasma levels of imatinib.[25] The pharmacokinetics do not differ whether imatinib is taken with food or when fasting.[26] Imatinib is metabolized predominantly in the liver by the CYP3A4/5 p450 enzyme system but it does not induce activity of this enzyme and therefore drug plasma levels remain stable over time. However induction of this enzymatic mechanism by other drugs may result in a decrease of the levels of imatinib (Table 3). Major inducers of this enzyme include phenytoin, carbamazepine and phenobarbital. Conversely drugs that inhibit the CYP3A4/5 enzyme apparatus might result in increased levels of imatinib.

Major inhibitors include erythromycin and ketoconazole. Grapefruit juice is also an inhibitor and excessive intake should be avoided. Patients on warfarin have demonstrated both increases and decreases in INR, so it is advisable to use low molecular weight heparin in place of warfarin for patients requiring anticoagulation.[27]

Table 3. CYP3A4/5 inducers and inhibitors *(adapted from Lacy et al., cytochrome P-450 enzymes and drug metabolism. 2000)*.[36]

Inducers	*Inhibitors*	
Carbamazepine	Amiodarone	Metronidazole
Dexamethasone	Anastrozole	Mibefradil
Ethosuximide (moderate)	Azithromycin	Miconazole
Glucocorticods	Cannabinoids	Nefazodone
Griseofulvin	Cimetidine	Nelfinavir
Nafcillin	Clarithromycin	Nevirapine
Nelfinavir	Clotrimazole	Norfloxacin
Nevirapine	Cyclosporine	Norfluoxetine
Oxcarbazepine	Danazol	Omeprazole (weak)
Phenobarbital	Delavirdine	Oxiconazole
Phenylbutazone	Dexamethasone	Paroxetine (weak)
Phenytoin	Diethyldithiocarbamate	Propoxyphene
Primidone	Diltiazem	Quinidine
Progesterone	Dirithromycin,	Quinine
Rifabutin	Disulfiram	Quinupristin and
Rifampin	Entacapone (high dose)	Dalfopristin
Rofecoxib (mild)	Erythromycin	Ranitidine
St John's wort	Ethinyl estradiol	Ritonavir
Sulfadimidine	Fluconazole (weak)	Saquinavir
Sulfinpyrazone	Fluoxetine	Sertindole
Troglitazone	Fluvoxamine	Sertraline
	Gestodene	Troglitazone
	Grapefruit juice	Troleandomycin
	Indinavir	Valproic acid (weak)
	Isoniazid	Verapamil
	Itraconazole	Zafirlukast
	Ketoconazole	Zileuton

Treating a patient with imatinib

Switching a patient from hydroxyurea or interferon α to imatinib

Patients whose counts were well controlled on interferon α do not normally experience problems when the interferon is discontinued abruptly in order to start treatment with imatinib. For patients receiving hydroxyurea it was at one time our practice to stop the drug abruptly when starting imatinib, but on occasion this resulted in dramatic increases in leukocyte and/or platelet counts. Thus we now routinely taper the dosage of hydroxyurea over a few weeks after starting imatinib if the patient's hydroxyurea dosage was 1.5 g per day or more or if the leukocyte count was not well controlled; for patients on lower doses of hydroxyurea, abrupt discontinuation may be reasonable. Imatinib may take 6 weeks or longer to control the platelet count. If, at the time of starting treatment with imatinib, the platelet count is raised, the count may rise very rapidly if hydroxyurea is withdrawn abruptly; in such cases gradual withdrawal of hydroxyurea or short-term use of anagrelide may be advisable. One possible schedule is to combine imatinib 400 mg daily with anagrelide 2 mg daily and to reduce the anagrelide by 0.5 mg decrements every one or two weeks. If the patient was previously receiving a combination of two drugs (e.g. hydroxyurea and anagrelide or hydroxyurea and interferon-α) we usually replace one drug and then taper the other according to blood counts. For example, if the combination was hydroxyurea and anagrelide it may be preferable to substitute imatinib for hydroxyurea while temporarily continuing the anagrelide at full dosage.

We usually administer allopurinol until the white cell count is consistently in the normal range. Although only rare cases of tumor lysis syndrome have been reported thus far in advanced phase

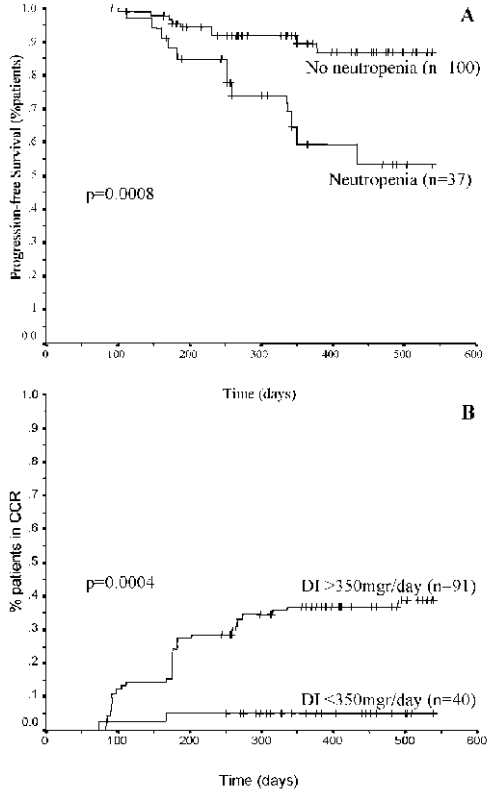

Figure 3. A. Progression-free survival according to the presence of neutropenia, defined as neutrophil count <1 × 10⁹ /L on at least one occasion between days 45 and 90 of treatment, in 137 of the 145 patients who remained in chronic phase at 3 months. B. Achievement of CCR according to the dose intensity of imatinib. Dose intensity (DI) was calculated as the sum of the daily doses between days 45 and 90 divided by 45. Similar results were obtained when patients in whom imatinib was interrupted on at least one occasion because of cytopenias during the same period of time were compared with those who had no interruption.

patients,[4] patients should ideally be monitored closely for this complication and advised to increase their fluid intake when treatment is started.

We currently perform a full blood cell count and tests of renal and liver chemistry weekly for the first 4 weeks, then every 2-3 weeks for the next 3 months and every 4-8 weeks thereafter. Some 10-20% of patients will experience temporary cytopenias within the first few weeks of treatment with imatinib. This is probably more common in patients who have been treated previously with interferon-α but has also been observed in newly diagnosed patients. The dose of imatinib can be adjusted as described below and the majority of these patients will stabilize within 12 weeks of starting treatment. The remaining patients will tolerate imatinib without hematologic problems. Most patients are actually very stable on imatinib; once a patient is stable on a given dose, he/she seldom needs any dose adjustment. Thus, a change in blood counts may indicate disease progression or a new pharmacological interaction.

Imatinib dosage

Imatinib is used at standard doses of 400 mg/day for patients in chronic phase and 600 mg/day for patients in accelerated phase and blastic transformation. There is no relationship between the body mass and response rates or the incidence of side effects[13,25] in patients treated with these standard doses. In patients with cytopenias before starting treatment, this may judged to be due to preceding chemotherapy or to the effects of the leukemia. In the former case initiation of treatment may be delayed by one or two weeks; in the latter case treatment should be initiated at full dose in the hope of reversing the cytopenia.

Dose adjustment is often necessary due to side-effects (*see below*). When serious non-hematologic adverse events develop, it is usually necessary to stop imatinib until the toxicity resolves and if more than 2 weeks have elapsed, re-start at a lower dose. Corticosteroid cover (0.5 to 1.0 mg/kg/day) may be useful to prevent recurrence of allergic reactions or to treat recurrent hepatotoxicity. Hematologic and cytogenetic responses have been observed in patients taking 200 or 300 mg/day but are less frequent at the 300 mg dosage and rare at 200 mg daily (Figure 3b). Every effort should, therefore, be made to achieve at least 400 mg/day.

Monitoring the response to therapy with imatinib

For patients in chronic phase, cytogenetic responses can occur within 3 months of starting therapy. We recommend bone marrow assessment with metaphase cytogenetics (± fluorescence *in situ* hybridization) every 3 months for the first year and six-monthly thereafter. Patients in major cytogenetic remission should be monitored by real-time reverse transcriptase polymerase chain reaction (RT-PCR) for the presence of BCR-ABL transcripts. Ideally blood samples should be tested by PCR at -3 monthly intervals. It is important to continue to perform conventional cytogenetics at regular intervals since this is the only method able to detect additional chromosomal abnormalities. These can occur in both Ph-positive and Ph-negative cells.[28]

For patients in advanced phase we assess the morphology of the bone marrow after treatment for 4-6 weeks and 3 monthly thereafter. In most cases cytogenetic responses are infrequent or transient. Hematologic remissions in blastic transformation are short-lived (median duration 8-12 weeks), so alternative strategies should be provided.

Side effects - Myelosuppression

Grade III-IV neutropenia (neutrophils < 1.0×10^9/L [= grade III], <0.5×10^9/L [=grade IV]), thrombocytopenia (platelets <50×10^9/L [= grade III], <10×10^9/L [= grade IV)] and anemia (Hb < 8.0 g/dL [= grade III], < 6.5 g/dL [= grade IV]) are common and potentially serious complications of imatinib treatment. The frequency of myelosuppression clearly depends on the disease stage.[3,4]

Anemia

Our policy for managing anemia (hemoglobin < 10.0 g/dL) is not to adjust the dose of imatinib but rather to transfuse the patient when required. This approach is in part inherited from the design of the phase II trials. It is not based on solid clinical data but rather on the analogous considerations that apply to the management of neutropenia and thrombocytopenia. We have not explored the possibility of treating anemia with erythropoietin.

Neutropenia and thrombocytopenia

There are some general points that may apply to the neutropenia and thrombocytopenia that occur during treatment with imatinib. Myelosuppression may be an indicator of therapeutic benefit. This is true particularly in advanced phase patients with little or no residual normal hematopoiesis. In this case therapy with imatinib should not be interrupted.

Our data suggest that patients who receive imatinib as treatment for chronic phase disease on account of intolerance of or refractoriness to interferon-α and who then experience significant degrees of neutropenia or thrombocytopenia may obtain less benefit from the drug than those whose blood counts are maintained during therapy. Moreover, in our series,[29,30] patients in chronic phase in whom imatinib has been interrupted or reduced on account of myelosuppression are significantly less likely to achieve cytogenetic responses and have a higher risk of progression to advanced phase than those whose treatment has not had to be interrupted (Figure 3). Whether it is the fact that the imatinib was stopped that is responsible for the lack of response or whether these patients would have not responded even it had been possible to continue treatment needs further study. It is clear, however, that these patients belong to a higher risk group.

The management of the myelosuppression is difficult and must be *tailored* to the individual circumstances of each patient. General principles are suggested below.

Chronic phase patients. Our current policy is to interrupt imatinib at the first episode of grade III-IV neutropenia and/or thrombocytopenia. Treatment can be resumed once the absolute neutrophil count (ANC) has risen above 1×10^9/L and/or the platelet count has risen above 100×10^9/L. If the blood count fails to recover within two weeks, we reintroduce imatinib at the lower dosage of 300 mg daily and attempt to increase the dose thereafter if the blood count permits. With this approach in a considerable proportion of patients the neutropenia or thrombocytopenia does not recur. If, however, the neutropenia does recur we add granulocyte colony-stimulating factor (G-CSF) (e.g. 5 mg/kg 2 to 5 times per week) adjusting the G-CSF dosage to keep the ANC above 1×10^9/L. In the majority of patients in whom we have used this approach it has been possible to reduce the frequency of G-CSF or discontinue it after a few months of therapy. Some of these patients have then achieved cytogenetic remissions.[30]

If grade III-IV thrombocytopenia recurs we normally interrupt the treatment again. In many cases the thrombocytopenia recurs when the dose is escalated, in which case (if there are no other risk factors for hemorrhage) we maintain imatinib therapy unless the platelet count falls below 40×10^9/L. Some patients reach a plateau before that point. This is particularly true for patients who had low platelet counts before starting imatinib. If the patient does not reach a plateau the options include use of platelet transfusions or reducing the dose to below 400 mg/day.

Accelerated phase. For patients in accelerated phase it is more difficult to give general advice. Cytopenic episodes may be handled depending on the estimated risk of disease progression. Patients thought to have a high risk of progression should be managed as blastic phase patients. However, for patients in less aggressive accelerated phase, a more conservative approach akin to that used in chronic phase may be appropriate. These considerations may need to be revised after 3-4 months of imatinib therapy since, in our hands, patients who continue to have more than 5% blasts in the bone marrow are at high risk for progression to blastic

transformation.

Blastic phase patients. When treating these patients with imatinib we recommend support with red cell and platelet transfusions and G-CSF. Imatinib should continue at a minimum dose of 600 mg/day for 4-6 weeks in order to assess the response. Hematologic remissions usually occur without peripheral blood recovery. Once an optimal response has been obtained, we try to introduce conventional combination chemotherapy or SCT since we know that the benefit of imatinib will not usually be maintained.

Side effects other than myelosuppression

Nausea

Nausea due to the local irritant properties of imatinib occurs in about 70% of patients and is the single commonest side effect. It is usually mild and self-limited and can be prevented in many cases by taking imatinib with food. The pharmacokinetics do not differ whether imatinib is taken with food or when fasting.[26] We recommend taking imatinib during or soon after the main meal of the day. Antiemetics are sometimes necessary.

Edema and fluid retention

Peripheral edema occurs in about 60% of patients. It is clearly dose-related but often limited to facial and periorbital regions. Most patients will have significant weight gain. Only 1% of the patients may have more generalized fluid retention including pulmonary edema, pleural or pericardial effusions, ascites or anasarca. Generally the fluid retention does not necessitate cessation of therapy and the addition of a mild diuretic is enough to control it.

Muscle cramps

Muscle cramps are also common. We try to maintain a good fluid intake. Oral administration of calcium and/or magnesium supplements (magnesium glycerophosphate 4 to 8 mM *tds* and calcium carbonate 500 mg *tds*) can sometimes relieve these cramps even when the patient's Ca^{2+} and Mg^{2+} serum levels are normal. This scheme is completely empirical and other schemes may be equally valid. Treatment with quinine sulphate may be useful in some cases. The cause of this problem is unknown and the response to the treatment mentioned above is very variable.

Bone pain and arthralgias

Bone pain and/or arthralgias may occur in up to 30% of patients and are more common in patients with a previous history of arthritis. Normally the patients respond well to non-steroidal anti-inflammatory drugs such as ibuprofen or diclofenac, but some cases require the addition of morphine or tramadol. In some cases the pain due to imatinib may be mistaken for pain due to progression of leukemia. The intensity of the pain declines with time and with discontinuation of imatinib.

Skin rashes

Allergic type skin rashes occur in about 30% of patients and usually appear soon after commencing imatinib therapy, but may develop many months later. The typical rash is maculopapular and pruritic and is distributed most prominently over the forearms, trunk, legs and face. It is rarely responsive to antihistamines. Mild cases will need no action but in severe cases our policy is to discontinue the drug, wait until the rash has resolved and then restart imatinib at 50-100 mg/day. Most of these patients will need the addition of prednisolone 0.5-1 mg/kg/day for several weeks and we usually start corticosteroids a few days before reintroducing the imatinib. Once the full dose of imatinib has been achieved, the steroid may be tapered.

Hepatotoxicity

Grade II-IV liver toxicity has been reported in 2% of the patients. It typically presents as mild hepatitis, but a cholestatic pattern can also be seen. Imatinib should be discontinued until the liver toxicity has resolved and then reintroduced at lower doses with the addition of prednisolone 0.5-1 mg/kg. A full dose of 600 mg/day may be difficult to achieve. Initial reports suggested an increase in hepatotoxicity of imatinib in combination with paracetamol. There is no evidence to support this at present. Although we do not avoid the use of paracetamol, some caution may be needed with prolonged and high doses.

Other less frequent side effects

Other non-hematologic side-effects reported in patients receiving imatinib include fatigue, weakness, dizziness, insomnia, dyspepsia, pyrexia, abdominal pain, cough, anorexia, constipation, diarrhea, nasopharyngitis, night sweats and hypokaliemia.

Definitions of response and subsequent management

Although about 30% of patients in chronic phase who were resistant to or intolerant of interferon α and 60% of the newly diagnosed patients have achieved a CCR, 10% of these patients who achieved CCR in chronic phase may have lost their response in 3-6 months.[5] In contrast to results seen

at other institutions, we have rarely observed CCR in patients in advanced phase. Despite the lack of long-term survival data, we currently recommend that patients in complete cytogenetic remission continue on the same dose of imatinib indefinitely. These patients should be monitored using quantitative RT-PCR. For patients who have not achieved CCR at 3 to 6 months after starting treatment with imatinib, we usually increase the dose to 600 mg daily if there is no obvious contraindication.

Peripheral blood stem cell collection

In patients who might be candidates for autografting, we collect peripheral blood stem cells (PBSC) as early as possible after they achieve CCR. Our current mobilization regimen consists of G-CSF 10 mg/kg for six consecutive days. We collect PBSC from day 5 onwards. The target is to collect 2×10^6 $CD34^+$ cells/kg. Imatinib is not discontinued or reduced throughout the procedure. With this strategy we have managed to harvest enough cells from as many as 50% of these patients.[31] For patients who fail to mobilize sufficient numbers of PBSC, we repeat the procedure 3-6 months later. We believe that in some patients it may be preferable to stop treatment with imatinib for 2-4 weeks before the harvest, but this strategy could be associated with the loss of the CCR or an increase in the BCR-ABL/ABL ratio and has not yet been tested extensively. Cells collected in this way have not yet been used in autologous transplant procedures so we are unable to comment on their ability to reconstitute hematopoiesis.

Definitions of non-response and subsequent management

Definition of non-response

All chronic phase patients should have normal or low counts with no left shift within 12 weeks of starting treatment. Normally this is achieved in 6 weeks. The bone marrow examination performed at 3 months should show a normo- or hypocellular marrow with less than 5% blasts and no left shift. In many cases there is hyperplasia and dysplasia of the erythroid and megakaryocytic series. The reticulin fibrosis may need more time to normalize.[32] Patients who lose hematologic control generally progress rapidly. Cytogenetic responses follow a similar time frame and most patient who are going to respond, do so within 9-12 months of starting on imatinib. Patients who do not achieve major cytogenetic responses at 3 months have an increased risk of progression;[5] patients who do not achieve even a minor cytogenetic response at 3 months (Figure 4) and also sustain cytopenia on imatinib belong to a particularly poor prognosis group.[29,30]

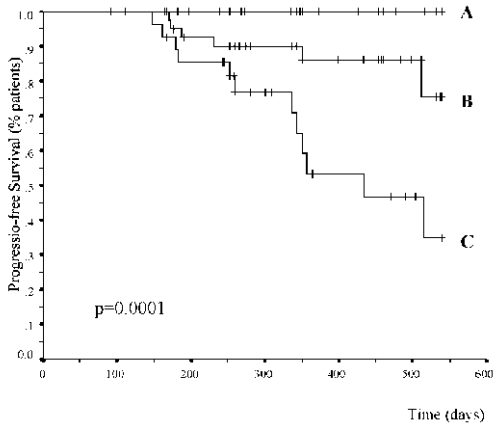

Figure 4. Progression-free survival according to the cytogenetic and hematologic responses at 3 months. Patients were classified for their risk of progression into three different groups: A. Patients who achieved at least minor cytogenetic response at 3 months and did not have neutropenia (<1×10⁹/L) between days 45 and 90 (n=38). B. Patients who did not achieve minor cytogenetic response at 3 months but did not suffer neutropenia, or patients who achieved minor cytogenetic response but had neutropenia (n=53). C. Patients who suffered neutropenia and did not achieve minor cytogenetic response at 3 months or patients who still were in chronic phase, but without hematologic control (ie WBC >13×10⁹/L) (n=33).

Based on these data we consider that the response to imatinib is inadequate if there is: a) absence of complete hematologic response by 3 months; b) absence of any cytogenetic response (>95% Ph-positive) at 3 months associated with grade III neutropenia ($<1\times10^9$/L) beyond 6 weeks of treatment; c) absence of a major cytogenetic response at 12 months; or d) loss of a previous hematologic response or major cytogenetic remission.

Escalating the dose of imatinib

There are no good data to support the value of increasing the dose of imatinib if a patient does not respond properly to standard doses. In our hands, increasing the dose of imatinib doers not usually improve the response and in many cases only adds toxicity. There are exceptions to this rule. In some cases in which a patient has achieved good hematologic control but has failed to achieve or has lost a cytogenetic response, dose escalation may on

occasion increase the degree of Ph-negativity. The maximal recommended dose is 800 mg/day which should be taken as 400 mg *bd*. We do not believe that increasing the dose of imatinib is appropriate in cases of disease progression.

Therapeutic options

It is not yet clear how to manage patients who are *imatinib failures*. In many circumstances the failure to respond to imatinib implies disease progression and this is true particularly when a patient fails to achieve or loses a hematologic response. In some cases an apparent failure of response may be reversed by use of hematologic growth factors (*see above*). We are currently exploring the capacity of autologous stem cell transplantation in combination with imatinib as a method of reversing the lack of response.[33] This has been shown for interferon resistance.[34] Other possible ways may be to treat the patient with imatinib in combination with other agents such as farnesyl transferase inhibitors (FTI), cytarabine or homoharringtonine. These approaches are all still experimental.

Final considerations

Clinical trials with imatinib have shown remarkable, although preliminary results. Despite almost 4 years' experience with imatinib there is still much to be learned regarding the best way to use this promising new agent. The story bears a striking resemblance to that of the introduction of all trans retinoic acid (ATRA) used for treating acute promyelocytic leukemia (APL). It has not been until very recently, several years after the original clinical trials, that a rational approach to using ATRA in combination with chemotherapy (mainly anthracyclines) has been established. However, the extraordinary improvement in the outcome of APL induced by ATRA should serve as an incentive for clinicians involved in the management of CML.

This paper attempts to summarize the current experience with the use of imatinib but will doubtless need to be revised when we and others become more familiar with the drug's use. The ultimate objective must be to prolong the patient's survival and to this end the goal of imatinib therapy (in combination with other agents) must be the achievement of sustained RT-PCR negativity. Perhaps the combination of several therapeutic strategies (protein inhibition with imatinib, immunomodulation with interferon α and chemo-reduction with autologous SCT) either concomitantly or sequentially, will lead to a higher proportion of patients surviving long-term.

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