Second generation tyrosine kinase inhibitors for the treatment of chronic myelogenous leukaemia with intolerance of hematologic resistance to imatinib

The application seeks the addition of the second generation TKIs nilotinib (representative of class) and dasatinib (an alternative) to the core list of the Essential Medicines List for the treatment of chronic myelogenous leukaemia in adult and paediatric patients.

Introduction

Chronic myelogenous leukaemia (CML) is a myeloproliferative disorder affecting the haematopoietic stem cell compartment. It can occur in all age groups but is predominantly a disease of adults, accounting for 20% of adult leukaemias. The incidence rate in the United States is roughly 1.7 per 100 000. There appears to be no association with race or ethnicity (1). While there are few reliable data from resource-poor countries, extrapolation from existing data would suggest that CML will affect more than 100 000 patients worldwide every year and represent a significant global health burden. Because treatment with imatinib results in prolonged remissions in the majority of patients, the prevalence of CML is much higher and it may account for up to 15% of all leukaemias in the developed world (2), although global prevalence is not known.

CML arises from a translocation between the BCR gene on chromosome 22 and the ABL gene on chromosome 9. This reciprocal translocation creates the Philadelphia chromosome t(9;22) and the consequent formation of a unique BCR-ABL protein product. This protein has constitutive kinase activity that drives uncontrolled proliferation of haematopoietic stem cells. The natural history of CML is characterized by progression through three phases – chronic phase, accelerated phase and blast crisis (3). Patients presenting in the chronic phase can be relatively asymptomatic or have fatigue, early satiety or complications of hyperviscosity such as visual disturbances or priapism. The chronic phase is characterized by a proliferation of white blood cells, and sometimes platelets, and splenomegaly. Symptoms can be controlled by agents such as hydroxyurea or interferon. However, neither can prevent progression to accelerated phase, where a progressive loss of white cell differentiation with an accumulation of blasts occurs, or to eventual blast crisis, characterized by a disease indistinguishable from acute myelogenous leukaemia or acute lymphoblastic leukaemia. This blast phase is refractory to treatment and results in imminent death. The median survival for patients is 3–5 months (4) and conventional therapies such as hydroxyurea and interferon do not alter the course of disease. While CML is less common in the paediatric population there is no evidence that there are significant biological differences based on age (5, 6).
Before the advent of imatinib the only therapy that could offer long-term survival was allogeneic bone marrow transplantation (BMT), a modality not available in most of the world. Even in developed countries BMT is costly and associated with a significant treatment-related mortality. While BMT can lead to long-term disease survival in 50–70% of patients, toxicity markedly increases with age and even in younger patients major obstacles exist. Another obstacle is that for up to 60% of patients no appropriate donor can be identified (7); this number is even larger in patients of African or Hispanic descent due to underrepresentation in international registries. Transplant has associated morbidities (infertility, graft-versus-host disease) and mortality (20–50% at one year depending on patient and donor characteristics). Most critically, allogeneic BMT requires a sophisticated and expensive infrastructure and complicated extended follow-up care. It is thus offered only in tertiary-care hospitals. There are limited facilities able to perform BMT in the WHO Eastern Mediterranean Region and currently none in sub-Saharan Africa (8).

Although imatinib is highly efficacious as first line therapy and produces durable cytogenetic remission in majority of patients with CML, a small minority of patients will develop hematologic resistance to imatinib whose outcomes are poor without a second line drug TKI such as dasatinib or nilotinib. Hematologic resistance to imatinib is a well-documented phenomenon and may be primary or acquired (16,40). Primary resistance in chronic phase CML is defined as failure to achieve a complete hematologic response with 400mg/day of imatinib for at least three months or WBC ≥ 10,000/mm3 and rising on 2 consecutive measurements at least 14 days apart with at least one measurement demonstrating WBC>15,000/mm3 on imatinib 400mg/day. In the advanced phase of CML, primary resistance is defined as failure to achieve a minor or major hematologic response after 3 months of treatment of imatinib treatment. Secondary or acquired resistance is defined as achieving a complete hematologic response in the chronic phase or major or minor hematologic response initially with imatinib, and subsequently developing relapsed disease (38).

**Public health relevance**

According to GLOBOCAN, worldwide total leukaemia incidence for 2012 is estimated at 351,965, with an age-standardized rate (ASR) of 4.7 per 100,000 per year, a 5-year prevalence of 1.5% and a male:female ratio of approximately 1:4. Leukaemia incidence in more developed regions in 2012 was estimated at 7.2 per 100,000 (ASR) compared with 3.8 per 100,000 in less developed regions (9). GLOBOCAN provides no specific information about CML.

Information on CML incidence and prevalence is scarce, as CML is a rare disease. A European study published in 2007 estimated annual incidence to be 1 or 2 cases per 100,000
people (10). The same study stated that CML is most common in older populations, with a median age at diagnosis of around 65 years, and is more common in men (although women tend to have a higher survival rate than men). Disease incidence appears to be consistent across geography and ethnicity, although it is noted that survival rates in some countries are likely to be impacted by the availability of drugs and diagnostic technologies. In the United States, for instance, rates for new CML cases have been stable over the last 20 years, but death rates have dropped significantly, with 5-year relative survival rising from about 30% to 63% (1).

Approximately one fifth of patients are intolerant of imatinib and will discontinue therapy. The Unmet Needs in CML (UNIC study), a cross-sectional study with retrospective chart review of patients currently treated for CML across eight European countries, estimated the proportion of imatinib-treated patients who experienced imatinib resistance and/or intolerance (11, 12). A total of 20–23% of patients stopped – and did not restart – imatinib during the study period.

The most common toxicities that lead to drug discontinuation include nausea, vomiting, diarrhoea and muscle cramps. Other less common reasons for discontinuing imatinib include oedema, heart failure, rash and arthralgias as well as severe myelosuppression and hepatic toxicity.

In addition, five years of more after achievement of complete cytogenetic remission, therapeutic effects of imatinib will be unsatisfactory in about one third of patients; recurrent disease will then develop (13, 14). Second-generation tyrosine kinase inhibitors – nilotinib and dasatinib – have therefore been developed.

**Requirements for diagnosis, treatment, and monitoring**

**Diagnostics**

2nd generation TKIs like Imatinib are selective inhibitors of the BCR-ABL tyrosine kinase. 2nd generation TKIs are effective only in patients whose leukaemia cells carry the t(9;22) chromosomal translocation, and identification of the translocation is therefore critical before a decision is made to use imatinib therapy and thus TKI therapy. Although more than 90% of CML cases do indeed demonstrate this translocation, CML can be confused with other myeloproliferative diseases that do not.

Testing can be performed by a variety of molecular techniques; it is routinely available in most cancer centres in the developed world but often unavailable in laboratories in developing countries. Where testing is unavailable, it is possible for centres to partner with referral laboratories to have testing performed. Newer technology is rapidly making tests more generally available in developing countries. (30) (31)
Administration and care of patients

Until haematological remission (i.e. normalization of blood counts) has been achieved, weekly or two-weekly testing is needed to ensure that neutropenia or thrombocytopenia do not develop. Once haematological remission has been demonstrated by a normal complete blood count (CBC), further CBCs and physical examinations may be warranted every 3–6 months to assess continuing response, as well as patient education about reporting possible adverse events.

Overview of regimens

The following are the basic details of administration and dosing for treatment of CML with intolerance or hematologic resistance to imatinib.

- **Standard regimens**
  - nilotinib 300 mg orally every 12 hours for newly diagnosed patients (chronic phase) (Pediatric dosing 170 mg/m^2 every 12 hours)
  - nilotinib 400 mg orally every 12 hours for patients resistant to or intolerant of imatinib (chronic or accelerated phase) (Pediatric dosing 230 mg/m^2 every 12 hours)

  or

- **Alternative regimen**
  - dasatinib 100 mg orally daily for newly diagnosed patients (chronic phase) (Pediatric dosing 60 mg/m^2/day)
  - dasatinib 140 mg orally daily for patients resistant to or intolerant or imatinib (accelerated or blast phase) (Pediatric dosing 80 mg/m^2/day)

Review of benefits and harms

**Benefits - Dasatinib / nilotinib**

In a single group multi-center phase II trial 5% of patients treated with imatinib firstline had primary resistance to imatinib (35). The 5-year follow-up of patients in the IRIS study estimated annual rate of treatment failure after the start of imatinib therapy was 3.3% in the first year, 7.5% in the second year, 4.8% in the third year, 1.5% in the fourth year, and 0.9% in the fifth year. Among the 454 patients who had a complete cytogenetic response, the annual rates of treatment failure were 5.5% in the first year, 2.3% in the second year, 1.1% in the third year, and 0.4% in the fourth year after a response was achieved (40).
The most common reason for development of resistant disease is the occurrence of mutations within the binding region. Approximately 50% of patients who are resistant to imatinib will achieve a complete cytogenetic remission when treated with either nilotinib or dasatinib (22, 23); responses are durable in about 80% of patients. The application stressed the importance of having alternative treatments for patients with CML who are intolerant or develop resistance to imatinib-based therapy.

In a phase I dose escalation study evaluating the safety and efficacy of nilotinib in imatinib resistant or intolerant CML, 92% of patients with resistance or intolerance to imatinib achieved a complete hematologic response following treatment with nilotinib (39). A phase II open-label study investigated the effectiveness of nilotinib, 400 mg twice daily, in 321 patients with chronic-phase CML who had failed or were intolerant to imatinib (23). All patients were followed for more than 24 months. The rate of major cytogenetic response was 59%. Forty-four percent of the patients who achieved a major cytogenetic response attained a complete response. Estimated survival at 12 months was 87%. Adverse events were reported to be mild to moderate, with grades 3–4 neutropenia and thrombocytopenia occurring in 30% of patients.

Dasatinib has been studied in imatinib-resistant or -intolerant patients with CML in different phases. In the phase I study patients 92% of patients with chronic phase CML resistant to or intolerant of imatinib, achieved complete hematologic response with dasatinib (38). Efficacy of dasatinib 70 mg twice daily has also been shown in the myeloid or lymphoid blast phase in phase II trials (22, 24). In the study by Cortes et al., after at least 12 months’ follow-up, major cytogenetic responses were achieved in 33% and 52% of patients respectively. Twenty-six percent of myeloid blast-phase patients and 46% of lymphoid blast-phase patients achieved a complete cytogenetic response. Median progression-free survival was 6.7 months and 3.0 months in myeloid blast-phase and lymphoid blast-phase patients, respectively; median overall survival was 11.8 months and 5.3 months. Dasatinib was associated with acceptable tolerability.

A systematic review and network meta-analysis assessed the efficacy of imatinib, dasatinib and nilotinib in newly diagnosed chronic myeloid leukaemia (25)(36,37). Eight randomized controlled trials (RCTs) (3520 participants) were included. At 18 months, compared with imatinib 400 mg, the probability of a complete cytogenetic response was greater, and statistically significant, for dasatinib 100 mg (79.1%; 95% credibility interval (CrI): 72.0–85.1%), nilotinib 600 mg (83.1%; 95% CrI: 76.7–88.4%), and nilotinib 800 mg (80.0%; 95% CrI: 73.0–85.5%). In indirect comparisons with each other, dasatinib and nilotinib showed similar efficacy. However, evidence is weak and limited as findings are based on comparisons of only one or two RCTs, with high uncertainty. Other clinically relevant outcomes, such as survival, were not explored.

A second systematic review, with economic analyses, showed both dasatinib and nilotinib to be associated with a statistically significant advantage compared with imatinib in
terms of complete cytogenetic and major molecular response (26). However, in the first-line treatment setting and assuming cost–effectiveness based on a willingness-to-pay decision threshold of £20 000 – £30 000 per QALY, nilotinib was found to be cost–effective compared with imatinib, while dasatinib was not. Again, data were based on immature surrogate outcomes, assumptions of life expectancy, and extreme uncertainty. More and longer-term data are needed for assessing the predictive usefulness of surrogate outcomes within the CML population, especially for dasatinib and nilotinib.

The applicant is therefore not recommending nilotinib or dasatinib as first line agents for CML, but stressing the survival benefit of these second line TKIs as second line treatment in the small minority of CML patients with resistance to imatinib.

Harm considerations

Common

Tyrosine kinase inhibitors (TKIs) are well tolerated in the vast majority of patients. The most common non-haematological adverse reactions are oedema, muscle cramps and gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain; most adverse effects are mild, however (19, 27). In the initial patient cohort, at 6 years of follow-up, only 5% of patients discontinued imatinib because of side-effects or adverse events (13).

Specifically, dasatinib is associated with gastrointestinal bleeding in up to 25% of patients; however, the bleeding is typically mild to moderate and resolves given a drug holiday. Patients treated with dasatinib may also experience pulmonary complications including pleural effusions which can be grade 3–4 in up to 10% of patients (28). In children imatinib can lead to growth retardation, predominantly in prepubertal children.(32) Many children exhibit decreased serum levels of calcium and phosphorus and the long-term effects on bone health in patients still undergoing bone growth is unknown.(33)

Serious

Oedema can occasionally be severe and may result in cardiac complications in patients treated with imatinib who have underlying cardiac disease and/or heart failure (27). Additionally, nilotinib and dasatinib are associated with QT prolongation (27). Nilotinib is also associated with peripheral vascular disease and atherosclerosis-related events; however, the incidence of this adverse effect is low (<5%) although it may be higher with longer follow-up. (34)
References


35. Kantarjian et al. NEJM 2002
36. Kantarjian et al. NEJM 2010
37. Saglio et al NEJM 2010
38. Talpaz et al NEJM 2006