

CHRONIC MYELOGENOUS LEUKEMIA
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

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Executive Summary

We propose the inclusion of treatment options for chronic myelogenous leukemia (CML), in the category of anti-neoplastic agents, including imatinib, nilotinib, and dasatinib, because of the profound benefit in survival and quality of life for both adult and pediatric patients.

As global health efforts broaden to address the burden of non-communicable diseases, imatinib is an excellent choice as an essential medication. It delivers easily administered oral therapy that has few toxicities and provides major therapeutic benefit for a common oncologic disease affecting both the pediatric and adult populations. Additional drugs for the treatment of chronic myelogenous leukemia (CML) are being recommended and include dasatinib and nilotinib.

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder affecting the hematopoietic stem cell compartment. It can occur in all age groups but is predominantly a disease of adults, accounting for 20% of adult leukemias. The incidence rate in the United States is roughly 1.6/100,000 and it is predicted that 5430 cases will be diagnosed in 2012. There appears to be no association with race or ethnicity. (21) While there is a paucity of reliable data from resource poor countries, extrapolation from existing data would suggest that CML will affect over 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 leukemias in the developed world (14) though 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 hematopoietic stem cells. The natural history of the disease is characterized by progression through three phases, chronic phase, accelerated phase and blast crisis.(10) 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, nor to eventual blast crisis characterized by a disease indistinguishable from acute myelogenous leukemia or acute lymphoblastic leukemia. This blast phase is refractory to treatment and results in imminent death. The median survival for patients is 3-5 months (7) and conventional therapies such as hydroxyurea and interferon do not alter the course of disease. However, reviewers recommend that hydroxyurea (a.k.a. hydroxycarbamide) remain in the List of Essential Medicines as a part of CML patient care. While CML is less common in the

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pediatric population there is no evidence that there are significant biologic differences based on age. (13,22)

Prior to 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 (16) ; this number is even larger in patients of African or Hispanic descent due to under-representation 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 only offered in tertiary care hospitals. There are limited facilities able to perform BMT in Africa and currently none in the Sub-Saharan region.(2)

Public Health Relevance

GLOBOCAN estimates worldwide incidence of overall leukemia in 2012 to be 351,965 cases (ASR of 4.7 per 100,000). The incidence of overall leukemia in more developed regions in 2012 was estimated as 141,274 (ASR of 7.2 per 100,000) versus an incidence of 210,691 (3.8 per 100,000) in less developed regions (25). GLOBOCAN does not provide specific information about chronic myelogenous leukemia (CML).

Information on CML incidence and prevalence is scarce, as CML is a rare disease. A European study published in 2007 estimates the CML incidence to be 1 or 2 cases per 100 000 people every year (26). The same study states that CML is most common in older populations, with a median age at diagnosis of around 65 years. CML is more common in men, yet women tend to have a higher survival rate than men. According to the 2007 study, 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.

Requirements for diagnosis, treatment, and monitoring

Diagnosics:

Imatinib is a selective inhibitor of the BCR-ABL tyrosine kinase, resulting from the t(9;22) chromosomal translocation. Imatinib is effective only in patients whose leukemia cells carry this translocation, and therefore identification of the translocation is critical prior to a decision to use imatinib as a therapy for this disease. Though more than 90% of cases of CML demonstrate this translocation, CML can be confused with other myeloproliferative diseases which do not. Therefore testing prior to treatment initiation is critical. Testing can be performed by a variety of molecular techniques and is routinely available in most cancer centers in the developed world, but often not available in laboratories in the developing world. Where not available, it is possible

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for centers in the developing world to partner with laboratories in developed countries to have the test performed. (For example, Partners in Health hospitals have an arrangement with the Brigham and Women's Hospital at Harvard Medical School to perform BCR-ABL testing free of charge with generation of a formal report.)

Newer technology is rapidly making this test more generally available in developing countries. An example of this is Gene Xpert which can give point of care testing for this translocation with an affordable, relatively easy to use device. These units are currently being deployed in developing countries for this purpose (though they were originally designed for other testing including for multi-drug resistance tuberculosis).

Imatinib is dosed at 400 mg daily for adults and 260-340 mg/m²/day in children.(22)

Please note that dasatinib and nilotinib are discussed in further detail below.

Administration and Care of Patients

Until hematologic remission has been achieved (ie normalization of blood counts) weekly or every other weekly testing is needed to insure that neutropenia or thrombocytopenia do not develop. Once hematologic remission has been documented by a normal complete blood count (cbc), a cbc and physical examination may be warranted every 3-6 months to assess ongoing response in addition to patient education about reporting possible side effects. The role of ongoing monitoring of cytogenetic and molecular response is not standardized, particularly in settings where 2nd generation tyrosine kinase inhibitors are not available.

Overview of Regimens

The following tables include basic information on administration and dosing for CML.

Standard Regimen

Imatinib 400 mg PO daily

Alternative regimens for patients who are intolerant of imatinib, or whose disease develops resistance to imatinib

Nilotinib 300 mg PO q 12 hours for newly diagnosed patients (chronic phase)
400 mg PO q 12 hours for patients resistant or intolerant to imatinib
(chronic or accelerated phase)

Dasatinib 100 mg PO daily for newly diagnosed patients (chronic phase)
140 mg PO daily for patients resistant or intolerant to imatinib
(accelerated or blast phase)

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Review of Benefits and Harms

Benefits

Imatinib was introduced into clinical trials in 1998 and has radically changed the prognosis for patients with CML. Imatinib is a selective competitive inhibitor of the BCR-ABL tyrosine kinase and thus causes apoptosis of the malignant hematopoietic cells expressing BCR-ABL. In the seminal study of imatinib use, it was shown to produce major cytogenetic responses in almost 2/3 of patients with interferon-refractory CML. (6,12). This early promise culminated in an international randomized trial enrolling over 1000 patients in 16 countries. Imatinib at 400 mg orally per day was compared to interferon/low dose cytarabine as first line therapy for patients with chronic phase CML. (15). Significantly more patients obtained hematologic and cytogenetic responses in the imatinib arm. Imatinib was not only more effective (96% vs 80% freedom from disease progression at one year), but also better tolerated. Together these studies supported the use of imatinib as the standard of care for patients with newly diagnosed chronic phase CML as well as showing it could be effectively delivered in an international arena. These results have been updated at intervals (11) with recent data showing a mortality at 8 years of 16% in those patients able to achieve a complete response. Also of great significance, the toxicity profile remained unchanged after years of use. Thus it is now a realistic goal that the majority of patients diagnosed with CML and receiving imatinib will die of causes unrelated to CML or its treatment. The majority will achieve durable clinical and cytogenetic remissions with excellent quality of life. Monitoring needs are minimal and most patients return to a normal productive life.

Estimated survival with first-line imatinib is greater than 15 years in early studies, and probably longer with more experience and improved patient management. This compares with 9 years for interferon and low-dose cytarabine. Initial estimates of cost-effectiveness estimated \$43,000 per QALY.(18) As the cost of imatinib decreases coming off patent, and survival of patients taking imatinib increases with better management, these numbers are likely to become much more favorable. In addition, the toxicity profile for imatinib vs interferon/low-dose cytarabine is substantially better resulting in greatly improved quality of life for patients. In fact, data, including a large recently published study, suggests that the quality of life for patients on imatinib for a median of 5 years was comparable to that of population norms.(8,9)

There is a small body of published literature on imatinib use in developing countries.(3,17,19) Aziz reported on 275 patients in Pakistan and found response rates similar to that in Western countries with a major cytogenetic response in almost 2/3 of patients after a median follow-up of 18 months. Patients demonstrated good compliance and there was limited toxicity in this patient population. The concordance between the timing and degree of response also provides supportive evidence that the biology of CML is not different in different parts of the world.

Although the use of imatinib for the treatment of chronic phase chronic myeloid leukemia has represented a paradigm shift, there exist patients who are either intolerant, relapse or have refractory disease. Approximately 15 to 20 percent of patients are intolerant to imatinib and will discontinue therapy as a result. The most common toxicities that lead to drug discontinuation include nausea, vomiting, diarrhea and severe muscle cramps. Other less common reasons for discontinuing imatinib include edema, heart failure, rash and arthralgias as well as severe

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myelosuppression and hepatic toxicity. In addition approximately 20 percent of patients will not have an appropriate response.

An impressive 85 percent of patients receiving imatinib therapy will eventually achieve a complete cytogenetic remission, but only 60 percent will do so within the first year and this is the standard 'milestone' that all CML directed therapies are judged. Furthermore, once a complete cytogenetic remission is achieved about 15 to 20 percent of patients on imatinib will progress. That is they will develop recurrence of their disease. Thus the development of second generation tyrosine kinase inhibitors have been able to fill this void of medical necessity.

Both dasatinib (Sprycel) and nilotinib (Tasigna) were developed for use in patients with CML who are intolerant or have resistant disease. There are many reasons for the development of resistant disease, but the most common is the occurrence of mutations within the binding region leading to drug resistance. Approximately 50 percent of patients who are resistant to imatinib will achieve a complete cytogenetic remission to either dasatinib or nilotinib. The responses are durable in about 80 percent of patients. Therefore, it remains important to have alternative options for patients with CML who are intolerant or develop resistance to imatinib based therapy.

Harm Considerations

Common

Tyrosine kinase inhibitors (TKIs) are well tolerated in the vast majority of patients. The most common non-hematologic adverse reactions are edema, muscle cramps, and GI symptoms including nausea, vomiting, diarrhea, and abdominal pain, though most adverse effects are mild.[3,27] In the initial patient cohort at 6 years of followup only 5% of patients discontinued imatinib due to side effects or adverse events. [11] Specifically, dasatinib is associated with GI bleeding in up to 25% of patients, however it 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]

Serious

Edema 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%).

Systematic Reviews

- Andolina, JR et al. How I treat childhood CML. Blood 2012; 23: 119(8): 1821-1830.
 - After review of efficacy, side effects and cost of tyrosine kinase inhibitor therapy (TKI) versus allogeneic stem cell transplantation the authors recommend

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TKI as frontline therapy for pediatric patients presenting with CML in chronic phase

- Hochhau, A et al. Six-year follow-up of patients receiving imatinib for the first line treatment of chronic myeloid leukemia. *Leukemia* 2009; 23: 1054-1061
 - 6 year follow-up of patients in initial randomized trial of interferon vs imatinib. 83% event free survival at 6 years for imatinib group and 93% freedom from progression to accelerated phase or blast crisis. Only 5% of patients stopped imatinib due to toxicity or adverse events.
- Jain, N et al. The frontline treatment of chronic myeloid leukemia in the chronic phase: current clinical decision and future prospects for treatment. *Expert Review of Hematology* 2013; 6(5):575-586.
 - TKI therapy has revolutionized treatment of CML. Frontline treatment with imatinib in patients presenting in 1st chronic phase leads to an event free survival of > 80% at 8 years.
- Schigger, C. BCR-ABL Tyrosine Kinase Inhibitors for Chronic Myelogenous Leukemia. *The New England Journal of Medicine* 2007; 357:258-265.
 - Review of TKI therapy based off a case discussion. Reviews dosing, toxicity, follow-up guidelines.
- Kantarjian, Hagop M., et al. "Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance." *Blood* 110.10 (2007): 3540-3546.
 - **Abstract:** Nilotinib, an orally bioavailable, selective Bcr-Abl tyrosine kinase inhibitor, is 30-fold more potent than imatinib in pre-clinical models, and overcomes most imatinib resistant *BCR-ABL* mutations. In this phase 2 open-label study, 400 mg nilotinib was administered orally twice daily to 280 patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) after imatinib failure or intolerance. Patients had at least 6 months of follow-up and were evaluated for hematologic and cytogenetic responses, as well as for safety and overall survival. At 6 months, the rate of major cytogenetic response (Ph ≤ 35%) was 48%: complete (Ph = 0%) in 31%, and partial (Ph = 1%-35%) in 16%. The estimated survival at 12 months was 95%. Nilotinib was effective in patients harboring *BCR-ABL* mutations associated with imatinib resistance (except T315I), and also in patients with a resistance mechanism independent of *BCR-ABL* mutations. Adverse events were mostly mild to moderate, and there was minimal cross-intolerance with imatinib. Grades 3 to 4 neutropenia and thrombocytopenia were observed in 29% of patients; pleural or pericardial effusions were observed in 1% (none were severe). In summary, nilotinib is highly active and safe in patients with CML-CP after imatinib failure or intolerance.

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- Cortes J, Kim DW, Raffoux E, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. *Leukemia* 2008;22:2176–2183.
 - **Abstract:** Dasatinib is an inhibitor of BCR-ABL and SRC-family kinases for patients with imatinib-resistant or -intolerant chronic myelogenous leukemia (CML). In this international phase II trial, dasatinib was administered orally (70 mg twice daily) to patients with myeloid blast phase (MBP, $n=109$) or lymphoid blast phase (LBP, $n=48$) CML. After a minimum follow-up of 12 months (range 0.03–20.7 months), major hematologic responses were induced in 34% (MBP-CML) and 35% (LBP-CML) of patients. Major cytogenetic responses were attained in 33% (MBP-CML) and 52% (LBP-CML) of patients and complete cytogenetic responses were attained in 26 and 46%, respectively. Median progression-free survival was 6.7 (MBP-CML) and 3.0 (LBP-CML) months. Median overall survival was 11.8 (MBP-CML) and 5.3 (LBP-CML) months. Overall, dasatinib had acceptable tolerability. Fluid retention events were more frequent in the MBP-CML than the LBP-CML cohort: pleural effusion occurred in 36 and 13% (all grades) and 15 and 6% (grades 3/4), respectively. Other non-hematologic side effects were primarily grade 1/2; grade 3/4 events were recorded in $\leq 6\%$ of patients, except febrile neutropenia (15%). Cytopenias were noted in the majority of patients, and were manageable with dose interruptions/reductions. Dasatinib is associated with a promising rate of response in this high-risk population.

Recommendations

The reviewers recommend the incorporation of CML treatment options into the WHO Model List of Essential Medicines, and recommend specifically that imatinib, dasatinib, and nilotinib be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

Imatinib
Dasatinib
Nilotinib

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