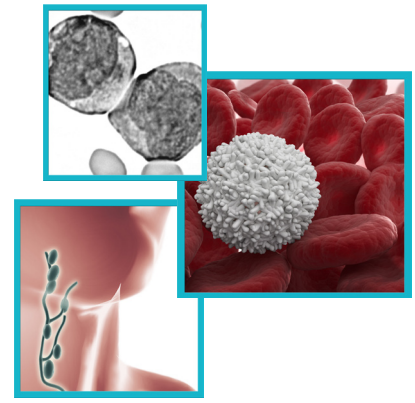
EDITORIAL

The challenge to chronic myeloid leukemia: are we close to cure?



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"The cooperation of the specialist and of the family doctor is clearly necessary to achieve maximum benefit and to ensure proper use of resources."

Since its description in 1961, the Philadelphia (Ph) chromosome has been a symbol and a paradigm of malignancy, because all Ph chromosome-positive leukemia resulted in the death of the patients, either in months or in years [1]. The Ph chromosome was originally described as a derivative of chromosome 22, due to a partial deletion of the long arm of that chromosome. Then, it was shown that there was not a deletion, but a reciprocal translocation of a part of the long arm of chromosome 22 into the long arm of chromosome 9, and *vice versa*, (t[9;22]; q2.2;q 1.1), leading to a loss of a variable part of chromosome 9 and to the formation of a new gene on chromosome 22, due to the fusion of c-ABL from chromosome 9 with BCR (coding for a serine–threonine kinase) on chromosome 22. The new fusion gene, *BCR–ABL*, is located in the cytoplasm, is a constitutively activated tyrosine kinase (TK), and activates several downstream signals that affect cell proliferation and maturation, leading to the leukemic transformation of hemopoietic cells [1–4]. This results in an uncontrolled proliferation of the hemopoietic tissue in the bone marrow, in the spleen and in the liver, with leukocytosis and circulating progenitors – the clinical and hematologic picture of chronic myeloid leukemia (CML), as it was described by Bennett and Virchow more than 150 years ago [1,3].

The *BCR–ABL* gene is not only responsible for the expansion of the myeloid tissue, but causes a genetic instability, whose molecular mechanisms have not yet been elucidated, that leads to further genomic alterations, resulting in the acquisition of an acute leukemia-like phenotype that is resistant to any treatment and leads inexorably to death [1–4]. While the molecular bases of Ph chromosome-positive CML are well known, the causes are unclear. On one hand, we know that BCR–ABL can be generated *in vitro* upon experimental exposure to radiation, and that the atomic bomb explosions in Hiroshima and Nagasaki caused an excess number of cases of CML [1,3]. But, on the other hand, BCR–ABL is exceedingly rare in the cases of leukemia secondary to radiation and cytotoxic agents, and although the frequency of CML increases with age, as it does for most cancers, the Ph chromosome is never found in acute myeloid leukemia and myelodysplastic syndrome, which are so frequent in the elderly.

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Future Medicine part of fsg

The incidence of Ph chromosome-positive CML has not been sufficiently investigated. It is believed that it ranges between 1 and 1.5 new cases, per 100,000 people, per year, age-adjusted. There are no data suggesting geographic, ethnic or social differences. The median age at presentation is around 60 years in western countries, but may be significantly lower in countries where the median age of the population is lower. While the incidence of Ph chromosome-positive CML is likely to be stable, it should not be overlooked that, because of recent progress in treatment, the prevalence is increasing at such a rate that it is becoming an important social and financial challenge [5].

The success of current treatment is a rational consequence of the knowledge of the molecular basis of the disease, which has led to the identification and the selection of a class of small molecules targeting the TK activity of BCR–ABL [6]. The first of the class was imatinib, which was developed initially (CGP 57148) as an inhibitor of other TKs, then as a inhibitor (STI571) of BCR–ABL [7,8]. Imatinib is one of the first and best examples of cancer-targeted therapy, that is to say, of an intelligent therapy targeting cancer and saving the patient [9]. Imatinib was registered for the first-line treatment of Ph chromosome-positive CML (Glivec or Gleevec, Novartis Pharma, NJ, USA) approximately 10 years ago [10,11], and since then has been the gold standard of treatment of Ph chromosome-positive CML worldwide [6,12,13]. With imatinib, approximately 95% of patients achieve a complete hematologic response, approximately 65% of patients achieve a complete cytogenetic response (CCgR), and approximately 50% of patients achieve a major molecular response (MMR); that is, a decrease of at least 3-log of the BCR–ABL transcripts level, for a progression-free survival of approximately 80% at 10 years [12,13]. Imatinib is only the beginning of a story that is rapidly developing, because, however good the results of imatinib treatment are, 10–15% of patients discontinue the treatment because of side effects, which are usually minor, but eventually affect their quality of life, and 15–20% of patients fail to respond, either because of primary or secondary resistance [14,15]. Therefore, 30–40% of patients need another therapy, and such a therapy has rapidly been developed as a result of a successful search of other tyrosine kinase inhibitors (TKIs). There are many other TKIs, more or less specific for BCR–ABL. Among them, nilotinib (Tasigna, Novartis Pharma) and dasatinib (Sprycel, Bristol–Myers Squibb, NJ, USA) have been quickly tested and registered for the second-line treatment of imatinib-resistant or -intolerant patients, where they can induce approximately 50% CCgR [16,17]. Both drugs have already been compared with imatinib as a first-line treatment, and were rapidly approved by the US FDA and by the EMA in Europe, also for first-line treatment of CML [18,19]. Nilotinib is more specific for BCR–ABL and dasatinib has broader activity, targeting more TKs. Both are more potent than imatinib *in vitro* and inhibit most imatinib-resistant BCR–ABL kinase domain point mutations. Both induce more CCgR and more MMR than imatinib, and do so more rapidly. Both are likely to reduce the rate of progression to blast crisis, but the observation is still too short to assess the effects on progression-free survival and overall survival. Both drugs are inactive against the T315I mutation of BCR–ABL, but a third-generation class of TKI is developing. One of these new TKIs is ponatinib (Ariad, MA, USA), which has already been shown to induce a high rate of CCgR and of MMR in cases with the T315I mutation and, more generally, in all patients who are, or become, resistant to imatinib, nilotinib and dasatinib [20,21]. Ponatinib should be registered very soon for the second-, third- or fourth-line treatment of Ph chromosome-positive CML. Nilotinib, dasatinib, other TKIs such as bosutinib, and now also ponatinib present promising therapeutic options for the treatment of Ph chromosome-positive CML, that is to ensure to all patients a normal quantity and quality of life [22]. However, again, this is not the end of the story, but the beginning of a new, even more ambitious story, aiming at the cure of the disease, as defined by stable molecular negativity in the absence of treatment. It has already been shown that some patients who have been treated continuously with imatinib for years, and have become molecular negative, can discontinue the treatment without hematologic, cytogenetic and molecular recurrence of Ph chromosome-positive cells [23]. At less than 10%, the number of such patients is currently small, but the introduction of the second-generation TKI, either in first- or second-line therapy, is expected to substantially increase

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that proportion, and to allow more and more patients to become leukemia- and treatment-free. This will be an important goal, as it will allow patients to plan, and to live, their life without the psychologic and physical restrictions of having leukemia. In addition, it will have important social and financial implications, because achieving more cures will limit the logarithmic increase of the prevalence of the disease.

To realize the target of moving from complete remission and normal survival to cure, it is necessary that the management of Ph chromosome-positive CML is trusted to reference centers with high-technology laboratories and with specifically trained professionals, who can interplay with family doctors, so as to ensure the best treatment (that means the best survival and the best quality of life), as well as the proper use of the financial resources available. On the one hand, the management of Ph chromosome-positive CML requires a sensitive and sophisticated control system of the cytogenetic and molecular response, and of the development of mutations, a control that cannot be easily accomplished by family doctors [13,24,25]. On the other hand, many patients with Ph chromosome-positive CML are old, have a substantial number of comorbidities and must be cared for lifelong, taking into account not only CML, but also the other pathologic conditions that are related to aging. The cooperation of the specialist and of the family doctor is clearly necessary to achieve maximum benefit and to ensure proper use of resources.

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