LETTERS

Dynamics of chronic myeloid leukaemia

Franziska Michor[1], Timothy P. Hughes[2], Yoh Iwasa[3], Susan Branford[2], Neil P. Shah[4], Charles L. Sawyers[4,5] & Martin A. Nowak[1]

The clinical success of the ABL tyrosine kinase inhibitor imatinib in chronic myeloid leukaemia (CML) serves as a model for molecularly targeted therapy of cancer[1–4], but at least two critical questions remain. Can imatinib eradicate leukaemic stem cells? What are the dynamics of relapse due to imatinib resistance, which is caused by mutations in the ABL kinase domain? The precise understanding of how imatinib exerts its therapeutic effect in CML and the ability to measure disease burden by quantitative polymerase chain reaction provide an opportunity to develop a mathematical approach. We find that a four-compartment model, based on the known biology of haematopoietic differentiation[5], can explain the kinetics of the molecular response to imatinib in a 169-patient data set. Successful therapy leads to a biphasic exponential decline of leukaemic cells. The first slope of 0.05 per day represents the turnover rate of differentiated leukaemic cells, while the second slope of 0.008 per day represents the turnover rate of leukaemic progenitors. The model suggests that imatinib is a potent inhibitor of the production of differentiated leukaemic cells, but does not deplete leukaemic stem cells. We calculate the probability of developing imatinib resistance mutations and estimate the time until detection of resistance. Our model provides the first quantitative insights into the *in vivo* kinetics of a human cancer.

Chronic myeloid leukaemia (CML) represents the first human cancer in which molecularly targeted therapy leads to a dramatic clinical response[1–4]. In most patients, however, the rapid decline of the leukaemic cell burden induced by the ABL tyrosine kinase inhibitor imatinib fails to eliminate residual disease. Bone marrow studies have shown that the residual cells are part of the leukaemic stem cell compartment[6,7]. This observation raises the question of whether imatinib is capable of impairing the proliferation of leukaemic stem cells. Moreover, a substantial fraction of patients develops acquired resistance to imatinib. Mutations in the ABL kinase domain are the main mechanism of resistance and account for 70–80% of cases with treatment failure[8–13]. Sometimes, resistance mutations are present in leukaemic cells prior to imatinib therapy[13–15].

We design a mathematical model which describes four layers of the differentiation hierarchy of the haematopoietic system (see Methods and Supplementary Information). Stem cells give rise to progenitors, which produce differentiated cells, which produce terminally differentiated cells. This hierarchy applies both to normal and leukaemic cells. Therefore, the leukaemic cell population consists of leukaemic stem cells and three types of leukaemic differentiated cells; only leukaemic stem cells have an indefinite potential for self-renewal. The *BCR-ABL* oncogene is present in all leukaemic cells. It leads to a slow clonal expansion of leukaemic stem cells and accelerates the rate at which these cells produce leukaemic progenitors and differentiated cells.

We analysed 169 CML patients. The levels of BCR-ABL transcripts in the blood of the patients is measured by a quantitative real-time PCR (RQ-PCR) assay[10,16]. *BCR* is used as the control gene and BCR-ABL values are expressed as a percentage of the BCR transcript levels to compensate for variations in the RNA quality and efficiency of reverse transcription. Because the blood predominantly contains terminally differentiated cells, the obtained values give an estimate of the fraction of terminally differentiated leukaemic cells.

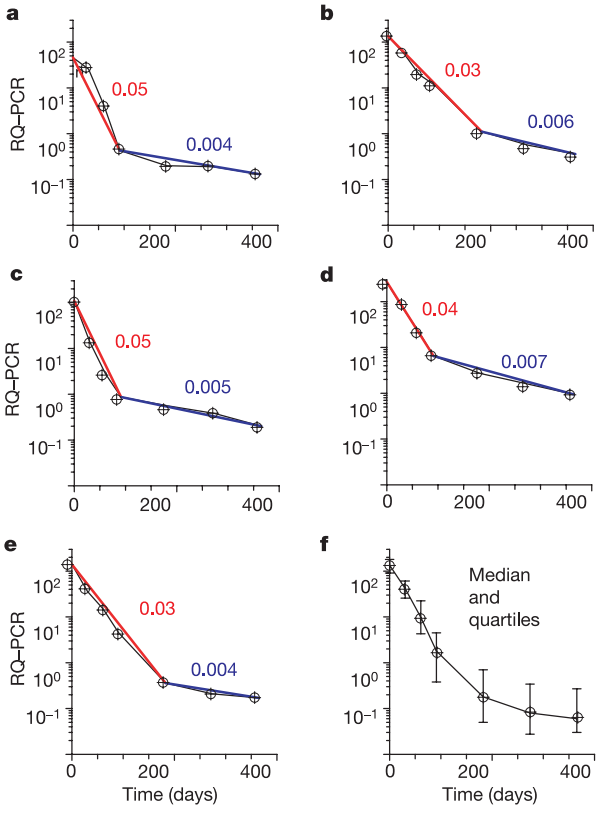

Figure 1 | Imatinib leads to a biphasic decline of leukaemic cells. a–e, The levels of BCR-ABL transcripts in the blood of five patients are shown during 12 months of therapy starting at day 0. In these patients, the first slope ranges from 0.03 to 0.05 per day and the second slope from 0.004 to 0.007 per day. The first slope represents the death rate of leukaemic differentiated cells and the second slope the death rate of leukaemic progenitors during imatinib therapy. Panel **f** shows the median with quartiles taken over all patients who do not have a rise in the leukaemic cell burden during the first 12 months of therapy. The circle represents the 50 percentile, and the bars the 25 and 75 percentiles.

[1]Program for Evolutionary Dynamics, Department of Organismic and Evolutionary Biology, Department of Mathematics, Harvard University, Cambridge, Massachusetts 02138, USA. [2]Institute of Medical and Veterinary Science, Adelaide, Australia. [3]Department of Biology, Kyushu University, Fukuoka 812-8581, Japan. [4]Department of Medicine, and [5]Howard Hughes Medical Institute, Molecular Biology Institute, Department of Urology, Department of Medical and Molecular Pharmacology, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA.

Successful therapy leads to a biphasic exponential decline of leukaemic cells (Fig. 1). The first slope is determined by calculating the exponential decline between 0 and 3 months; a mean value of 0.05 ± 0.02 per day is obtained, which corresponds to a decline of 5% per day. The second slope is determined by calculating the exponential decline between 6 and 12 months; a mean value of 0.008 ± 0.004 per day is obtained, which corresponds to a decline of 0.8% per day. This analysis considers only patients who do not have any rise in the leukaemic cell burden during the first 12 months of therapy, in order to exclude the effect of acquired resistance.

Fitting our model to the data, we conclude that the first slope represents the turnover rate of differentiated leukaemic cells. Therefore, these cells have an average lifespan of 1/0.05 = 20 days. Upon reaching a steady state with the leukaemic progenitors, the number of differentiated leukaemic cells decreases at the same rate as the number of leukaemic progenitors. The second slope represents the turnover rate of leukaemic progenitors. Hence, these cells have an average lifespan of 1/0.008 = 125 days. Both estimates denote average lifespans during imatinib therapy. Any process that removes cells from the corresponding subpopulation (including further differentiation) contributes to the average lifespan.

The first slope leads to an approximately 1,000-fold decline in the leukaemic cell burden. Therefore, imatinib reduces the rate at which leukaemic differentiated cells arise from leukaemic progenitors about 1,000-fold. This effect is as if imatinib prevented about ten rounds of cell division of leukaemic cells ($2^{10} = 1{,}024$), either by increasing their death rate or by reducing their division rate.

Some patients ceased imatinib therapy because of complications or side effects (Fig. 2). Even if imatinib had been administered for many months (up to three years), the numbers of BCR-ABL transcripts in those patients rose within three months after discontinuation of therapy to levels at pre-treatment baseline or above. Other studies of patients who ceased imatinib led to similar findings[17,18]. We conclude that long-term imatinib treatment does not deplete the cell population that drives this disease. This conclusion is consistent with the hypothesis that leukaemic stem cells are insensitive to chemotherapy[19–21]. The average rate of the exponential increase after stopping treatment is 0.09 ± 0.05 per day, corresponding to a doubling time of 8 days. This timescale indicates the rate at which terminally differentiated leukaemic cells arise from leukaemic stem cells in the absence of imatinib.

A comparison between model and data suggests the following two concepts. (1) Imatinib treatment leads to a competitive disadvantage of leukaemic progenitors and leukaemic differentiated cells; their production rates are dramatically reduced. The consequence is a biphasic decline of the abundance of the BCR-ABL transcript in response to therapy. (2) Leukaemic stem cells, however, are not depleted during imatinib treatment. The total leukaemic cell burden rapidly returns to the baseline value (or beyond) when imatinib is discontinued.

Acquired imatinib resistance usually develops owing to mutations in the ABL kinase domain[8–13]. Resistant leukaemic cells emerge after an initially successful response to imatinib therapy and lead to a relapse of disease (Fig. 3). The average slope was determined by calculating the exponential increase after the first appearance of resistance mutations in 30 patients; a value of 0.02 ± 0.01 per day was obtained. Of those patients who start imatinib in the early chronic, late chronic, and accelerated phase of CML, respectively, 12%, 32%, and 62% develop detectable resistance mutations within two years of treatment[22].

Our basic model can be extended to include the stochastic evolution of resistance. Consider an exponentially growing leukaemia continually producing resistant cells at rate u per cell division. The probability of having resistance mutations once leukaemic stem cells have reached a certain abundance, y_0, is given by $P = 1 - \exp(-uy_0\sigma)$ where $\sigma = (1 + s)\log(1 + 1/s)$. The parameter s denotes the excess reproductive ratio of the exponentially growing leukaemia, which is the relative difference between birth and death rates. This calculation assumes that resistance mutations are neutral prior to therapy.

If the point mutation rate is about 10^{-8} per base per cell division[23], then resistance due to any one of about forty known mutations[7–14]

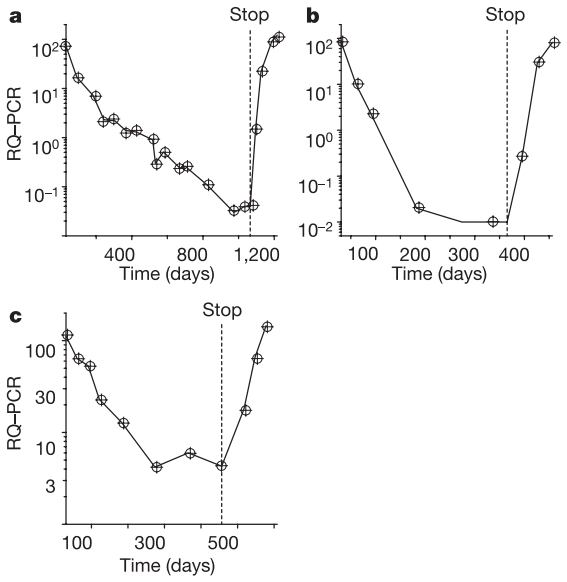

Figure 2 | Discontinuation of imatinib therapy in three patients after 1–3 years led to a rapid increase of leukaemic cells to levels at or beyond pre-treatment baseline. We conclude that leukaemic stem cells, which drive CML disease, are not depleted by imatinib therapy. The rapid upslope of 0.09 ± 0.05 per day corresponds to a doubling time of roughly 8 days, which characterizes the rate at which differentiated leukaemic cells are regenerated from leukemic stem cells. Each of panels **a**, **b** and **c** corresponds to one of the three patients.

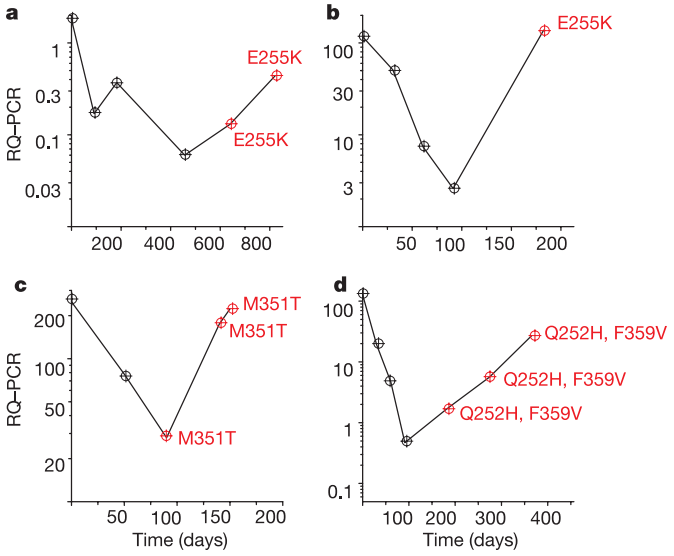

Figure 3 | About 40 different point mutations in BCR-ABL have been identified that confer various degrees of resistance to imatinib therapy. **a–d**, We show evolutionary dynamics of resistance in four patients. The labels denote the individual mutations that are detected at various time points. Resistance mutations lead to a relapse of leukaemic cells. The upslope ranges from 0.003 to 0.06 per day in 30 patients, with an average of 0.02 ± 0.01 per day. The characteristic timescale for the rise of resistance is given by the rate at which resistant leukaemic stem cells expand during therapy.

arises at rate $u = 4 \times 10^{-7}$ per cell division. The abundance of leukaemic stem cells at diagnosis in early chronic phase[24,25] is estimated to be about $y_0 = 2.5 \times 10^5$. For these values and $s = 1$, we calculate that about 13% of patients harbour resistance mutations at the time of diagnosis. If imatinib therapy commences at a later stage of the disease, when the leukaemic stem cell population has expanded to 10^7 cells, for example, then 100% of those patients have some resistant leukaemic stem cells. Therefore, the higher incidence of resistance in patients who start imatinib therapy in a later phase of disease can be explained by an increased leukaemic stem cell burden.

We expect that the frequency of resistance mutations at the start of imatinib therapy is below detection limit in most patients. We can use the deterministic model to calculate the time until detection of resistance mutations and treatment failure (see Supplementary Information). In our model, the characteristic timescale is given by the rate at which the resistant leukaemic stem cells are expanding during therapy. Therefore, a faster-growing leukaemia leads to an earlier emergence of resistance, while a slower-growing leukaemia might allow many years of successful therapy, even if resistant cells are present at low frequencies. The reason for this unusual behaviour is that leukaemic stem cells, with or without resistance mutations, continue to expand during treatment. Imatinib acts by reducing the abundance of leukaemic progenitors, differentiated and terminally differentiated cells without resistance mutations.

There is evidence that some resistance mutations confer a growth advantage even in the absence of imatinib[8,13]. These 'advantageous mutations' have a higher probability of being present in patients prior to treatment and can lead to a more rapid expansion during therapy.

Figure 4 summarizes the dynamical features of our mathematical model. Normal haematopoietic cells are in a steady state. Leukaemic stem cells expand exponentially at a slow rate. Imatinib reduces the rate at which leukaemic stem cells produce progenitors. Hence, the abundance of leukaemic progenitors declines once treatment is started. Similarly imatinib reduces the rate at which leukaemic progenitors produce differentiated cells. The abundance of differentiated leukaemic cells shows a biphasic decline. The first slope is determined by the average lifespan of leukaemic differentiated cells (20 days), while the second slope reflects the longer lifespan of leukaemic progenitors (125 days). We assume that imatinib does not affect the rate at which leukaemic differentiated cells produce terminally differentiated cells. This cell population has a fast turnover rate—on a timescale of one day—and simply tracks the biphasic decline of leukaemic differentiated cells. If imatinib is discontinued, there is a rapid resurgence of the leukaemic load because the cell population which drives the disease, the leukaemic stem cells, was not depleted during therapy. Resistant leukaemic stem cells might expand faster than leukaemic stem cells during therapy for two reasons: (1) either they have an inherent selective advantage; or (2) imatinib somewhat reduces the growth rate of leukaemic stem cells without depleting them. In any case, resistant leukaemic stem cells continue to produce large amounts of progenitors and differentiated cells during therapy. The total leukaemic cell burden declines initially, but rises again once resistant differentiated cells become abundant. In this case, the time to treatment failure is determined by the rate of expansion of resistant leukaemic stem cells.

Finding a cellular mechanism for drug resistance of leukaemic stem cells is a very important goal for future experimental research. Imatinib is a substrate for the multidrug resistance protein MDR p-glycoprotein and will therefore be excluded from cells that express significant MDR levels[26]. Stem cells naturally express higher levels of MDR[27]. It is unknown whether this is the actual mechanism for sparing leukaemic stem cells, because it has not been possible neither to measure accurately the imatinib concentration in leukaemic stem cells nor to measure BCR-ABL inhibition selectively in this compartment. Another possibility is that leukaemic stem cells are less dependent on BCR-ABL for growth and survival than are committed progenitors, and therefore BCR-ABL inhibition does not eliminate leukaemic stem cells. Indeed, there is evidence that BCR-ABL messenger RNA, but not protein, can be detected in a progenitor cell population[28].

In cell-culture systems using CML cell lines or murine haematopoietic cells transformed by BCR-ABL, imatinib leads to rapid inhibition of ABL kinase activity and subsequent induction of apoptotic cell death (on a timescale of hours). This very fast response to imatinib is in stark contrast to the 20 and 125 day half-lives we find in our *in vivo* data. This discrepancy might be explained by the fact that *in vitro* model systems are derived from (or resemble) blast crisis cells, wherease our data refer to chronic-phase CML. Since there are no *in vitro* models of chronic-phase CML, we cannot make a direct comparison. Curiously, the rate of clearance of leukaemic blasts from the blood of CML blast crisis patients is rapid (3–7 days) and may reflect increased dependence of blasts on the action of the *BCR-ABL* oncogene. In contrast, leukaemic cells from chronic-phase patients are not as dependent on the BCR-ABL signal and consequently do not undergo rapid apoptosis. Our analysis suggests that in chronic-phase

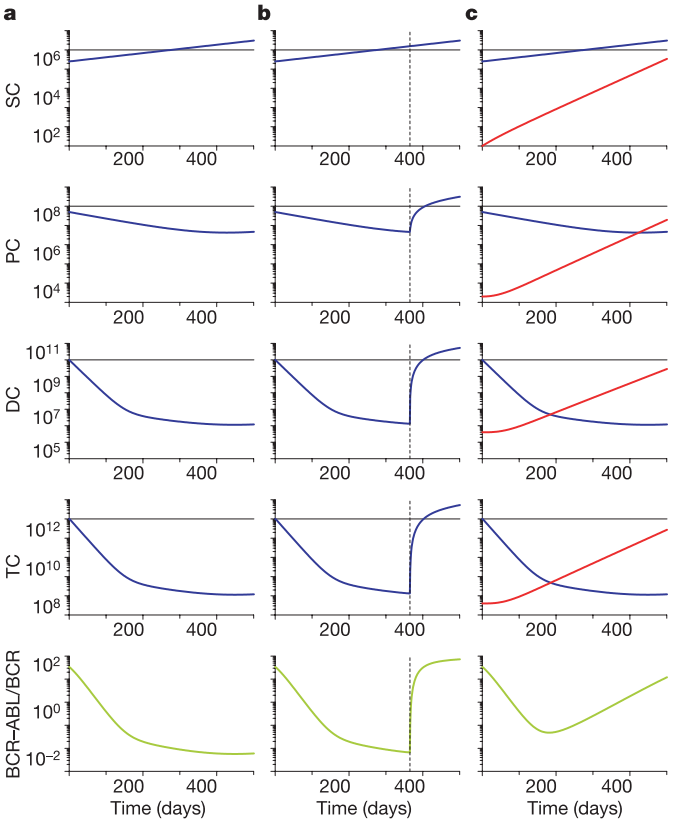

Figure 4 | Model dynamics of different treatment responses to imatinib. **a**, Without resistance mutations; **b**, when therapy is stopped after one year; and **c**, with resistance mutations. The rows show stem cells (SC), progenitor cells (PC), differentiated cells (DC), and terminally differentiated cells (TC); wild type cells are black, leukaemic cells blue, and resistant leukaemic cells red. The bottom row shows the ratio of BCR-ABL over BCR in % (green). **a**, Imatinib therapy is started at day 0. Treatment leads to a biphasic decline of the BCR-ABL/BCR ratio. Leukaemic stem cells continue to expand at a slow rate. **b**, Discontinuation of treatment (broken line) leads to a rapid rise of leukaemic cells to levels above the pre-treatment baseline, because leukaemic stem cells have not been depleted during therapy. **c**, Emergence of resistance mutations leads to an increase of the BCR-ABL/BCR ratio at a rate which is determined by the rise of resistant leukaemic stem cells. Parameter values are $d_0 = 0.003$, $d_1 = 0.008$, $d_2 = 0.05$, $d_3 = 1$, $a_x = 0.8$, $b_x = 5$, $c_x = 100$, $r_y = 0.008$, $a_y = 2a_x$, $b_y = 2b_x$, $c_y = c_x$, $r_z = 0.023$. During therapy we have $a_y' = a_y/100$, $b_y' = b_y/750$, $c_y' = c_y$, $a_z = a_z' = a_y$, $b_z = b_z' = b_y$, and $c_z = c_z' = c_y$. In **c**, we have $z_0(0) = 10$ and $u = 4 \times 10^{-8}$.

CML the mode of action of imatinib is to reduce the rate at which differentiated leukaemic cells are produced from progenitors and at which progenitors are produced from leukaemic stem cells. Hence, the *in vivo* action does not rely on massive and sudden apoptosis, but on a decline in the net proliferation potential of leukaemic cells.

We conclude that the comparison between model and data provides quantitative insights into the *in vivo* kinetics of CML. We obtain numerical estimates for the turnover rates of leukaemic progenitors and differentiated cells. Imatinib dramatically reduces the rate at which those cells are being produced from leukaemic stem cells, but it does not lead to an observable decline of leukaemic stem cells. The probability of harbouring resistance mutations increases with disease progression as a consequence of an increased leukaemic stem cell abundance. The characteristic time to treatment failure caused by acquired resistance is given by the growth rate of the leukaemic stem cells. Thus, multiple drug therapy[29] is especially important for patients who are diagnosed with advanced and rapidly growing disease.

METHODS

The basic mathematical model. The abundances of normal haematopoietic stem cells, progenitors, differentiated cells, and terminally differentiated cells are denoted x_0, x_1, x_2, and x_3. Their respective leukaemic abundances are given by y_0, y_1, y_2 and y_3 for cells without resistance mutations and by z_0, z_1, z_2 and z_3 for cells with resistance mutations. Stem cells produce progenitors, which produce differentiated cells, which produce terminally differentiated cells. The rate constants are given by a, b and c with appropriate indices distinguishing between healthy, leukaemic and resistant cell lineages. The death rates of stem cells, progenitors, differentiated and terminally differentiated cells are denoted by d_0, d_1, d_2 and d_3. Homeostasis of normal stem cells is achieved by an appropriate declining function, λ. Leukaemic stem cells divide at rate r_y, and resistant stem cells divide at rate r_z. The basic mathematical model is given by:

$$\dot{x}_0 = [\lambda(x_0) - d_0]x_0 \quad \dot{y}_0 = [r_y(1-u) - d_0]y_0 \quad \dot{z}_0 = (r_z - d_0)z_0 + r_y y_0 u$$

$$\dot{x}_1 = a_x x_0 - d_1 x_1 \qquad \dot{y}_1 = a_y y_0 - d_1 y_1 \qquad \dot{z}_1 = a_z z_0 - d_1 z_1$$

$$\dot{x}_2 = b_x x_1 - d_2 x_2 \qquad \dot{y}_2 = b_y y_1 - d_2 y_2 \qquad \dot{z}_2 = b_z z_1 - d_2 z_2$$

$$\dot{x}_3 = c_x x_2 - d_3 x_3 \qquad \dot{y}_3 = c_y y_2 - d_3 y_3 \qquad \dot{z}_3 = c_z z_2 - d_3 z_3$$

For further discussion and analysis of the model, see Supplementary Information.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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