Heterogeneity in chronic myeloid leukaemia dynamics during imatinib treatment: role of immune responses

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Previous studies have shown that during imatinib therapy, the decline of chronic myeloid leukaemia BCR-ABL transcript numbers involves a fast phase followed by a slow phase in averaged datasets. Drug resistance leads to regrowth. In this paper, variation of treatment responses between patients is examined. A significant positive correlation is found between slopes of the fast and the slow phase of decline. A significant negative correlation is found between slopes of the slow phase of decline and the regrowth phase. No correlation is found between slopes of the fast phase of decline and the regrowth phase. A mathematical model that is successfully fitted to diverse clinical profiles explains these correlations by invoking the immune response as a key determinant of tumour decline during treatment. Boosting immunity during drug therapy could enhance the response to treatment in patients.

Keywords: mathematical models; population dynamics; immune system; dynamics; cancer treatment dynamics

1. INTRODUCTION
Chronic myeloid leukaemia (CML; Shet et al. 2002; Calabretta & Perrotti 2004; Yoshida & Melo 2004) is a cancer of the haematopoietic system and progresses in three stages: the chronic phase, the accelerated phase and blast crisis. During the chronic phase, the tumour grows slowly and most cells show a high degree of differentiation. During the accelerated phase, and especially during blast crisis, cancer growth explodes and the fraction of immature blast cells increases sharply. The targeted drug imatinib (inhibiting the product of the BCR-ABL fusion gene that is thought to maintain the cancer) has been successful in suppressing the disease, especially when treatment is applied during the chronic phase (Gorre et al. 2001; Deininger & Druker 2003; Shah et al. 2004; Yoshida & Melo 2004). Alternative targeted drugs have since become available, most notably dasatinib and nilotinib (Bradeen et al. 2006; Talpaz et al. 2006; Deininger 2007; Weisberg et al. 2007). Datasets have been collected that document the dynamics of BCR-ABL transcript numbers (which are not equal to but reflect the dynamics of the cancer cells) during imatinib treatment (Michor et al. 2005; Roeder et al. 2006). On average, a bi- phasic decline of BCR-ABL transcript numbers is observed (figure 1), with an initial fast phase of decline followed by a second slower phase. In the case of treatment failure, BCR-ABL transcript numbers subsequently rise again. The reason for this bi-phasic decline is unclear; intrinsic cancer stem cell resistance and cellular quiescence have been suggested as possible causes (Michor et al. 2005; Roeder et al. 2006; Komarova & Wodarz 2007). This paper examines the heterogeneity among treatment responses in individual patients. Based on data analysis and computational methods, it is found that transient immune responses during imatinib therapy could be key to explaining the observed dynamics.

2. MATERIAL AND METHODS
Standard statistical methods were used to quantify the slopes of the various treatment dynamics taken from published data, and to determine correlations between the individual slopes. The mathematical model explored in the paper is given by a set of ordinary differential equations, which were analysed by standard methods. The mathematical model was fitted to the clinical data using nonlinear least-squares regression. Details regarding the patient data, the methods of analysis, the properties of the mathematical model and the model fitting are found in the electronic supplementary material.

3. RESULTS
Rather than looking at averages, individual treatment dynamics and the heterogeneity between patients are studied in this paper using data from the German cohort of the IRIS study published by Roeder et al. (2006). In many patients, the dynamics appear to begin with a shoulder phase upon start of treatment, during which BCR-ABL transcript numbers fall slowly, if at all. If present, this is followed by a relatively fast phase of exponential decline; otherwise, the treatment response begins with this fast phase of decline. In some patients, this decline continues for the duration of the study. In most patients, however, this fast phase of decline is followed by a slower phase of exponential decline, as
The negative correlation between the slopes of the slow phase of decline and the rise implies that both could be influenced by the presence of drug-resistant mutants (Gorre et al. 2001; Deininger & Druker 2003; Druker 2003, 2004; Gambacorti-Passerini et al. 2003; Nardi et al. 2004; Shah et al. 2004). The rise of drug-resistant mutants can slow down the decline of BCR-ABL transcript numbers and is responsible for the eventual rise of BCR-ABL transcripts. The fact that the slopes of the slow and fast decline phases are positively correlated means that these two phases share a common mechanism of cell death that varies over time in strength. One such factor could be the immune system, which has been suggested to play a role in CML therapy before (Wang et al. 2005; Chen et al. 2008; Kim et al. 2008). In particular, T cell responses (both CD4+ and CD8+) have been implicated. Data indicate that the level of immune responses against CML is low before treatment, rises as treatment is administered and declines again as the BCR-ABL transcript numbers fall to low levels. These are similar immune response dynamics to those observed in patients infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) who receive antiviral drug therapy (Kalams et al. 1999; Ogg et al. 1999; Barnes et al. 2002), and can be explained in the same way. While the cancer cells impair immunity, treatment reduces the amount of impairment, leading to a rise of immunity. As the number of cancer cells declines, withdrawal of antigenic stimulation causes a drop in immune responses. Such impairment dynamics have been explored extensively with mathematical models in the context of viral infections (Wodarz & Nowak 1999; Wodarz 2001; Komarova et al. 2003), and more recently also in the context of CML (Kim et al. 2008). The following will use a basic mathematical model that captures these assumptions. Model fitting to individual patient data demonstrates consistency with clinical observations, and the model further predicts the correlations found in the data.

A mathematical model is adapted that was previously published in the context of viral infections (Komarova et al. 2003) and that captures the necessary assumptions. It includes a population of cells that grow over time and that have the ability to impair immunity, as well as an immune response that reacts to this cell population and removes it. The mathematical model is part of a general class of models that share common properties (Komarova et al. 2003). Results obtained from the model are therefore not dependent on the particular mathematical formulation used, but are robust. The equations that describe the immune response make the very basic assumptions that cancer cells can both stimulate the specific immune cells to proliferate and impair the response. Because of the general nature of the model, this can be applied to any branch of the adaptive immune system, including the T cell responses that are thought to play a role during CML therapy (Wang et al. 2005; Chen et al. 2008; Kim et al. 2008). Further discussion of the biological assumptions, aspects of robustness and mathematical methods is given in the electronic supplementary material. The basic model is characterized by the following outcomes, assuming that the degree of stimulation of immune cells is strong enough to drive immune expansion: (i) an immune response is successfully established and the system converges to a stable equilibrium in which cancer is controlled at relatively low levels; (ii) the immune response goes extinct and the cancer cell population converges to an equilibrium characterized by a large number of tumour cells. If the degree of immune impairment is relatively low, only the cancer control outcome is stable. If the degree of immune impairment lies above a threshold, both outcomes are stable. To which outcome the system converges depends on the initial conditions, with a high initial number of immune cells and a low initial number of tumour cells promoting the cancer control outcome. For the current purposes, this general model was modified to include two sub-populations of cancer cells: drug-sensitive and drug-resistant cells. Since the analysis focuses on the treatment phase only, it is assumed that drug-sensitive cells simply decline exponentially, and
that this is brought about by a combination of the cells’ natural death rate and immune-induced death. On the other hand, it is assumed that drug-resistant cells expand exponentially during treatment. This expansion can, however, be countered by the immune response. Further details of this overview are given in the electronic supplementary material.

The model can give rise to treatment dynamics that can describe diverse clinical data well, shown by nonlinear least-squares fits of the model to selected patient data (figure 3). Figure 3a shows a response that involves an initial shoulder phase, followed by a faster and a slower phase of decline, eventually leading to a resurgence of the cancer. Immunity is low at the beginning, accounting for a relatively slow initial decline of cells during the shoulder phase. Immunity rises as the number of CML cells starts to decline because of reduced immune impairment. This accounts for the fast phase of CML decline. Immunity subsequently falls owing to lack of antigenic stimulation. This, together with the rise of a resistant mutant, accounts for the slower phase of decline. The rise of the resistant mutant eventually leads to resurgence of cancer. Figure 3b shows the same kind of profile without eventual resurgence of the cancer. In this case, a resistant mutant is not present. Figure 3c shows a single-phase exponential decline of CML cells, while figure 3d shows an exponential decline followed by regrowth of the cancer. In these cases, immunity does not expand during the treatment dynamics according to the model, correlating with a significantly slower decline rate of the cancer. In figure 3c, no resistant mutant exists, while in figure 3d, a resistant mutant grows during therapy.

To examine predicted correlations between the slopes, the simulation was run many times, randomly varying the growth rate of drug-resistant CML cells and the rate of immune expansion against CML. Consistent with the experimental data, the model predicts a significant positive correlation between the slopes of the fast and slow phase of decline, a significant negative correlation between the slopes of the slow phase of decline and the regrowth, and a lack of a significant correlation between the slopes of the fast phase of decline and the regrowth (figure 2b). The reason is as follows. The immune response largely drives the fast phase of decline. Part of the reason for the slower decline is a fall of immune responses as the number of CML cells drops to low levels. However, the strength of the declining immunity is still proportional to the strength of immunity at its peak, hence the positive correlation. Another reason for the slowing decline is the rise of drug-resistant mutants. In addition, growth of resistant mutants completely determines the eventual rise of CML cells, hence the negative correlation. Since the fast phase of decline is mostly determined by immunity while the initial rise of resistant mutants is mostly determined by their replication rate, there is no correlation between these slopes. Apart from these correlations, the model can give rise to alternative outcomes if the variation in one parameter is significantly more pronounced than variation in the second parameter, which is discussed further in the electronic supplementary material.
4. DISCUSSION

The correlations found between the various slopes in the clinical data are fully consistent with the hypothesis that a transient immune response during the initial stages of drug treatment is a major factor in shaping the dynamics of CML decline during therapy. Reduction of immune impairment after initiation of treatment induces a rise of immunity, which subsequently falls as the amount of antigenic stimulation diminishes. Such immune response dynamics have in fact been demonstrated in clinical data from imatinib-treated patients (Wang et al. 2005; Chen et al. 2008). This type of CML-immune dynamics has also been modelled previously in a different context (Kim et al. 2008), which in turn is similar to data and modelling results from other immunity-impairing diseases, such as HIV or HCV infections (Kalams et al. 1999; Ogg et al. 1999; Wodarz & Nowak 1999; Wodarz 2001; Barnes et al. 2002; Komarova et al. 2003). In addition, the analysis suggests that drug-resistant mutants contribute to the slowing down of the decline of CML cells, and to the possible regrowth of the cancer. The extent to which drug-resistant mutants slow down the...
decline depends on the growth rate of the mutants during therapy, which can vary between different mutants.

These notions give rise to the following implications: in the absence of the transient immune response during treatment, the CML decline occurs with a significantly slower rate (i.e. the fast initial phase of decline is absent). Conversely, if specific immune responses could be boosted during therapy, the rate of CML decline could be significantly accelerated. Variations in immune response dynamics during treatment are likely to significantly account for variations in the observed treatment dynamics.

If immune responses that arise during treatment are sustained, they could in principle suppress the population of drug-resistant cancer cells. In some patients, discontinuation of therapy after 2 years did not result in the relapse of the cancer (Rousselot et al. 2006). It can be hypothesized that in these cases, immunity became fully established during therapy rather than rising only temporarily. This possibility is demonstrated by computer simulation in figure 4. Establishment of sustained immune responses during therapy of immunosuppressive diseases has been found to occur in some experimental HCV and simian immunodeficiency virus (SIV) therapy regimes (Lifson et al. 2000; Barnes et al. 2002).

To summarize, the analysis of the clinical data performed here strongly supports an important role of immune responses in the dynamics of CML during therapy. Exploring this notion further could open doors to new therapy options that could improve the outcome of targeted drug treatment of CML. An important next step would be to address experimentally in detail the differences between the dynamics explored here and those described in previous work, which proposed alternative mechanisms (Michor et al. 2005; Roeder et al. 2006; Komarova & Wodarz 2007).

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