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Optimal use of novel agents in chronic lymphocytic leukemia

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ABSTRACT

Novel agents are changing therapy for patients with CLL, but their optimal use remains unclear. We model the clinical situation in which CLL responds to therapy, but resistant clones, generally carrying del17p, progress and lead to relapse. Sub-clones of varying growth rates and treatment sensitivity affect predicted therapy outcomes. We explore effects of different approaches to starting novel agent in relation to bendamustine-rituximab induction therapy: at initiation of therapy, at the end of chemo-immunotherapy, at molecular relapse, or at clinical detection of relapse. The outcomes differ depending on the underlying clonal architecture, raising the concept that personalized approaches based on clinical evaluation of each patient's clonal architecture might optimize outcomes while minimizing toxicity and cost.

1. Introduction

The typical paradigm for chronic lymphocytic leukemia (CLL) treatment has been an immunochemotherapy course followed by observation until disease progression. Targeted therapies are altering that approach. Progression may reflect regrowth of residual drug-sensitive, or selection of drug-resistant, clones. Therapy may select more aggressive and drug-resistant clones pre-existing at low levels at diagnosis [1–7]. Del17p clones become more prevalent over time [3–5,7]. Ibrutinib is approved for CLL therapy, but its optimal use is unclear. A predictive model to optimize dose/scheduling and mitigate clonal selection would speed clinical advancement. We previously modeled lymphoma growth, therapy response [8] and transformation based on pre-existing aggressive clones [9]. Here we apply similar modeling to CLL drug-resistance.

2. Model development

We propose a simplified parametric model (supplemental material) consisting of three B-CLL clone populations: one (N_1) sensitive to chemo- and immuno-therapy; two (N_2, N_3), present at low levels at diagnosis resistant to bendamustine-rituximab (BR) and/or ibrutinib. This accounts for initial predominance of a treatment-sensitive clone, common in CLL, and underlying del17p/mutp53 clones conferring resistance to standard therapy. Ibrutinib is recommended when del17p clones predominate at presentation. While we incorporate two resistant clones to permit variation in resistance and growth characteristics, the model is scalable to account for more complex clonal architecture and for therapy-induced changes in clone characteristics.

Our model assumes each clone is present at diagnosis to simulate the actual scenario identified by clonal evolution data [3–7]. The model can be modified to account for treatment-related acquisition of new mutations that also confer resistance. For simplicity, T-cell populations and immune response are omitted. The model factors in a maximum cell number due to competition for nutrients [10,11], i.e. higher cell death rates as cell number increases. We normalize actual time, t, by the inverse of the dominant clonal birth rate, and estimate that each dimensionless time unit, t*, corresponds to 1.5 months of actual time. This estimate derives from measured clonal growth rates of 1.5–1.8% per day [12] in approximate agreement with our previous analysis [8].

The model's fundamental parameter is K*, the ratio of cell death rate to birth rate in untreated cells. K* is modified (K′) when treatments are introduced that reduce cell birth rates, increase cell death rates, or both. Drug-induced killing rates are expressed relative to untreated death rates by parameter K″, assumed to be independent, to first order, of malignant cell death rates (i.e., no "sensitizing" pre-treatment synergies). Key model parameters (supplemental material) are amenable to experimental measurement with *in vivo* models. Parameters derived from experimental data or from individual patients are presumed invariant from the laboratory to the clinic.

3. Results

As an initial approximation we ask at what time (T*) an aggressive drug-resistant (del17p) clone overtakes the drug-sensitive clone. Given the very small relative populations of drug-resistant clones at time

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t* = 0, and subsequent exponential growth, T* has only a weak mathematical dependence on the initial prevalence ratio. Nevertheless, the dependence of the time to recurrence on this ratio has clinical relevance. We estimate that a 2-log reduction in the resistant clone population will translate into an increase in T* of 10 (~15 months) longer time to clinical recurrence (Supplemental Fig. S1). Without therapy ($K_1'' = 0$), if the del17p clonal population does not have a relative growth advantage, it will never become dominant. With effective therapy the drug-sensitive ($K_1'' > 0$) clone N_1 will decrease and the del17p clone population will eventually dominate. As expected, the aggressive del17p clone dominates earlier as its initial prevalence increases, and as the non-del17p clone drug sensitivity increases (larger K''_1). Treating the sensitive clone to achieve a response permits the more resistant clones to flourish earlier.

While ibrutinib decreases clonal birth rates, increasing K′, the model indicates that the del17p clone always overtakes the non-del17p clone at later times unless K′ > 1. Conversely, venetoclax increases malignant cell death rates, also increasing K′, while not affecting cell birth rates. If venetoclax can cause the del17p clone to be equally or more apoptotic than the non-del17p clone, the del17p clone can be controlled even if it is completely resistant to primary therapy. Ibrutinib may also affect cell death [13], and thereby synergize with venetoclax [13]. For illustration, we model adding either agent by doubling the death to birth rate when introduced at various non-dimensional times: t* = 0, 4, 15 and 30, or approximately months 0, 6, 23 and 45, to simulate four clinical scenarios: concurrent with start of bendamustine-rituximab (BR); maintenance starting after BR completion; at molecular detection of recurrence; and at clinical relapse.

If the BR-sensitive dominant clone has the same novel agent sensitivity as del17p clones, there is durable benefit in overall CLL burden, with re-growth of del17p clones delayed for as long as the novel agents are provided, assuming resistance does not develop (Fig. 1A). So, starting novel agents with BR will produce deeper remissions and prolong time to recurrence, however, overall duration of therapeutic benefit may not be altered (Fig. 1B). Unfortunately, some CLL clones are, or become, resistant to the novel agent. Where the chemotherapy-sensitive non-del17p clone is also insensitive to ibrutinib, even with inclusion of ibrutinib in initial therapy, the disease course will mimic the “baseline” computation (Fig. 1A), as if no ibrutinib were added.

Of clinical interest is intrinsic resistance, having low prevalence resistant (del17p) clones undetected at diagnosis [3–5,7,14]. We model this case, treated with BR-ibrutinib, and with one del17p clone resistant to both BR and ibrutinib and having a two-fold growth advantage (Fig. 1B). The dominant population responds, while this clone grows undetected. At relapse the resistant del17p clone dominates. Whether the other del17p clone is sensitive or resistant does not markedly affect clonal dominance. There is little difference in time to disease recurrence comparing BR alone (Fig. 1A) or BR + ibrutinib starting at t* = 0 (Fig. 1B). This is due solely to del17p clone characteristics, despite initial excellent response to therapy.

An alternative scenario is a del17p clone initially ibrutinib–sensitive that later acquires resistance [3–5,7,14]. We model this (Fig. 2) with initial ibrutinib sensitivity (K′ = 1.2), and hypothesize resistance developing after a certain duration of ibrutinib treatment; here after an elapsed time of t* = 15 (~23 months). Starting ibrutinib with BR at t* = 0 (Fig. 2A) yields a deeper response, but regrowth starts at 23 months when resistance develops, becoming molecularly detectable (here defined as 1% original disease burden) at t* ~ 35 (4 years), and clinically apparent at t* ~ 40 (year 5). If initiation of ibrutinib is delayed until CLL becomes molecularly detectable at t* ~ 15 (23 months), largely reflecting the growth of the BR-resistant del17p clone (Fig. 2B), then CLL is controlled until t* ~ 30 (month 45). While the depth of response for a period of time is better, overall results do not differ. This needs to be considered in interpreting early data from trials of immunochemotherapy plus ibrutinib. When we delay the start of ibrutinib further, until t* = 23 (~3 years), at the time of early clinical relapse (Fig. 2C, Suppl Fig. 2), results actually appear superior in terms of durability of disease control, even with resistance developing the same elapsed time after the start of ibrutinib. This is directly testable in clinical trials and, if confirmed, would improve disease control while reducing toxicity and cost.

4. Discussion

It is evident without modeling that resistant clones eventually predominate in relapsed CLL. Models may suggest, however, non-intuitive approaches to delay, or even prevent, that occurrence, improving overall outcomes for some patients with CLL. Even if innovative strategies to use novel agents do not prolong survival, determining the “optimal” time for introduction of these novel agents balances efficacy, toxicity, cost and patient acceptance. Use of novel agents with initial therapy may have early, but not necessarily durable, benefit, while introducing maximum toxicity risk and cost. Patients who harbor a pre-existing ibrutinib-resistant clone will not derive clinical benefit. Waiting until clinical relapse is an acceptable strategy to minimize exposure to ibrutinib, but not without risk, and patients with ibrutinib-sensitive del17p clones would miss the potential benefit of earlier therapy. Starting at the time of molecular detection, or at early clinical relapse as proposed by the modeling, are reasonable, but as yet untested, alternative strategies. A quantitative metric for assessing the

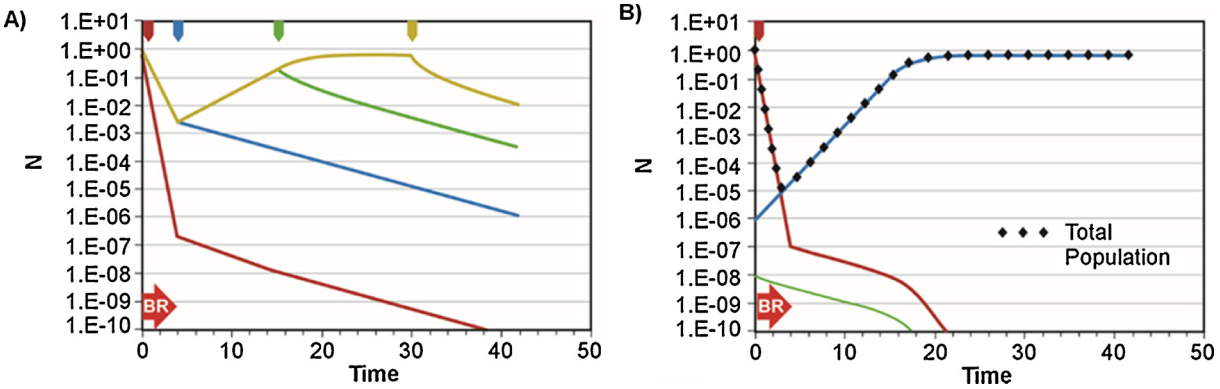

Fig. 1. Panel A. All clones sensitive to bendamustine-rituximab (BR) and ibrutinib. BR therapy from t* = 0–4. Ibrutinib added at t* = 0 (consolidation and maintenance, case 0, red), t* = 4 (maintenance, case 1, blue), t* = 15 (at molecular relapse, case 2, green), or t* = 30 (clinical relapse, case 3, yellow). Each t* unit on X-axis approximates 1.5 months. Panel B. Effect of pre-existing resistant clone. Clone 2 is resistant to BR and ibrutinib; clones 1 and 3 sensitive to BR and ibrutinib. $K'_1 = K'_3 = 1.2$; $K^*_2 = 0.6$; growth advantage for clone 2 indicated by A = 2, the ratio of birth rates. BR sensitivity indicated by K″ = 3 for t* < 4. Total clonal population plotted as black diamonds. Here BR is given as in panel 1A from t* = 0 to t* = 4; ibrutinib is started at t* = 0 and administered continuously, although clone 2 is resistant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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