

CML biology for the clinician in 2011: six impossible things to believe before breakfast on the way to cure

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ABSTRACT

Chronic myeloid leukemia (CML) is a model disease in oncology: it is the first human cancer linked to a distinct chromosomal abnormality, ultimately causing constitutive overactivity of a known oncogenic tyrosine kinase that represents a drug target. The introduction of the tyrosine kinase inhibitor imatinib into clinical practice has far exceeded expectations and resurrected hope that the fundamental insights from the "war on cancer" can lead to significant therapeutic advances. Nevertheless, the current perception among clinicians is that imatinib and its newer more potent cousins offer superb long-term disease control for most patients, but that cure without transplantation has remained elusive. However, several important laboratory-based observations over the last few years have changed those perceptions. Several of those developments are discussed here, including direct manipulation of the apoptosis pathway in cancer cells and prevention of disease progression with the use of antioxidants. Intriguing results from a French study indicate that, if disease progression is halted, a small but significant group of patients may be able to stop imatinib therapy without disease recurrence. And for patients whose disease, because of resistant stem cells, needs a more direct attack than tyrosine kinase inhibitors alone, several approaches investigated in laboratory and animal models seem promising, and some are ripe for clinical testing, including inhibitors of Smoothened and 5-lipoxygenase, and suppression of autophagy. Thus, there is realistic hope that true cure of CML, without transplantation, may be a feasible goal in the near future.

KEY WORDS

Leukemia, stem cells, targeted therapy, tyrosine kinase inhibitor, apoptosis

1. INTRODUCTION

The improvement in clinical outcome for treated patients with chronic myeloid leukemia (CML) arguably represents the most important advance in clinical oncology in the last decade—not only because of the magnitude of the difference (a more than 40% increase in 5-year survival over that with previously available therapies) [1], but also because of the means by which that increase occurred. In this sense, CML represents a model disease for oncology, with the Philadelphia chromosome being the first chromosomal translocation (and therefore genetic defect) identifiable in any human cancer [2]; the first human fusion-activated oncogene, by identification of Bcr-Abl as the translocation product [3]; the first cancer treated with targeted small-molecule therapy (imatinib, beginning in 1999); and the first disease in which a gene-based test to monitor disease bulk became a standard of clinical practice [1]. Other tyrosine kinase inhibitors (TKIs) that are more potent against Bcr-Abl are now available or in development.

Furthermore, the apparent long-term persistence of disease for many years despite excellent control represents the most obvious clinical correlate of the currently dominant, but still controversial, model of cancer stem cell biology, whose explanation for that persistence is the fact that the targeted therapy hits the differentiated progeny of the CML stem cell, which itself is immune to that therapy. Despite the many hidden biological and biochemical cellular complexities, the conceptual simplicity of that model is pedagogically pleasing and can easily be presented to non-oncology colleagues, medical students, patients and their families, and the mass media. However, as the English economist John Maynard Keynes noted, we are all prisoners of our implicit metaphysics, and clinicians are prisoners of the models they carry in their heads of the diseases that they treat.

The present article therefore examines several features of that model and points out where the current understanding of the cell biology and biochemistry of CML and Bcr-Abl indicate that parts of the model may be oversimplified or even wrong. Each of the new insights has implications for the prognosis and therapy of CML (and, by extension, other malignancies).

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Therefore, in the spirit of the Queen of Hearts, who told Alice that she needed to believe six impossible things before breakfast, many recently investigated features of CML biology are reviewed here with the aim of discovering where the science stands in 2011. This brief review is not intended to be exhaustive or complete—but it will focus on recent results that may have near-term clinical application because they involve agents or approaches that are currently available or will soon be undergoing clinical trial. Depending on the reader's degree of adherence to the current model of CML pathophysiology and treatment, the number of surprises presented may or may not exceed the Queen's quota of six.

2. SHUTTING DOWN KINASE ACTIVITY COMPLETELY: IS IT NECESSARY?

Initial characterization of the consequences for cell biology of the *BCR-ABL* fusion oncogene led to the conceptually pleasing notion that the Bcr-Abl product functioned as an autonomously active protein mimicking constant growth-factor signalling to activate many downstream pathways, including the well-characterized Ras pathway. Clinicians were thus presented with an easily identifiable phenotype that used growth factors to drive up white cell numbers. A constitutively active growth factor mimic as a downstream mediator would cause cell numbers to rapidly and persistently increase. Inhibiting that effect with TKIs such as imatinib would reverse the phenotype, but the disease would remain.

However, it is now clear that Bcr-Abl is a node for many different signalling pathways in hematopoietic cells, and that those pathways not only mediate proliferation, but also altered adherence to stroma and inhibition of programmed cell death (apoptosis). It is this latter important notion that has most recently come to the fore, with surprising results from Dr. Neil Shah's lab, where the pharmacodynamic effects of long-acting imatinib were compared with those of short-acting dasatinib [4]. The original clinical dosing for all currently active TKIs in CML was based on the assumption that continuous inhibition of Bcr-Abl was needed to prevent proliferation. It is now clear that the relevant goal is probably not prevention of proliferation (although it occurs as a consequence), but rather the induction of apoptosis. Recent insights from biologic models of the process indicate that, after a variable lag phase, apoptosis is triggered as an all-or-nothing process in a single cell once a threshold is reached, and therefore the threshold does not have to be "breached" continuously [5]. This threshold breaching occurs when antiapoptotic proteins of the Bcl-2 family (such as Bcl-2, Bcl-XL, or Mcl-1) are prevented from binding to the proapoptotic Bcl-2 family members Bax or Bak, which are then free to self-associate and form pores in the outer mitochondrial membrane [6]. This last step is the one that makes the irreversible commitment to cell death.

The process that peels Bcl-2/Bcl-XL off Bax/Bak is the activation of the third class of the Bcl-2 family of proteins (called BH3 proteins), which includes Bim, Bad, Bmf, tBid, and others. These BH3 proteins act as sensors for various types of cell stress, such as growth factor deprivation, DNA damage, loss of intercellular adherence, and many others [6]. Thus the role of growth-factor stimulation—and "fake" growth-factor stimulation (such as Bcr-Abl!)—that works through the Ras and phosphoinositide-3 kinase pathways is to keep those proteins absent or inactive. When kinase activity in the CML cell is switched off with inhibitors such as imatinib or dasatinib, several BH3 proteins are released or activated [7,8]. Furthermore, a rapid shut-off by Bcr-Abl of constitutive phosphorylation of Stat5, which is a key transcriptional upregulator of Bcl-XL, also occurs [4]. The combined effect is therefore to tip the balance in favour of "freed" Bax to kill the cell, and Dr. Shah's work has demonstrated that it is the magnitude of this downstream effect (resulting from a deep, but potentially brief, kinase inhibition) that determines the cell's fate [4]. Because the final decision to die is the result of a "titratable" balance between antiapoptotic proteins such as Bcl-XL and proapoptotic activators such as Bim and Bad (a balance adjusted by kinase inhibition), any direct tipping of the balance in favour of the latter would enhance the effects of TKIs.

That balance is the target of a newly developed class of drugs designed to be BH3 mimetics, some of which, such as navitoclax [9] and obatoclax, are already in phase I/II clinical trials in lymphoid malignancies [10]. Work with CML-like cell lines and patient samples, including putative CML CD34+ CD38– progenitor cells, have demonstrated marked synergy of TKIs and the BH3 mimetics *in vitro* [11], suggesting a promising future for such clinical combinations in markedly enhancing the extent of leukemic cell kill.

3. IS THE CML STEM CELL THAT DRIVES THE DISEASE ISOLATED, PERPETUAL, AND UNASSAILABLE?

Despite the enormous clinical and conceptual strides made by the introduction of TKI therapy in CML, the current clinical consensus is that these drugs represent excellent ways to control, but not to cure, the disease, because they do not affect the behaviour of the stem cell in which the disease started and that represents an ongoing source of new leukemic cells, leading to indefinite disease persistence and risk of progression despite control. The next step is therefore to examine the nature and likelihood of this "indefinite control" and then to ask whether cure, in the conventional sense of the word, is ever possible without transplantation—that is, with the application of TKI therapy by itself or in combination with other drugs that enhance the effect.

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With respect to the nature of indefinite control, the invaluable, well-characterized database from the pivotal IRIS (International Randomized Interferon Versus STI-571) trial of patients with CML treated using TKIs over prolonged periods of time has indicated a diminishing likelihood of progression to blast crisis as time goes on [1]. The current model that best explains these data is that progression actually happens in a target population that is different from, and more mature than, the CML stem cell. In certain instances at least, the cellular target for the transforming event during myeloid blast crisis has been identified as a granulocyte–macrophage progenitor. Elegant work by Catriona Jamieson has indicated that the mediator of this transformation is the acquisition of unregulated beta-catenin activity in this specific cell type that now makes it behave like a stem cell, with indefinite self-renewal capacity and the decreased differentiation that gives it the myeloid blast phenotype [12]. The most recent work from her laboratory has identified a potential molecular mediator of this upregulation, with aberrant splicing of *GSK3B,* a loss-of-function mutation that prevents the physiologic degradation of beta-catenin by the proteosome [13]. The ultimate cause of this abnormal splicing that ultimately leads to myeloid blast crisis is still under investigation. It is thought that the transformation itself is directly or indirectly a result of mutagenesis mediated by reactive oxygen species (ROS) that are a consequence of overactive kinase activity caused by Bcr-Abl. Experiments at the laboratory of Dr. Tomas Skorski showed that this ROS-mediated mutagenesis is also associated with deficient DNA repair that, together, yield the genomic instability of untreated CML [14]. Skorski and others also showed that inhibition of kinase activity by TKIs inhibits ROS generation, with the clinical consequence that mutagenesis should decrease in frequency. In addition, as treatment with TKI progresses, it is theoretically possible that the actual target population in which a transforming mutation such as beta-catenin activation would lead to myeloid blast crisis (granulocyte–macrophage progenitor for myeloid blast crisis, common lymphoid progenitor for lymphoid blast crisis) decreases to the extent that the chance of it occurring within the individual's lifetime would be vanishingly small. Therefore, in a subpopulation of patients, true indefinite disease control that would be functionally equivalent to cure is a possibility, at least with ongoing therapy. However, as pleasing as that outcome may be for at least a proportion of patients, evidence is now increasing that the controversial proposition that TKIs (plus or minus other medications) may cure CML is now an achievable reality.

A powerful counter-argument to such optimism is found in a mathematical model from the Harvard evolutionary dynamics group [15]. The data used to test the model reflected the decline in *BCR-ABL* transcripts precisely measured in patients on the IRIS trial. The model makes the assumption that the small stem-cell fraction slowly and continuously expands during treatment, even as the more differentiated progeny that are readily detectible die. Because their model fits the clinical IRIS data, the assumption of stem cell invulnerability to TKIs was taken to be correct "as demonstrated." However, another mathematical model proposed by a group in Leipzig [16] fits the IRIS clinical data just as closely, but makes other assumptions: namely, that the CML stem cell occupies a specific kinetic niche in a competitive fashion and that the prevention of the expansion of this stem cell pool by TKIs will not permit it to continue to compete for that niche [16]. As a clinical consequence, this latter model predicts that provided a mutation-causing blast crisis or resistance to TKI does not develop (as discussed earlier), the CML stem cell population will just slowly peter out. When this model was proposed, it was looked at with great skepticism in the clinical community; however, more recent data from a select group of patients with well-controlled disease who have stopped their therapy under close monitoring have given early indications that, for at least a proportion of patients, disease eradication may be feasible. Several groups are trying this approach, with a French group being the largest and having the longest follow-up [17]. Their trial, STIM (the Stop Imatinib trial), has allowed patients who, by the most sensitive molecular techniques, have shown no detectible disease for a 2-year period to stop therapy in conjunction with frequent monitoring. Interestingly, the Harvard and the German models both predicted that any relapses would occur within a period of approximately 6 months. However, in approximately half the patients studied, it appears that the disease has not recurred over time intervals varying between 6 and 24 months. The risk of relapse seems to be slightly increased in patients who did not receive interferon therapy before the imatinib, but the proportions were not significantly different in these two subgroups, at least at early analysis, indicating that, contrary to earlier preliminary reports from the same group, prior interferon therapy is not required for a disease-free state to persist off-therapy [18]. Longer-term follow-up on this intriguing trial is anxiously awaited.

4. IF TKIs CANNOT CURE BY THEMSELVES, CAN WE OFFER THEM HELP?

If long-term inhibition of Bcr-Abl by effective TKIs still does not cure the disease (even if resistance is prevented and the direct downstream effects are enhanced by BH3 mimetics), these drugs may nevertheless be the backbone of combination therapy when added to agents that specifically target a CML stem cell that is potentially resistant to TKI alone. Over the past few years, several intriguing reports in the literature have indicated a differential susceptibility

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between normal stem cells and CML stem or precursor cells in animal models or from patients.

On the one hand, tantalizing evidence from a murine CML transplant model suggests that the CML stem cell may require a physical niche that is different from that for normal stem cells and therefore therapeutically exploitable. Richard Van Etten's group demonstrated both with antibodies and with knockout mice that the cell adhesion molecule CD44A is required for engraftment of a model CML, but not for engraftment of normal bone marrow [18]. Given that anti-CD44 antibodies potentially capable of exploiting this differential sensitivity are currently in preclinical development, that group's discovery may represent an exciting new therapeutic avenue [19].

On the other hand, several groups have also identified intrinsic cellular factors that are required for CML initiation or propagation and that may also be differentially expressed or required in CML stem cells compared with normal stem cells. One of the newest results involves one of the oldest drugs. A high-profile publication has delineated a complex effect of interferon on normal stem-cell proliferation: promotion of cell-cycle entry with short-term administration that turns into prevention of cell cycling with chronic administration [20]. That publication did not study CML stem cells; nevertheless, despite uncertainty about the exact mechanism or timing of administration, the independent activity of interferon against CML has prompted at least four national trials in Europe to investigate the combination of interferon and imatinib in newly diagnosed patients. Getting the right dosing schedule to avoid treatment delays for toxicity has been a bit tricky, but the preliminary results seem to indicate that in patients who can tolerate treatment, the response is deeper and faster. These results have prompted newer trials looking at lower-dose interferon to mop up the residual stem cells after an imatinib "induction," with the hope that the sequence will eradicate CML stem cells [21].

There are also many indications that combinations of TKIs with newer agents may lead to significant advances in eliminating CML stem cells. Two separate groups have demonstrated in murine models that Hedgehog signaling is required for the maintenance and expansion of stem cells positive for Bcr-Abl [22,23]. Both of these elegant experiments used knockout mice to demonstrate that the downstream mediating target of Hedgehog, Smoothened (SMO), is required for the development of Bcr-Abl–induced CML. The SMO knockout did not affect normal hematopoiesis, and an exciting extension of this work by both labs indicates that administration of the SMO inhibitor cyclopamine inhibited growth both in the murine models and in patient samples from long-term *in vitro* cultures. Cyclopamine is too toxic to be administered as a drug to patients, but several SMO inhibitors are already advanced in clinical development because of the interest in this pathway, which is critical for other malignancies such as basal cell carcinoma and glioblastoma. The newer drugs also show synergy with TKIs against CML progenitor cells from *in vitro* patient cultures. Preliminary indications are that no major safety concerns are connected with these agents, and so combination therapy with TKIs for selected groups of patients may be feasible relatively soon.

Another potential intracellular target susceptible to drug treatment has been revealed by the laboratory of Dr. Pandolfini [24]. This group's studies were motivated by the observation that CML patients had a worse prognosis with higher expression of the nuclear factor PML, well known to hematologists in the context of the PML RAR-alpha translocation in acute promyelocytic leukemia (APL). Using patient samples and a mouse model, these workers demonstrated that degradation of PML by arsenic trioxide retards the self-renewal of CML stem cells. Because arsenic trioxide is currently in clinical use for the treatment of APL, their finding may represent a chance to add an easily testable agent to TKI. However, particular attention would have to be paid to toxicity of the combination, because both agents can prolong the QT interval.

Both of the foregoing approaches use a tactic of finding differentially expressed pathways in CML stem cells that are required for their self-renewal; another tactic is to try to find something that enhances the killing of TKIs such that CML stem cells are included, as with the use of BH3 mimetics already described. Exciting progress along those lines has been made as well. Recent investigations have demonstrated that the autophagy pathway, a current hot topic in cancer cell death, is activated as cells try to salvage themselves from apoptosis. When both pathways are circumvented, regulated necrosis occurs, with rapid cell death. This escape route appears to be relevant in CML progenitor and stem cells from patients, such that exposing them to imatinib caused them to turn on the autophagy pathway and achieve at least some cell survival [25]. In combination with imatinib, inhibition of autophagy by chloroquine (a currently available drug) resulted in significantly increased cell death even if primitive and progenitor cells were otherwise resistant to imatinib because of *BCR-ABL* point mutations [25]! A clinical trial using this combination of therapy in patients having a good but incomplete preliminary response to imatinib alone is about to start in the United Kingdom.

As a clear indication of the fact that one never knows under which stone gold may be found, a recent report has indicated that, in a mouse model, the enzyme 5-lipoxygenase, which is involved in leukotriene biosynthesis, is a required pathway to maintain CML stem cells, but not necessarily normal stem cells [26]. A drug that specifically targets this enzyme is currently used (and is well tolerated) in the treatment of asthma, and so tests of a combination therapy directed at the CML stem cell and Bcr-Abl may be feasible and practical.

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Finally, the laboratory of Dr. Tessa Holyoake in Glasgow has pioneered extensive investigations into potential agents that could directly cause cell death (rather than prevent self-preventing self-renewal) in quiescent CML stem cells. She identified a compound previously investigated as a farnesyl transferase inhibitor (FTI) as a novel therapeutic agent. The experiments demonstrated direct induction of apoptosis in CML stem and progenitor cells from patients, regardless of their responsiveness to imatinib; synergy when added to imatinib; and relative lack of toxicity when tested on normal hematopoietic stem cells [27]. Intriguingly, those effects do not require the FTI activity, because a closely related congener that is equally active as an FTI lacks those effects, suggesting that activity against some other target (which might still require FTI as a partner) is doing the job [27,28]. Preliminary evidence indicates that this new compound works by upregulation of protein kinase C beta activity, leading to apoptosis, because inhibition of that activity abrogated the effect of the new drug [28]. Work on identifying the relevant target and enhancing the unique property has been somewhat slowed because the drug's patent has migrated from one pharmaceutical company to another, but hopes are high that applications will be found not only against CML, but also against other cancer stem cells.

5. SUMMARY

The novel and exciting avenues being pursued in the attempt to get at the CML stem cell are many, if that cell cannot simply be exhausted by long-term ongoing and effective Bcr-Abl inhibition. Although all the experiments so far have been based on *in vitro* or mouse models (or both), the multiple points of attack give hope that at least one will be effective, and that true cure of CML without an allogeneic transplantation is a realistic hope within the next decade, if not sooner.

6. CONFLICT OF INTEREST DISCLOSURES

BL is a member of the medical advisory boards and speakers' bureaus for Novartis Canada and Bristol–Myers Squibb Canada.

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