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CHRONIC MYELOID LEUKEMIAS (G SAGLIO, SECTION EDITOR)

What Does Chronic Myeloid Leukaemia Tell Us About Other Leukaemias?

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Abstract
Purpose of Review Determine if therapy of chronic myeloid leukaemia (CML) is a model for treating other cancers.
Recent Findings CML has a relatively homogeneous phenotype and genotype and is caused by one mutation, *BCRABL1*, in every instance. In contrast, most other leukaemias, haematologic cancers and solid cancer have more heterogeneous phenotypes and extraordinarily greater genotypic diversity and mutational complexity.
Summary Lesions learned from treating CML have little applicability to other leukaemias, haematologic cancers or solid cancer.

Keywords Chronic myelogenous leukaemia · Tyrosine kinase-inhibitor therapy · TKI-therapy · Therapy-free remission · Acute myeloid leukaemia · Leukaemia stem cell

Introduction

There is substantial progress treating chronic myeloid leukaemia (CML) with tyrosine kinase-inhibitors (TKI). In several, but not all studies, persons with CML are reported to have a life-expectancy like normals without CML. [1–4]. Moreover, about 20% of persons with CML can stop TKI-therapy without leukaemia recurrence for a substantial interval (for example, [5]). At least some of these persons can be consider operationally cured but this is controversial. [6]. These data raise the question of to what extent lessons learned from treating CML with TKIs apply to other leukaemias and haematologic cancers and solid cancers.

The Answer

Not much. Chronic myeloid leukaemia (CML) is unique leukaemia in several aspects. First, one mutation (*BCRABL1)* is all that is necessary to cause the disease and second, everyone with CML has a similar mutation and gene product with only slight variations (reviewed in [7, 8]). Transfecting mice with a human cDNA to BCRABL1 mRNA produces a disease resembling CML in humans. [9]. Contrast to this, for example with acute myeloid leukaemia (AML) where the average person has 13 mutations and where the mutation topography of every person differs [10].

Most persons with *BCRABL1* in a cell with the biological capacity to cause leukaemia have or will develop CML. Although some normal persons are reported to have BCRABL1 transcripts, this does not mean the cell(s) transcribing *BCRABL1* have the biological ability to cause CML. For example, a fibroblast with *BCRABL1* has the mutation but lacks the biological capacity to cause CML.

It is often said CML is a model for cancers in general and leukaemia specifically. We disagree. CML is a relatively homogeneous cancer. The phenotype and genotype of CML are relatively consistent compared with other cancers, say lung, prostate or breast [11–13]. There is, of course heterogeneity in CML. In the pre-tyrosine kinase-inhibitor era, some persons had a chronic phase of < 1 year whereas in others, it was > 20 years. However, this discordance can be explained if we consider transition from chronic to acute phase a stochastic process with a relatively constant risk of 5–15% per year [14]. Interestingly, and often mis-understood, time is never really running out on a person with chronic phase CML: Actuarial risk of transformation to acute phase remains constant

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regardless of the interval from diagnosis. It is simply that there are fewer persons remaining at-risk. So even if you have had chronic phase CML for 15 years, risk of transformation to acute phase in the next year is the same as at diagnosis. Recently, mutations in epigenetic genes were described in persons with CML [15, 16]. Whether these additional mutations explain the limited heterogenicity of CML is controversial and a stochastic model for transformation to acute phase seems equally likely.

There has been extraordinary success in treating CML. This derives from the fact everyone with CML has the same abnormal $P210^{BCRABL1}$ protein encoded by *BCRABL1* (reviewed in [17]). The tyrosine kinase activity of $P210^{BCRABL1}$ causes CML, and inhibiting kinase activity reverses much of the phenotype of CML and delays transformation to acute phase. Several tyrosine kinase-inhibitors (TKIs) are active against $P210^{BCRABL1}$ and prolong probability of progression to acute phase and survival. These drugs have different efficacy and safety profiles against $P210^{BCRABL1}$ but their overall effects are mostly similar.

One might consider chronic phase CML a preleukaemia rather than a leukaemia. Although the mass of myeloid cells is markedly increased in chronic phase CML, cells respond to normal regulatory signals such as infection, myeloid growth factors (granulocyte and granulocyte/macrophage stimulating factors [G- and G/M-CSFs]; filgrastim and sargramostim) and cycle as in persons with cyclic neutropenia. These are fundamentally normal granulocytes; there are simply too many of them which can be explained by a few too many cell divisions before a myeloblast becomes a granulocyte and dies. This contrasts with the differentiation block typical of AML of which acute progranulocytic leukaemia is an example. Other examples are *IDH1* and *IDH2* mutations (see below).

An important lesson in CML is it is not necessary to eradicate the cell in which CML originates to *cure* CML[1] (reviewed in [18]). About one-half of persons with CML achieving a sustained > 4 log-reduction in BCRABL1 transcripts can stop TKI-therapy without leukaemia recurrence for several years (reviewed in [5, 6]).

In some ways, this situation mimics AML. For example, about one-half of young persons with AML are cured by a few courses of cytarabine and an anthracycline, typically daunorubicin followed by 1–2 course of high-dose cytarabine. This therapy which has no specificity for AML compared with normal stem cells can be effective. This again suggests many aspects of leukaemia recurrence are stochastic.

As discussed, although almost everyone with CML, at least initially, responds to one class of drugs (TKI-inhibitors). This differs in part from AML. For example, although it was common to give the same induction therapy to all (appropriate) persons with AML, typically cytarabine and an anthracycline, this has changed. For example, persons with acute progranulocytic leukaemia now receive instead arsenic and all-trans retinoic acid.

Others with specific mutations such as *FLT3, IND2* and *IDH1* receive midostaurin or gilteritinib, enasidenib or ivosidenib (reviewed in [19, 20]). However, in contrast to TKIs in CML, these so-called targeted therapies are unlikely to cure persons with AML. This difference results from the mutational complexity of AML compared with CML.

As discussed above, one way to compare CML and AML is to think of chronic phase CML as a *preleukaemia* and acute phase as leukaemia. This contrasts with AML where there is no detected preleukaemia phase in at least one-half of people.

Recently, conditions variously termed age-related clonal haematopoiesis (ARCH) or clonal haematopoiesis of indeterminate potential (CHIP) were described (reviewed in [21]). One might think of these as the parallel of chronic phase CML. However, there are important differences.

For example, before TKI-inhibitor therapy, almost everyone with chronic phase CML progressed to acute phase. This is not so of age-related clonal haematopoiesis (ARCH and CHIP) where progression to a haematological disorder is generally rare. Moreover, everyone with chronic phase CML has the same mutation, *BCRABL1,* whereas persons with ARCH and CHIP have one or more mutations, typically in epigenetic control genes such as *DMT3A*, *TET2* and *IDH1* or-*IDH2*.

The implication of these diverse biologies to therapy of AML is considerably more complex than that of CML. Although it is often said CML is a model of AML, we think not. The challenge of curing AML is far more complex. We have progress but the road is arduous.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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[1] By cure we mean having a life-expectancy like age- and sex-matched persons without CML.

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