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Molecularly targeted therapy in myeloid leukaemias

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Until recently it was difficult to detect the impact of recent advances made in the understanding of the biology of leukaemogenesis on the treatment of the myeloid leukaemias. However, in the past five years the therapeutic benefits which can flow from advances in basic biomedical research have been conclusively demonstrated by the remarkable clinical activity of imatinib, a small molecule inhibitor of the *BCR-ABL* tyrosine kinase fundamental to the pathogenesis of chronic myeloid leukaemia (CML). This has provided a model for the development of novel therapies in acute myeloid leukaemia (AML).

Targeted therapy in chronic myeloid leukaemia

CML is a myeloproliferative disease which typically presents with a high white count, splenomegaly and constitutional symptoms. Its natural history is to evolve within three to five years from a chronic phase (CP) into an advanced stage (accelerated phase or blastic transformation) which is usually rapidly fatal.[1] The presence in over 95% of patients of the Philadelphia (Ph) chromosome, characterised cytogenetically by the presence of a reciprocal translocation between chromosomes 9 and 22, led to the identification of the *BCR-ABL* fusion gene, the molecular hallmark of CML. The *BCR-ABL* oncogene is a constitutively activated tyrosine kinase with the capacity to transform haematopoietic cells *in vitro* and in mouse models through its ability to activate downstream pathways which confer increased proliferation, decreased growth factor independence and reduced apoptosis on haematopoietic progenitors. Consequently, *BCR-ABL* represents an attractive therapeutic target in CML.

Imatinib

Pioneering work in the 1990s by medicinal chemists identified imatinib mesylate as an oral inhibitor of *BCR-ABL* which acts through its ability to bind in the region of the ATP binding site of the BCR-ABL protein.[2] Imatinib is able to induce selective cytotoxicity of *BCR-ABL*-positive leukaemic cell lines; this has led to its rapid introduction into clinical practice where it has shown remarkable activity in patients with CML.

Earlier therapies

Treatment options in CML before the development of imatinib were limited to the long-term administration of interferon (IFN) alpha or allogeneic stem cell transplantation. IFN was in many ways a spectacularly ineffective therapy which combined toxicity with lack of activity in most patients. However, a minority of patients (ca 15%) achieved a complete cytogenetic remission (CCR), defined as the absence of Ph+ve metaphases in a bone marrow aspirate. Importantly, such patients demonstrated markedly improved survival, supporting the notion that elimination of the Ph+ clone from the bone marrow could be used as a surrogate marker of improved survival.[3] Allogeneic transplantation remains an important curative procedure in younger patients with an available sibling or unrelated donor, and is the only treatment with the proven ability to produce long-term disease-free survival in patients with CML.[4] The lack of activity of IFN alpha in most patients and the toxicity of transplantation meant that the great majority of patients with CML had no effective treatment option until the development of imatinib.

Treatment with imatinib

The demonstration in 1999 of the ability of imatinib to induce haematological and cytogenetic remissions in patients who had failed to respond to IFN alpha

or whose disease had progressed to the accelerated or blastic phase rapidly led to its study as a new treatment option for patients in early CP.[5,6] A recent five-year follow-up of patients treated in early CP has confirmed its remarkable clinical activity, with 98% of patients achieving a haematological remission and 87% CCR (Fig 1).[7] As a result, imatinib (400 mg daily) has become the treatment of choice for almost all patients with newly diagnosed CML.

In contrast to allogeneic transplantation, where most patients achieve molecular remission, persistent leukaemia (as demonstrated by real-time polymerase chain reaction detection of residual *BCR-ABL* transcripts) is evident in all but 7–10% of patients treated with imatinib. This led to concerns that the durability of haematological and cytogenetic responses to imatinib might be short. This has proved to be the case in patients with advanced phase disease, but responses in early CP are durable in the great majority of patients. As a result, imatinib is now the treatment of choice in almost all patients with newly diagnosed CML. As a result allogeneic transplantation is generally agreed not to be indicated as first-line therapy in newly diagnosed patients with CML.

Accumulating experience with imatinib has shown approximately 30% of patients either fail to tolerate imatinib or demonstrate primary or acquired resistance.[8] A significant number of patients experience peri-orbital oedema, cytopenias (typically reversible neutropenia and thrombocytopenia) or gastrointestinal side effects (nausea or altered bowel habit). These are usually tolerable but, together with other rarer side effects such as hepatoxicity, can preclude long-term use of this agent in about 10% of patients.

Primary imatinib resistance manifests as failure to achieve either a haematological remission or, more commonly, a major response or CCR in a timely fashion. Current definitions of primary imatinib resistance include failure to achieve either a major cytogenetic response (<35% Ph+ve metaphases) within 12 months of commencing imatinib or a CCR within 18 months (Table 1).[9] Acquired resistance manifests as loss of a previously acquired cytogenetic or haematological response. Consequently, all patients treated with imatinib require monitoring three-monthly, with assessment of the proportion of Ph+ metaphases in the bone marrow until a CCR is achieved, and thereafter quantitation of *BCR-ABL* transcript numbers in the peripheral blood.[10] In many patients imatinib resistance is consequent on the acquisition of mutations in the ATP binding domain of the *BCR-ABL* oncogene which interfere with the binding of imatinib. A proportion of them may respond to an increased dose of imatinib (600 mg daily) but such responses are often of short duration.

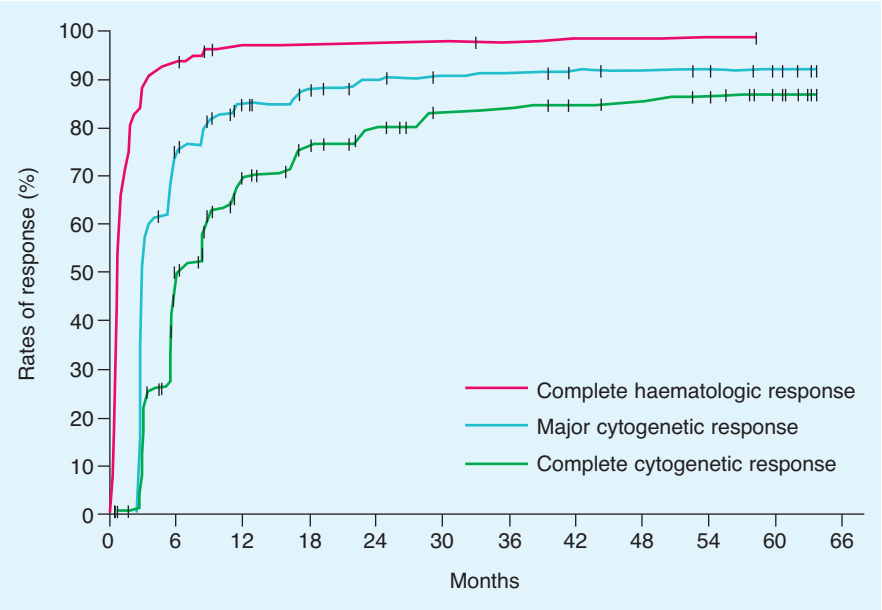

Fig 1. Kaplan-Meier estimates of cumulative best response to imatinib treatment in newly diagnosed patients with chronic myeloid leukaemia. Copyright © 2007 Massachusetts Medical Society. All rights reserved.[7]

Table 1. Operational definition of treatment failure for patients with newly diagnosed chronic myeloid leukaemia treated with imatinib (400 mg daily). This research was originally published in *Blood* © American Society of Hematology.[9]

Time (months)	Criteria for failure
3	No haematological response
6	Less than complete haematological response Ph+ >95%
12	Less than major cytogenetic response
18	Less than complete cytogenetic response

Second-generation tyrosine kinase inhibitors

The development of second-generation tyrosine kinase inhibitors, dasatinib and nilotinib, which display 100–400 times greater ability to inhibit the kinase activity of *BCR-ABL*, provides an important new therapeutic option for patients with imatinib resistance or intolerance. Dasatinib and nilotinib show minimal cross-reactivity in imatinib intolerant patients; both agents have the ability to induce haematological remissions in over 50% of resistant patients – with approximately 30% achieving a CCR.[11,12] Both dasatinib and nilotinib are associated with a significant risk of cytopenias which usually resolve on treatment interruption. There is also a small but distinct risk of pleural and pericardial effusions with dasatinib.

In patients with an available donor, allogeneic transplantation is also an important consideration in patients with imatinib resistance. Furthermore, the advent of reduced intensity conditioning regimens has increased the prospect of

extending the potentially curative effect of allogeneic transplantation to older patients in whom transplantation was previously contraindicated on the grounds of age or comorbidity.

Targeted therapy in acute myeloid leukaemia

The clinical activity of imatinib in CML raised hopes that a similar targeted strategy may be effective in AML. The outcome for children and young adults with AML has improved over the last two decades, but disease-free survival rates in patients over the age of 50 are below 20%. A notable exception has been the effectiveness of all-*trans* retinoic acid in combination with conventional chemotherapy in the rare acute promyelocytic leukaemia (APML). The failure of current therapeutic strategies, particularly in older adults, reflects the fact that non-APML AML is a complex and molecularly heterogeneous disease complicating rational drug design.

Novel pharmacological therapies

Targeting epigenetic change. The growing realisation that acquired abnormalities of chromatin structure are an important mechanism underlying the pathogenesis of AML has led to the development of a number of therapeutic strategies designed to target epigenetic abnormalities. At present, the two most interesting classes of drug are histone deacetylase inhibitors (HDI) and demethylating agents. Importantly, a number of recent phase 2 studies have demonstrated clinical responses to sodium valproate and demethylating agents such as 5-azacitidine and decitabine in patients with high risk AML.[13] In view of the intimate relationship between changes in histone acetylation and DNA methylation, there has been considerable interest in the antileukaemic activity of combined treatment with an HDI and a demethylating agent. Preliminary reports suggest this is a potentially valuable therapeutic strategy, with response rates in the region of 20–30% in patients with relapsed AML.

Inhibitors of tyrosine kinase and RAS pathway. Mutations in the tyrosine kinase *FLT3* are present in up to 30% of adults with AML and associated with a decreased overall survival. Currently, a number of small molecule *FLT3* inhibitors have entered clinical trials in patients with relapsed AML. When administered as monotherapy responses are uncommon and of short duration,[14] but there is interest in the possibility of administering an *FLT3* inhibitor such as CEP-701 and PKC412 in combination with salvage chemotherapy in patients with relapsed or newly diagnosed AML. Mutations of *RAS* oncogenes have been identified in up to 25% of patients with AML and the activity of farnesyltransferase inhibitors is currently being studied in patients with high risk AML.[15]

Conclusions

Chronic myeloid leukaemia provides an exemplary model of how an understanding of the molecular basis of leukaemogenesis can be translated into new and outstandingly effective therapies. The availability of second-generation *BCR-ABL* tyrosine kinase inhibitors has further extended treatment possibilities and mandates the use of molecular monitoring of minimal residual disease levels as part of the standard care of a patient with CML.

In contrast, the molecular complexity of AML has made the introduction of effective targeted therapies considerably more challenging. With the availability of agents which can target the dysregulated signalling pathways and acquired abnormalities of chromatin structure documented in AML, the results of targeted therapies, alone or in conjunction with conventional chemotherapy or allogeneic transplantation, are keenly awaited.

Key Points

- **The tyrosine kinase inhibitor imatinib is now standard of care for newly diagnosed patients with chronic myeloid leukaemia (CML)**
- **A second-generation tyrosine kinase inhibitor, such as dasatinib or nilotinib, is indicated in patients with imatinib resistance or intolerance**
- **Allogeneic stem cell transplantation remains an important, potentially curative treatment in CML and should be considered in eligible patients with imatinib resistance**

KEY WORDS: acute myeloid leukaemia, chronic myeloid leukaemia, targeted therapy, tyrosine tinase inhibitor

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