Visual Guide for Clinicians

CHRONIC MYELOID LEUKAEMIAS

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CLINICAL PUBLISHING
OXFORD
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Abbreviations

aCML  atypical chronic myeloid leukaemia
ALL  acute lymphoblastic leukaemia
AML  acute myeloid leukaemia
CCyR  complete cytogenetic response
CD  cluster of differentiation
CML  chronic myelogenous leukaemia
CMML  chronic myelomonocytic leukaemia
CNL  chronic neutrophilic leukaemia
CRR  complete remission rate
CyR  cytogenetic response
EFS  event-free survival
FAB  French–American–British (classification)
FISH  fluorescence in situ hybridization
FSC  forward scatter (of light)
GM-CSF  granulocyte-macrophage colony-stimulating factor
H&E  haematoxylin and eosin
HLA-DR  human leucocyte antigen DR
ITD  internal tandem duplication
JMML  juvenile myelomonocytic leukaemia
M CyR  major cytogenetic response
MDS  myelodysplastic syndrome/syndromes
MDS/MPN  myelodysplastic/myeloproliferative neoplasm
MGG  May–Grünwald–Giemsa
MMR  major molecular response
MPN  myeloproliferative neoplasm/neoplasms
NK  natural killer
ORR  overall response rate
OS  overall survival
PCR  polymerase chain reaction
PEG  polyethylene glycol
PFS  progression-free survival
Ph  Philadelphia
RQ-PCR  real-time quantitative PCR
SCT  stem cell transplantation
SSC  sideways scatter (of light)
TKD  tyrosine kinase domain
TKI  tyrosine kinase inhibitor
WBC  white blood cell count
WHO  World Health Organization

We should like to acknowledge the generous help of colleagues who provided illustrations – Professor Daniel Catovsky, Mr Ricardo Morilla and Mr John Swansbury (Royal Marsden Hospital, London), Professor Letizia Foroni, Dr Gareth Gerrard and Ms Philippa May (Imperial College and Imperial College Healthcare NHS Trust, London), Dr Francisco Cervantes (Clinic Hospital Universitari, Barcelona), and Dr Helen Wordsworth and Mr Ross Brookwell (Sullivan and Nicolaides Pathology, Brisbane).

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Normal haemopoiesis

In the adult, normal haemopoiesis occurs predominantly in the bone marrow, although haemopoietic stem cells circulate in the blood stream and the potential for haemopoiesis in liver, spleen or other tissues is retained. All blood cells are derived ultimately from a pluripotent haemopoietic stem cell, able to give rise to lymphoid and myeloid lineages [1]. The pluripotent stem cells are capable not only of renewal but also of generating multipotent myeloid stem cells and common lymphoid stem cells (Fig. 1.1). The multipotent stem cell gives rise in turn to committed progenitor cells from which cells of the major myeloid lineages are derived. Differentiation and maturation are controlled by a variety of cytokines which are to some extent specific for particular cell lines. In addition, the microenvironment and accessory cells such as fibroblasts, osteoblasts and fat cells have a role in the differentiation and maturation of stem cells. Cells of haemopoietic origin include mast cells and osteoclasts.

Figure 1.1 A diagram of the stem cell hierarchy and myeloid and lymphoid differentiation pathways. Abbreviation: NK, natural killer.
The nature of leukaemia and leukaemogenesis

Leukaemia may be viewed as a cancer of the blood and derives its name from the German term, *leukämie*, coined by Rudolf Virchow in 1848 and meaning ‘white blood’, from the Greek λευκός – leukos, white and αἷμα – haima, blood. Although initially recognized as a disease affecting the blood, leukaemia is in fact a disease that usually originates in the bone marrow. Leukaemia arises by an acquired somatic mutation in a single cell, giving that cell and its progeny some advantage over normal polyclonal cells, which are gradually replaced by leukaemic cells. In common with other neoplasms, leukaemia can thus be viewed as an acquired genetic disease in the sense that it results from genetic alteration in the cell that gives rise to the leukaemic clone. The host immune response also has a role in disease development, since the body’s immune response includes some ability to recognize tumour cells and destroy them.

Myeloid neoplasms arise by mutation of a haemopoietic stem cell or a progenitor cell that has acquired stem cell characteristics (Fig. 1.2). Many neoplasms, including most types of acute myeloid leukaemia (AML) and the myelodysplastic syndromes (MDS), arise from a mutated multipotent stem cell. It is possible that some subtypes of AML arise by mutation of a committed progenitor cell without the capacity to differentiate into cells of erythroid or megakaryocyte lineages. Some chronic myeloid leukaemias arise from mutation in a pluripotent stem cell so that at one stage of the disease the leukaemia may manifest itself as a lymphoid leukaemia or lymphoma. This is true of Philadelphia (Ph)-positive chronic myeloid leukaemia associated with a *BCR-ABL1* fusion gene (in which B-lineage and less often T-lineage blast transformation can occur) and of *PDGFRA*- and *FGFR1*-related neoplasms, which at various stages of the disease may be manifest as chronic eosinophilic leukaemia, T-lineage lymphoblastic leukaemia/lymphoma, B-lineage lymphoblastic leukaemia/lymphoma or AML.

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**Figure 1.2** A diagram of the stem cell hierarchy and myeloid differentiation pathways showing the cell in which the causative mutation appears to occur in various haematological neoplasms. Abbreviations: AML acute myeloid leukaemia; CML chronic myeloid leukaemia; MDS myelodysplastic syndrome(s); MPN myeloproliferative neoplasm(s).
Classification of haematological neoplasms

Classification of haematological neoplasms is moving from a period when the basis was clinicopathological features, including morphology and, to a lesser extent, immunophenotype, to a period when definitions are based, as far as possible, on identified molecular abnormalities. Although certain syndromes are defined mainly by the genetic abnormality, this must be interpreted in the light of the clinicopathological features. Thus, the BCR-ABL1 fusion gene resulting from t(9;22)(q34;q11.2) is the hallmark of chronic myelogenous leukaemia (CML), but it can also be observed in acute lymphoblastic leukaemia (ALL) and, uncommonly, AML. Similarly, t(15;17)(q22;q12) is the hallmark of acute promyelocytic leukaemia, including its variant form, but can be observed, albeit rarely, in transformation of CML. The conditions that are defined largely on a molecular basis are CML and the group of neoplastic conditions resulting from rearrangement of PDGFRA, PDGFRB or FGFR1. A second group of disorders are currently defined on the basis of clinicopathological/morphological features supplemented by cytogenetic/molecular genetic information. This applies to AML, MDS, polycythaemia vera, essential thrombocythaemia, primary myelofibrosis, systemic mastocytosis and juvenile myelomonocytic leukaemia (JML). There remains a third group of disorders where the disease definition is essentially based on clinicopathological/morphological features, even though relevant cytogenetic/molecular genetic abnormalities are sometimes found. At present, chronic myelomonocytic leukaemia (CML) and atypical chronic myeloid leukaemia (aCML) fall into this group.

Myeloid neoplasms have been classified by various expert groups under the aegis of the World Health Organization (WHO), as shown, in simplified form, in Table 1.1 (overleaf). It will be seen that various types of chronic myeloid leukaemia are assigned to three broad groups: myelo-proliferative neoplasms (MPN); myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1; myelodysplastic/myeloproliferative neoplasms (MDS/MPN).

Terminology of chronic myeloid leukaemias

It is important to have unambiguous names for specific disease entities. Unfortunately this has not been achieved for the chronic myeloid leukaemias, since the term ‘chronic myeloid leukaemia’ is used both as a generic term for all chronic myeloid leukaemias (analogous with the use of the term acute myeloid leukaemia), and also as a term to designate specifically Ph-positive, BCR-ABL1-positive chronic myeloid leukaemia. Alternative designations – chronic myelogenous leukaemia (the preferred WHO terminology) and chronic granulocytic leukaemia, are unambiguous referring only to this specific entity. It should also be mentioned that ‘atypical chronic myeloid leukaemia’ does not refer to a case of chronic myelogenous leukaemia with atypical features, but rather to a different disease that is Ph- and BCR-ABL1-negative.

Oncogenic mechanisms

Oncogenic mechanisms differ between the acute and chronic myeloid leukaemias. The essential difference between the genetic events in the two groups of disorders is that in the chronic myeloid leukaemias and other MPN, mutation results in an expanded clone of proliferating cells able to differentiate into functional end cells of one or more myeloid lineages; whereas, in AML, cells continue to proliferate but are mainly unable to differentiate to end cells.

Mutations in myeloid malignancies include novel fusion genes and mutated genes. Fusion genes can result from a translocation, inversion, insertion or cryptic deletion. Mutated genes may harbour a point mutation, a partial duplication, or a small insertion or deletion that alters the reading frame. Genes can be triplicated as the result of trisomy. Genes can be amplified (multiple copies) in double minute chromosomes or in homogeneously staining regions within chromosomes. There can also be epigenetic effects, such as an altered methylation status that alters gene expression. All these changes are related to the formation or activation of oncogenes. In addition, deletion or inactivation of tumour suppressor genes can contribute to oncogenesis.

In the chronic myeloid leukaemias there is often a mutation in a gene encoding a protein on a signalling pathway between the surface membrane and the nucleus; often this protein is a tyrosine kinase that becomes constitutively activated as a result of the mutation. The neoplastic cells are thus able to proliferate and differentiate without being dependent on growth factors. Examples of such constitutively activated tyrosine kinases include the products of the BCR-ABL1 fusion gene in CML and of the FIP1L1-PDGFRα fusion gene in eosinophilic leukaemia and related conditions.

In AML there appears to be a need for at least two mutations to convey the leukaemic phenotype to the
<table>
<thead>
<tr>
<th>Category</th>
<th>Important subcategories</th>
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</table>
| Acute myeloid leukaemia (AML) | Therapy-related AML and myelodysplastic syndromes (MDS)  
AML with recurrent cytogenetic/genetic abnormalities  
AML with multilineage dysplasia and related conditions  
  Following MDS  
  With multilineage dysplasia  
  With myelodysplasia-associated cytogenetic abnormalities  
AML not otherwise categorized |
| The myelodysplastic syndromes (MDS) | Refractory cytopenia including refractory anaemia  
Refractory anaemia with ring sideroblasts  
Refractory cytopenia with multilineage dysplasia (with or without ring sideroblasts)  
Refractory anaemia with excess of blasts  
5q– syndrome  
Myelodysplastic syndrome, not otherwise categorized |
| Myeloproliferative neoplasms (MPN) | Chronic myelogenous leukaemia (with BCR-ABL1 fusion gene)  
Chronic neutrophilic leukaemia  
Polycythaemia vera (usually has JAK2 V617F mutation)  
Essential thrombocythaemia (often has JAK2 V617F mutation)  
Primary myelofibrosis (often has JAK2 V617F mutation)  
Mast cell disease  
  Cutaneous mastocytosis including urticaria pigmentosa  
  Systemic mastocytosis (usually associated with KIT D816V mutation)  
  Mast cell leukaemia |
| Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1 | Myeloid and lymphoid neoplasms with PDGFRB rearrangement  
Myeloid neoplasms with PDGFRB rearrangement  
Myeloid and lymphoid neoplasms with FGFR1 rearrangement |
| The myeloproliferative/myelodysplastic syndromes (MPD/MDS) | Chronic myelomonocytic leukaemia  
Atypical chronic myeloid leukaemia  
Juvenile myelomonocytic leukaemia (often associated with mutation of PTPN11, NF1, RAS or CBL) |
neoplastic cells, and in some types of AML there are multiple mutations. Particularly in AML with multilinage dysplasia, secondary AML, therapy-related AML and AML in the elderly, there are likely to have been multiple mutational events (which can include those leading to loss of activity of tumour suppressor genes). It has been postulated that for any case of AML there is a need for two different types of mutation, one designated class I to indicate a mutation that conveys a proliferation or survival advantage to the cells and another, designated class II, which interferes with differentiation and conveys the capacity for self-renewal [2, 3]. Class I and II mutations are associated with each other in a non-random manner. It is the class II mutation that can be related most closely to the clinical and haematological phenotype of the disease, but the class I mutation is also likely to be essential for leukaemogenesis and often affects prognosis (Table 1.2).

In MDS, multiple genetic events occur, which can include changes in oncogenes and tumour suppressor genes, and haploinsufficiency of normal genes. Specific mechanisms of oncogenesis include oncogenic mutations (e.g. in NRAS), haploinsufficiency (e.g. loss of RPS14 in MDS associated with 5q–) and deletion or loss of function of a tumour suppressor gene (e.g. loss of TP53 at 17p13.1). The net result is continuing cell proliferation but with ineffective haemopoiesis, i.e. with an increased rate of apoptotic death of haemopoietic cells in the bone marrow and a resultant failure of production of adequate numbers of end cells. The MDS/MPN are also genetically complex.

Chronic myeloid leukaemias that result from a class I mutation, such as BCR-ABL1, ETV6-PDGFRB or FIP1L1-PDGFR, can acquire class II mutations during acute transformation. At least five class II mutations that are usually associated with AML have been observed in association with acute transformation of CML [3]. Loss of function of tumour suppressor genes can also occur during disease evolution. The JAK2, MPL and KIT mutations that occur in other myeloproliferative neoplasms are also class I. Similarly, the mutations in NF1, PTPN11, NRAS and KRAS that are observed in JMML are all class I mutations.

### Table 1.2. Class I and class II mutations that can interact in the pathogenesis of AML

<table>
<thead>
<tr>
<th>Class I mutation (conveys proliferation or survival advantage) (reported incidence in subtype shown in brackets)</th>
<th>Class II mutation (interferes with differentiation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT mutation (12–47% of cases)</td>
<td>RUNX1-RUNX1T1, usually resulting from t(8;21)(q22;q22)</td>
</tr>
<tr>
<td>NRAS (c 10%)</td>
<td>CBFB-MYH11, usually resulting from inv(16)(p13q22) or t(16;16)(p13;q22)</td>
</tr>
<tr>
<td>FLT3-ITD* (c 4%)</td>
<td>PML-RARA, usually resulting from t(15;17)(q22;q12)</td>
</tr>
<tr>
<td>NRAS (c 30–40%)</td>
<td>CEBPA mutated</td>
</tr>
<tr>
<td>FLT3-ITD (c 7%)</td>
<td>NPM1 mutated</td>
</tr>
<tr>
<td>KIT mutation (22–47% of cases)</td>
<td></td>
</tr>
<tr>
<td>FLT3-ITD (c 30%)</td>
<td></td>
</tr>
<tr>
<td>NRAS (c 2%)</td>
<td></td>
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<tr>
<td>FLT3-ITD</td>
<td></td>
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<tr>
<td>FLT3-ITD</td>
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* ITD = internal tandem duplication
† TKD = tyrosine kinase domain
Aetiology

The aetiology of most instances of myeloid neoplasms is unknown. AML, MDS and MDS/MPD can result from exposure to radiation, anticancer chemotherapy and chemical carcinogens such as benzene. Cigarette smoking also increases the incidence of AML. CML can follow exposure to irradiation or topoisomerase-IIinteractive drugs. Genetic predisposition also has an aetiological role. Down syndrome predisposes to transient leukaemia in the neonatal period and to acute megakaryoblastic leukaemia in infants. Inherited defects in proto-oncogenes can predispose to leukaemia, e.g. germ line mutation in RUNX1 and in CEBPA predispose to AML. Germline mutation of NF1 in neurofibromatosis type 1 and of PTPN11 in Noonan syndrome predispose to JMML. Inherited defects in tumour suppressor genes likewise predispose to various types of leukaemia. Germ line mutation of TP53 in the Li Fraumeni syndrome, of RB1 in familial retinoblastoma families and of WT1 in familial Wilms tumour families predispose to AML.

Principles of treatment

The aim of treatment for chronic myeloid leukaemias may be relief of symptoms and, therefore, improved quality of life, prolongation of life or cure. Treatment modalities are disease specific and include chemotherapy, immune modulation, molecularly targeted therapy and haemopoietic stem cell transplantation. For some patients with certain types of chronic myeloid leukaemia cure is a realistic option. For others, a remarkable prolongation of life is possible with currently available therapies. There remain, however, some leukaemias where palliation is the only currently feasible aim.

References