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Haemopoietic Diseases 1: Leukaemias

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Chapter summary

- Leukaemias are generally classified by their cell of origin into myeloid and lymphoid leukaemias.

  Acute myeloid leukaemia is primarily subclassified on the basis of karyotype into various subgroups including acute promyelocytic leukaemia (t(15;17)), core binding factor AML (inv(16) and t(8;21)), normal karyotype AML, and complex karyotype AML.

  One of the most important decisions dictated by molecular/cytogenetic testing in AML is whether to perform an allogeneic stem cell transplant in first remission.

  Minimal residual disease testing is routinely used to monitor the response to therapy in t(15;17), t(8;21) and inv(16) AML.

  The defining genetic lesion in **chronic myeloid leukaemia** is t(9;22), also known as the Philadelphia chromosome, which creates the BCR-ABL1 fusion protein.

- Different BCR-ABL1 transcript types are possible in CML and the most common ones are e13a2 and e14a2.
- BCR-ABL1 monitoring by RT-PCR is used to monitor response to therapy and to detect resistance to therapy.
- BCR-ABL1 mutations can occur that impart resistance to TKI therapy. An important one is the Thr318Ile which imparts resistance to almost all tyrosine kinase inhibitors apart from ponatinib.
- Acute lymphoblastic leukaemia can be divided into those derived from B lymphocyte progenitors (B-ALL) or T lymphocyte progenitors (T-ALL).
- B-ALL is genetically characterised by aneuploidies and recurrent translocations, for example t(12;21).
- T-ALL can be subdivided into an early T-progenitor type, which have a mutational profile with some characteristics similar to myeloid malignancy and a cortical/mature type, which have NOTCH1 pathway dysregulation as a central theme.
- Minimal residual disease testing is important in both B-ALL and T-ALL and can be performed by following the individual patients rearranged IGH/TR sequence.
- Important cytogenetic lesions in chronic lymphocytic leukaemia are del 17p, del 11q, del 13q and trisomy 12.
- CLL mutations that impart an inferior prognosis are TP53, NOTCH1, SF3B1 and BIRC3.
- Almost all cases of hairy cell leukaemia contain the BRAF Val600Glu mutation and this has been utilized for targeted therapy with mutation specific inhibitors in relapsed/refractory disease.
- Clonality in T-cell lymphoproliferative disorders can be established by looking for uniformity of length of PCR products of various TR loci indicating the presence of a single clone.
- The earliest lesions in multiple myeloma are hyperdiploidy and translocations involving the IGH loci on chromosome 14.
- Mutations in multiple myeloma tend to recurrently involve the RAS/MAPK pathway.