Contents

Preface *xi*

1 Introduction to Blood Cancer *1*
1.1 Fundamental Aspects of Blood *1*
1.1.1 Haemopoiesis *2*
1.1.2 The Function of Blood Cells *4*
1.1.3 The Organs of Blood *5*
1.2 Tools for Investigating Blood Cancer *6*
1.2.1 Haematology *6*
1.2.2 Biochemistry *8*
1.2.3 Immunology *8*
1.2.4 Histology *10*
1.3 A Historical Perspective of Blood Cancer *11*
1.3.1 Leukaemia *11*
1.3.2 Lymphoma *12*
1.3.3 Myeloma *12*
1.3.4 Other Blood Cancers *13*
1.3.5 The Epidemiology of Blood Cancer *14*
1.4 The Molecular Pathology of Cancer *15*
1.4.1 Carcinogenesis *15*
1.4.2 Chromosomes *17*
1.4.3 Intra-chromosomal Pathology *19*
1.4.4 Implications for Clinical Practice *21*
1.5 Chapter Summary *23*
References *23*

2 Methods in Molecular Pathology *24*
2.1 First-generation Techniques *25*
2.1.1 Cytogenetics and Karyotyping *25*
2.1.2 Fluorescence In-situ Hybridisation *26*
2.1.3 High-resolution Melt Analysis *28*
2.1.4 DNA Sequencing *29*
2.1.5 Polymerase Chain Reaction *30*
2.1.6 Microarray Technology *32*
2.2 Next-generation Sequencing *32*
2.2.1 Pyrosequencing *33*

COPYRIGHTED MATERIAL

2.2.2 Ion Torrent Technology *34*
2.2.3 Illumina Sequencing *35*
2.2.4 Sequencing by Oligo-ligation and Detection *36*
2.2.5 Wider Applications of NGS *36*
2.3 Third-generation Sequencing *39*
2.3.1 Nanopore Technology *39*
2.3.2 Pacific Biosystems *40*
2.3.3 Further Aspects of Molecular Pathology *40*
2.4 Chapter Summary *42*
References *42*

3 Molecular Pathology of the Myeloid Lineage: Part 1 *43*
3.1 The Classification of Myeloid Neoplasms *44*
3.1.1 The French–American–British and REAL Systems *44*
3.1.2 The WHO Classification *44*
3.1.3 Multi-lineage Disease and Clonal Haematopoiesis *45*
3.1.4 Mortality and Myeloid Neoplasms *46*
3.2 Acute Myeloid Leukaemia (AML) *46*
3.2.1 Historical Perspective *46*
3.2.2 Molecular Pathology of AML in the Age of NGS *47*
3.2.3 Paediatric AML *49*
3.2.4 Links Between Mutations and Transformation *49*
3.3 Acute Promyelocytic Leukaemia (APL) *50*
3.3.1 The Promyelocyte *50*
3.3.2 Historical Perspective *50*
3.3.3 Molecular Pathology of APL *50*
3.4 Chronic Myeloid Leukaemia (CML) *51*
3.4.1 Historical Perspective *51*
3.4.2 The Philadelphia Chromosome *51*
3.4.3 The Importance of t(9;22)(q34;q12) *52*
3.4.4 Other Genetic Lesions in CML *52*
3.4.5 Blast Transformation *52*
3.5 Chronic Neutrophilic Leukaemia (CNL) *53*
3.6 Myelomonocytic Leukaemia (MML) *53*
3.6.1 Historical Perspective and Classification *54*
3.6.2 MML Genetics in the Age of NGS *54*
3.7 Monocytic Leukaemia *55*
3.7.1 Historical Perspective and Classification *55*
3.7.2 Molecular Genetics of Monocytic Leukaemia *55*
3.8 Histiocytic/Dendritic Cell Neoplasms *55*
3.8.1 Historical Perspective and Classification *55*
3.8.2 Molecular Pathology *57*
3.9 Chapter Summary *57*
References *58*

4 Molecular Pathology of the Myeloid Lineage: Part 2 *59*
4.1 Eosinophilic, Basophilic and Mast Cell Neoplasms *59*
4.1.1 Eosinophilic Leukaemia *59*
4.1.2 Basophilic Leukaemia *60*
4.1.3 Mast Cell Neoplasms *60*
4.2 Myelofibrosis and Myelodysplastic Neoplasms *61*
4.2.1 Myelofibrosis *61*
4.2.2 Myelodysplastic Neoplasms *63*
4.2.3 Miscellaneous and Overlapping Conditions *64*
4.3 The Erythroid Lineage *64*
4.3.1 Erythrocytosis and Polycythaemia *65*
4.3.2 Polycythaemia Vera *65*
4.3.3 Erythroleukaemia *66*
4.4 The Megakaryocyte Lineage *67*
4.4.1 Cell Biology and Historical Perspective *67*
4.4.2 Megakaryoblastic Leukaemia *67*
4.4.3 Megakaryocytic Leukaemia *68*
4.4.4 Essential Thrombocythaemia *69*
4.5 The Molecular Pathology of PV, MF and ET *70*
4.6 Chapter Summary *71*
References *72*

5 Molecular Pathology of the Lymphoid Lineage *73*
5.1 Lymphomas *73*
5.1.1 Classification *73*
5.1.2 Hodgkin Lymphoma *74*
5.1.3 Burkitt Lymphoma *75*
5.1.4 Mature B Cell Neoplasms *76*
5.1.5 T Cell and NK Cell Lymphomas *76*
5.1.6 Precursor B Cell Neoplasms *77*
5.2 Lymphocytic Leukaemias *77*
5.2.1 Acute Lymphoblastic Leukaemia *78*
5.2.2 Paediatric ALL *79*
5.2.3 Chronic Lymphocytic Leukaemia *80*
5.2.4 Other Leukaemias *81*
5.3 Myeloma and Related Conditions *82*
5.3.1 Monoclonal Gammopathy of Unknown Significance *82*
5.3.2 Smouldering Multiple Myeloma *82*
5.3.3 Malignant Myeloma *83*
5.3.4 Plasma Cell Leukaemia *84*
5.3.5 Molecular Pathology of the Progression of Plasma Cell Neoplasms *85*
5.4 Chapter Summary *86*
5.5 A Summary of Molecular Pathology of the Blood Cancers *87*
References *88*

6 An Introduction to Clinical Blood Cancer *89*
6.1 Presentation of the Patient *89*
6.1.1 Signs and Symptoms *89*
6.1.2 Fortuitous Discovery *90*
6.1.3 Role of the Health Care Professional *90*
6.2 Leading Diagnostic Tools *91*
6.2.1 Imaging *91*
6.2.2 The Laboratory *93*
6.3 Treatments of Blood Cancer *95*
6.3.1 Initial Steps *95*
6.3.2 Treating the Disease 1: Traditional Chemotherapy *95*
6.3.3 Treating the Disease 2: Immunotherapy *97*
6.3.4 Treating the Disease 3: Molecular Therapy *98*
6.3.5 Treating the Disease 1: Combinations of Chemotherapy *99*
6.3.6 Treating the Disease 2: Radiotherapy *100*
6.3.7 Treating the Disease 3: Engineered CAR T Lymphocytes *100*
6.3.8 Treating the Disease 4: Transplantation *100*
6.3.9 Assessing Treatment Effectiveness *100*
6.4 Chapter Summary *101*

7 Diagnosis and Management of Myeloid Neoplasms *102*
7.1 The Aetiology of Myeloid Neoplasms Revisited *102*
7.2 Acute Myeloid Leukaemia (AML) *103*
7.2.1 Initial Considerations and Diagnosis *103*
7.2.2 The Bone Marrow and Imaging *104*
7.2.3 Immunophenotyping *105*
7.2.4 Molecular Pathology *105*
7.2.5 Clinical Value of Genetic Analysis *106*
7.2.6 Treatment of AML *106*
7.3 Acute Promyelocytic Leukaemia (APL) *108*
7.3.1 Immunophenotyping *108*
7.3.2 The Molecular Pathology of APL *109*
7.3.3 Treatment of APL *109*
7.4 Chronic Myelocytic Leukaemia (CML) *110*
7.4.1 The Cellular Phenotype *110*
7.4.2 Molecular Pathology *110*
7.4.3 Treatment of CML *111*
7.4.4 Blast Transformation *112*
7.5 Chronic Neutrophilic Leukaemia (CNL) *112*
7.5.1 First Steps in Diagnosis *112*
7.5.2 Molecular Pathology *113*
7.5.3 Treatment of CNL *113*
7.6 Eosinophilic, Basophilic and Mast Cell Neoplasms *113*
7.6.1 Eosinophilic Leukaemia *113*
7.6.2 Basophilic Leukaemia *114*
7.6.3 Mast Cell Neoplasms *116*
7.7 Monocytic Leukaemia *116*

7.7.1 Classification and Morphology *116*
7.7.2 Immunophenotyping *117*
7.7.3 Molecular Pathology *118*
7.7.4 Treatment of Monocytic Leukaemia *118*
7.8 Myelomonocytic Leukaemia (MML) *118*
7.8.1 Cell Phenotype and Diagnosis *118*
7.8.2 Molecular Pathology *120*
7.8.3 Treatment of MML *120*
7.9 Histiocytic and Related Neoplasms *120*
7.9.1 Initial Considerations *120*
7.9.2 Immunophenotyping *121*
7.9.3 Molecular Pathology *121*
7.9.4 Treatment of Histiocytic Neoplasms *121*
7.10 Myelofibrosis and Myelodysplastic Neoplasms (MDS) *122*
7.10.1 Myelofibrosis *122*
7.10.2 Myelodysplastic Neoplasms (MDS) *123*
7.11 The Erythroid Lineage *124*
7.11.1 Polycythaemia *124*
7.11.2 Erythroleukaemia *124*
7.12 The Megakaryocyte Lineage *126*
7.13 Chapter Summary *127*
References *128*

8 Diagnosis and Management of Lymphoid Neoplasms *129*
8.1 General Concepts in Lymphoma *129*
8.1.1 Initial Considerations *130*
8.1.2 Investigations *130*
8.2 Hodgkin Lymphoma *131*
8.2.1 Diagnosis *131*
8.2.2 Subtypes of Hodgkin Lymphoma *131*
8.2.3 Nodular Lymphocyte-predominant Hodgkin Lymphoma (NLPHL) *132*
8.2.4 Molecular Pathology *132*
8.2.5 Treatment *132*
8.3 Non-Hodgkin Lymphoma (NHL) *132*
8.3.1 Burkitt Lymphoma *133*
8.3.2 The Mature B cell Neoplasms *133*
8.3.3 T Cell and NK Cell Lymphomas (TCL, NKL) *136*
8.3.4 Other Lymphomas *137*
8.4 Acute Lymphoblastic Leukaemia (ALL) *138*
8.4.1 Introduction to Leukaemia of the Lymphocyte *138*
8.4.2 Initial Considerations and Diagnosis of ALL *138*
8.4.3 The Bone Marrow and Imaging *139*
8.4.4 Immunophenotyping *139*
8.4.5 Molecular Pathology *139*
8.4.6 Treatment of ALL *140*
8.4.7 Paediatric ALL *141*
8.5 Chronic Lymphocytic Leukaemia (CLL) *142*

8.5.1 Initial Considerations *142*
8.5.2 Investigations and Diagnosis *142*
8.5.3 Treatment *143*
8.5.4 Richter Syndrome *144*
8.5.5 Hairy Cell Leukaemia (HCL) *145*
8.5.6 Mature TCL and NKL *146*
8.6 Myeloma and Related Conditions *146*
8.6.1 Introduction *146*
8.6.2 Monoclonal Gammopathy of Undetermined Significance (MGUS) *148*
8.6.3 Smouldering Multiple Myeloma (SMM) *149*
8.6.4 Myeloma *150*
8.6.5 Plasma Cell Leukaemia *152*
8.6.6 Disease Progression *152*
8.7 Chapter Summary *153*
References *153*

Case Study *154*
Multiple Choice Questions *166*
Answers to Multiple Choice Questions *174*
Appendix A: Analysis of Genes and Chromosomal Abnormalities *178*
Subject Index *181*
Genes Index *185*
Fused Genes *189*
Chromosomal Abnormalities *190*