chapter 10

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Salient features of hematological diseases

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myeloid malignancies

acute myeloid leukemias

Acute myeloid leukemias (AMLs) are clinically and molecularly heterogeneous. AML blasts are clonal cell populations originating from transformed hematopoietic stem cells, and they typically show a maturation block at early stages of myelopoiesis. About half of all AML harbor chromosomal translocations creating leukemogenic fusion genes, which involve kinases, transcription factors, and/or receptors. The causes of AML are in most situations unknown. Some patients may report a history of exposure to ionic radiation or toxic substances such as benzenes. Patients treated with alkylating agents and radiation therapy, notably survivors of Hodgkin's disease (HD), may develop secondary AML after many years. Cancer survivors who received etoposide or other podophyllotoxins may develop AML with aberrations of chromosome 11q23, usually with a latent period of a few years only. In elderly patients, myelodysplastic syndromes (MDSs) may precede the development of frank AML by months or years.

AML patients usually present with nonspecific complaints, such as fatigue, bleeding (which may be particularly severe in APL), or infections. Occasionally, the diagnosis is a chance finding when peripheral blood smears are prepared for other reasons. In monocytic leukemias, infiltration of skin and particularly gums may be conspicuous. Isolated tumors composed of AML blasts are known as chloromas.

The diagnosis of AML is made by morphological examination of peripheral blood and bone marrow smears. Immunohistochemistry (for example, myeloperoxidase stains) helps to ascertain the myeloid characteristics of blasts rapidly. Karyotype aberrations are of paramount prognostic importance, and therefore cytogenetic and molecular analyses of malignant cells in an experienced laboratory are essential. In contrast to acute lymphoblastic leukemia (ALL), immunophenotyping is of lesser diagnostic importance in AML. Diagnostic data are comprised in the World Health Organization (WHO) AML classification which has replaced the former French-American-British (FAB) classification. Work-up should include a thorough search for concomitant disorders. Diabetes, heart disease, renal failure, severe neurological disorders, and other conditions may influence the decision of whether a patient will be fit for intensive curative treatment or not, particularly in the elderly. Information on the family pedigree must be obtained, specifically in patients who might qualify for allogeneic bone marrow transplantation (BMT).

The prognosis of AML is distinctly linked to chromosomal aberrations and particular molecular abnormalities. AML with the translocation t(8;21), or with aberrations of chromosome 16 (often with marrow eosinophilia), and APL with the typical translocation t(15;17) carry a good prognosis, as do AMLs with a normal karyotype and mutations of the C/EBPα gene. AMLs with complex chromosomal aberrations, with particular chromosomal deletions, or with the frequent molecular abnormalities in the FLT3 tyrosine kinase gene have an adverse outcome. Prognosis is also linked to age with younger patients faring much better than the elderly.

Treatment with curative intent comprises one to several inpatient induction cycles of intensive chemotherapy, usually combining an anthracycline and cytarabine. Patients with APL or AML with excessive leucocytosis are emergencies calling for immediate treatment, with the latter requiring leukapheresis. Very frequent complications of induction chemotherapy are systemic infections due to severe neutropenia (often septicemia and including fungal infections), requiring broad-spectrum antibacterial treatment or antifungal agents. Hematopoietic growth factors given to hasten neutrophil recovery seem to be safe with no increased risk of early AML relapse, but their routine use remains controversial. Prevention or treatment of bleeding due to severe thrombocytopenia requires platelet transfusions. Neutropenic enterocolitis and mucositis are also frequent. APL specifically responds to all-*trans*-retinoic acid (ATRA), a differentiating agent, which in addition to inducing APL remission considerably reduces the incidence of severe coagulopathy. ATRA needs to be combined with chemotherapy for optimal results. The drug may induce the ATRA syndrome or the APL syndrome that is characterized by fever and leakage of fluid into the extravascular space. Withdrawal of the drug and steroids is the appropriate therapeutic measure to be undertaken. AML remission status should be checked with bone marrow examinations after each treatment cycle. Complete remission is defined as the absence of morphologically discernible leukemic blasts in the marrow and return of peripheral blood counts to (near) normal values. In all, 70%–80% of AML can nowadays be expected to obtain remission upon induction. Patients responding early have the best prognosis and usually receive one to two cycles of intensive consolidation chemotherapy. Long-term maintenance chemotherapy is used in some centers but not universally accepted. Patients with AML in first remission are candidates for allogeneic BMT provided a human leukocyte antigen (HLA) -identical sibling is available as a donor. Exceptions

to this rule are selected patients with good-risk AML (including APL, AML with the t[8;21] or with aberrations of chromosome 16, as well as AML with a normal karyotype and a mutated C/EBPα gene). High-dose chemotherapy with autologous stem-cell transplants is still controversial and not routinely recommended outside clinical trials. Refractory AML patients have an adverse prognosis and may be candidates for allotransplants with an unrelated HLA-matched donor, if found within a reasonable period of time. Patients who are not fit for intensive chemotherapy, particularly the elderly, should receive supportive care including red-cell transfusions and low-dose chemotherapy (such as hydroxyurea) to treat excess leucocytosis. Platelet transfusions should be reserved for bleeding episodes, since patients receiving repetitive platelet transfusions may become refractory.

Prognosis and clinical outcome of AML vary with the type of AML and most importantly age. Younger AML patients may expect cure rates of up to 50%, whereas the average long-term survival is ∼20%–25%. Good-risk patients, particularly APL, may expect much better outcome with cure rates of 60%–70%. Very few patients, who experience relapse, can be cured.

myelodysplastic syndromes

MDSs are chronic clonal hematopoietic malignancies mainly seen in elderly patients. MDSs are derived from transformed pluripotent hematopoietic stem cells, which give rise to dysplastic and ineffective hematopoiesis in the marrow with little output of mature blood cells into the periphery. Hence, peripheral cytopenias result, often affecting erythroid, myeloid, and platelet lineages. The causes of MDS are in most cases unknown, but may be similar to those known for AML. Patients usually present with slowly progressive clinical sequelae of pancytopenia, and therefore may adapt well to anemia. Likewise, a bleeding tendency due to thrombocytopenia may insidiously increase over many months. MDS may enhance symptoms of concomitant disorders such as coronary heart disease or chronic obstructive pulmonary disease. Rare inherited chromosome fragility states may be risk factor for MDS, as are aplastic anemia and paroxysmal nocturnal hemoglobinuria.

Bone marrow and peripheral blood smear morphology are cornerstones of a diagnosis of MDS. Bone marrow smears should be stained for iron to detect ring sideroblasts in refractory anemia. The diagnosis of MDS is not always easy because morphological assessment of bone marrow pathology is to some extent on the basis of the subjective judgment of the hematologist. Reactive marrow alterations due to drugs or vitamin-deficiency states should be excluded, either by eliminating a suspect drug or by substitution of vitamin B12 or folic acid. The detection of clonal chromosomal abnormalities in a bone marrow karyotype may help to establish a diagnosis of MDS. MDSs often show chromosomal deletions rather than translocations, but their absence does not exclude the diagnosis. The karyotype may show complex patterns, deletions of chromosomes 7 and 5 [del(7q) and del(5q)] or of the Y chromosome. In unclear situations, observation over time and the examination of repeat marrow aspirates may greatly help. Immunophenotyping and molecular genetics are not very helpful in ascertaining the diagnosis of MDS. The FAB MDS classification was modified by the WHO. MDSs comprise a range of morphological marrow alterations from refractory anemia with or without ring sideroblasts (indicating defects of iron storage in the MDS clone) to refractory anemia with an excess of blasts (RAEB) and finally RAEB transforming to frank AML. Chronic myelomonocytic leukemia (CMML) has traditionally been lumped together with MDS, but there is no firm pathobiological basis for this. CMML typically shows peripheral blood monocytosis (hence, tuberculosis must be considered in the differential diagnosis) and an excess of myeloid blasts in the marrow. MDS patients should also receive a comprehensive work-up for concomitant disorders, which are frequent in a typically elderly MDS patient population. In the history, use of any kind of drugs (medical and other) should be carefully sought after. The prognosis of MDS covers a wide range from patients doing clinically well over many years to patients who rapidly progress to treatment-refractory AML shortly after diagnosis. An International Prognostic Scoring System (IPSS) has been developed on the basis of the degree of peripheral cytopenia, marrow blast counts, and karyotype abnormalities [isolated del(5q) conferring an excellent prognosis and patients with complex chromosome aberrations faring very badly].

Treatment of patients with MDS is frustrating. Intensive AML-type chemotherapy is much less effective in MDS, and often fails to promote a return of polyclonal multilineage hematopoiesis. Low-dose chemotherapy (e.g. low-dose cytarabine) may occasionally improve peripheral cytopenias, but often achieves deterioration of marrow function. The only curative option is allogeneic BMT, but this is only available to a small proportion of younger MDS patients with an HLA-matched donor. In most patients, treatment is restricted to supportive care. This comprises repetitive transfusions (which may result in iron overload), antibiotics to treat infectious episodes, and platelet transfusions (which should be limited to clinically relevant bleeding episodes). In a subset of MDS patients, demethylating agents, for example, 5-azacytidine, may delay leukemic transformation and death. Hematopoietic growth factors may transiently improve neutropenia (granulocyte colony-stimulating factor) or anemia (erythropoietin), but responses are inconsistent.

Patients with low-risk MDS according to the IPSS may expect a median survival of 6 years (12 years in patients under the age of 60), whereas high-risk patients rarely survive longer than a few months to 1 year after diagnosis. About two-thirds of MDS patients die because of their cytopenias, one-fourth because of progression to AML, and one-fifth of patients die of concomitant disorders.

chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a model disorder among the myeloproliferative syndromes with historic significance in basic and clinical oncology research. It was the first human malignancy to be linked to a specific recurrent chromosomal aberration, t(9;22) also known as the Philadelphia chromosome. The t(9;22) amalgamates two kinase genes, the ABL oncogene and the BCR gene, to form a leukemogenic fusion gene encoding a protein with aberrant tyrosine kinase function.

Cloning of the BCR–ABL fusion gene and molecular analyses of its role in leukemogenesis paved way to develop a small molecule, imatinib mesylate (Gleevec or Glivec) blocking its function, which epitomizes the principle of molecularly targeted cancer therapy.

CML patients often exhibit few symptoms at presentation, and the diagnosis is made by chance. Symptoms develop insidiously and are mostly related to anemia and/or splenomegaly. Splenomegaly is often the only pathological clinical feature at presentation. Peripheral blood analyses show anemia, and excess leucocytosis with all myeloid maturation stages represented, and typically no maturation block. In addition, thrombocytosis is a regular feature of CML in chronic phase. The diagnosis is made by morphology of peripheral blood films and bone marrow aspirates, where hypercellularity, increased myelopoiesis, an increase in small (micro-) megakaryocytes, and basophilia are typical. Immunophenotyping is not particularly important, but the detection of the Philadelphia chromosome either by classical cytogenetics or by molecular analysis with a specific RT–PCR assay (which is more rapid) is essential. Untreated CML may persist in chronic phase for months up to many years, but eventually progresses to blasts crisis with typical features of AML, which is usually rapidly fatal. The blasts in blast crisis can display myeloid or lymphoid markers or both, and additional cytogenetic abnormalities are frequent. Prognostic scores for CML patients such as the Hasford or Sokal scores all stem from data collected in the pre-imatinib era and are therefore difficult to extrapolate to present-day patients.

For many years, the standard treatment of chronic phase CML was cytostatic drugs given to reduce excess leucocytosis, such as hydroxyurea or busulfan. None of these ever resulted in cure. Recombinant interferon-α with or without chemotherapy provided a significant improvement, yielding not only morphological but also cytogenetic complete responses, which in turn convey a survival advantage. However, allogeneic BMT or stem-cell transplantation in chronic phase was the only therapy offering a chance of cure for many years. These treatment strategies were partly overthrown when imatinib mesylate (Glivec or Gleevec) was introduced. This small molecule, a tyrosine kinase inhibitor, competitively blocks the constitutional activity of the ABL kinase in the BCR–ABL fusion protein which is crucial to CML pathogenesis. Side-effects of imatinib mesylate are few, and remission rates in previously untreated patients rank up to 95% (hematological), 80% (cytogenetic), and $\sim$50% (molecular—using sensitive quantitative BCR–ABL RT–PCR assays), respectively. Responses take time, with maximum hematological responses seen at approximately 6 months after start of treatment, and full cytogenetic responses require three to six more months to develop. Patients failing to respond or progressing under imatinib now have an option to be treated with a newer generation of small tyrosine kinase inhibitors, which may overcome imatinib resistance. The combination of imatinib mesylate with interferon-α or cytarabine seems to improve results. Since no long-term results of imatinib mesylate are available, definitive cure rates are unknown. It now is a challenge to select appropriate CML patients for allogeneic transplantation in chronic phase, given its much higher morbidity and mortality compared with imatinib. Increasingly, allogeneic transplants are restricted to CML patients with suboptimal response to imatinib therapy. No substantial progress has been made in the treatment of blasts crisis, where the malignant cells are invariably treatment refractory and outcome often rapidly fatal. Treatment algorithms have changed in CML. Imatinib yields durable responses, an annual mortality rate of only 1%–2%, and estimated median survival may rise to become 10–15 years.

chronic myeloproliferative disorders

In addition to CML, polycythemia vera (PV), idiopathic myelofibrosis (IMF), and essential thrombocythemia (ET) are classified together with CML as chronic myeloproliferative disorders (MPS). All are clonal disorders derived from a transformed hematopoietic progenitor cell, but in contrast to CML, and possibly PV (see below), no consistent diagnostic cytogenetic or molecular markers have been described in either IMF or ET. Recently, a mutation in the JAK2 gene has been identified, occurring frequently in PV, ET, and IMF.

Clinically, PV often produces few symptoms. Erythrocytosis, its hallmark, may lead to sluggish microcirculation and stasis due to the increase in the hematocrit (HCT). Pruritus in the legs, particularly after exposure to water (showering, etc.), may be noteworthy in the patient's history. Patients with PV show a high risk of thrombosis and embolism, with arterial thrombosis more common than venous thrombosis. PV is the most common cause of hepatic vein thrombosis. On clinical examination, the spleen is enlarged, and generalized erythema may be conspicuous. On laboratory examination, erythrocytosis and increase in the HCT are the leading findings. Their differential diagnosis, which is not always easy, includes many disorders leading to chronic tissue hypoxemia which should be ruled out by measuring arterial oxygen saturation. Unfortunately, there is no single easy diagnostic test to diagnose PV with certainty. *In vitro* assays demonstrating erythroid colony formation in bone marrow samples in the absence of erythropoietin may help to rule out secondary causes of an increased red-cell mass and establish clonal erythroid proliferation characteristic of PV. Mutations of a tyrosine kinase gene JAK2 (V617F) in myeloid cells have been linked with the PV phenotype. Reliable and easily implemented methods for detection of this mutation may revolutionize the way PV and related disorders are diagnosed and classified. Traditionally, treatment of PV is long-term repeated phlebotomy to induce chronic iron deficiency and to reduce efficient erythropoiesis in the marrow. A HCT of <45%–50% is a reasonable treatment goal. Chemotherapy, particularly hydroxyurea, may reduce excessive leucocytosis that can be a feature of PV. Anticoagulants are necessary in patients with venous thrombosis and platelet aggregation inhibitors in patients with arterial thrombosis. Intensive chemotherapy has no role in PV, unless patients progress to develop AML, which is rare. The role of allogeneic BMT has not been defined, but it is sometimes considered in very young patients.

IMF is the least common of all MPSs. IMF is a clonal stem-cell disorder in the marrow with reactive extensive fibrosis of bone marrow cavities, the molecular pathology of which is very

poorly defined. Fibrosis in the marrow leads to extramedullary hematopoiesis, particularly in liver and spleen, which are typically enlarged, often to an extreme extent. Clinical symptoms of IMF are non-specific. The peripheral blood films show crowding out of erythroid and myeloid precursors, a corollary of extramedullary hematopoiesis. Due to marrow fibrosis, attempts at aspirating marrow mostly end with a dry tap, and trephine biopsies must be obtained; they should be stained specifically for fibrous tissue. There is no specific diagnostic test to establish firmly a diagnosis of IMF, but the diagnosis rests on a histology of diffuse bone marrow fibrosis, the absence of the Philadelphia chromosome and a number of minor criteria. IMF and its major complications, progressive anemia, and splenic enlargement are difficult to treat. Chemotherapy with hydroxyurea may reduce splenomegaly, albeit transiently, as will therapy with interferon-α, at the cost of its unpleasant side-effects. Splenectomy may be helpful to improve the degree of cytopenias and to alleviate symptoms caused by an enlarged spleen. A prognostic scoring system has been developed, on the basis of the degree of anemia and the white blood cell count and circulating blasts. The median survival of good-risk patients may extend to 10 years, whereas poor-risk patients (with marked cytopenias or marked leucocytosis, etc.) fare much worse with median survival times of 1–2 years only.

ET is a clonal hematopoietic stem-cell disorder, where platelets are produced in excess without an appropriate stimulus. The diagnosis is frequently made on routine hematological analyses where platelet counts are incorporated. Definitive diagnostic tests are unavailable, and causes of secondary or reactive thrombocytosis must be ruled out. Due to elevated platelet counts, arterial or venous thromboses, or (paradoxically) spontaneous hemorrhage are typical clinical complications of ET. Thrombocytosis *per se* is not a good enough reason to start treatment, and no study has validated the concept that lowering platelets in asymptomatic patients may be of clinical long-term benefit. In patients having experienced an arterial or venous thrombotic event, the usual principles of treating thrombosis and embolism apply. If in this context, lowering of the platelet count seems warranted, drugs such as hydroxyurea, interferon-α, or anagrelide may be used. The latter two have unpleasant side-effects, while hydroxyurea is a mutagen, which is a special concern in these patients given their usually long natural history.

lymphoid malignancies

acute lymphoblastic leukemia

In adults, ALL is much rarer than AML. The presenting features are similar to AML, and include rapidly progressing malaise, fever, as well as weight loss. Lymphadenopathy and hepato-splenomegaly are more common than in AML. As in AML, ALL can be a chance finding on a blood film in asymptomatic patients. Clinical central nervous system (CNS) involvement is uncommon at presentation, but may occur at relapse. ALLs arise from malignant transformed stem cells committed to the lymphoid lineage, and blasts are frozen at distinct early stages of either B-cell or T-cell development. Chromosomal translocations typically include antigen receptor genes as one partner [immunoglobulin (Ig) heavy-chain genes in B-lineage ALL and T-cell receptor genes in T-lineage ALL] juxtaposed to an unrelated gene, mostly a transcription factor (such as the *myc* oncogene) or a kinase. The single largest subgroup of adult ALL patients are Philadelphia-chromosome-positive ALL, unfortunately with a bad prognosis. The causes of ALL are unknown, but in rare instances, previous exposure to radiation may play a role. Chemicals and previous cancer therapy very rarely induce secondary ALL. An uncommon human ALL, adult T-cell leukemia, is closely linked to infection with HTLV-1, a leukemogenic virus.

Morphological examination of blood and bone marrow is the basis for diagnosis. Bone marrow biopsies are often needed, as a fair number of patients show a packed marrow where aspiration is impossible (dry tap). Immunophenotyping plays a central role in defining clinically relevant subsets of ALL, such as common B-precursor ALL (CALLA+ ALL), Burkitt-type ALL, or T-ALL. Burkitt-type ALL must specifically be recognized at diagnosis, since it requires separate treatment protocols. This ALL entity mostly presents with impressive hepato-splenomegaly, and the malignant cells exhibit chromosomal translocations involving the *myc* oncogene on chromosome 8, express surface Ig, but lack terminal deoxy-transferase. Some acute leukemias co-express both lymphoid and myeloid antigens. Such patients tend to have a poor outcome regardless of whether they are treated along ALL or AML protocols. As in AML, molecular genetics and cytogenetics help to define prognostically distinct ALL entities. Philadelphia-positive ALLs fare worst, whereas T-cell ALLs enjoy a much better outcome. At work-up, important concomitant disorders should be taken into account when a treatment plan is established. Information on the family is important, since many adult ALL patients might require allogeneic BMT in first remission.

Induction treatment is geared toward obtaining complete remission. Drug combinations include steroids, anthracyclines, vinca-alkaloids, and alkylating agents, topped up with L-asparaginase, and initial remission rates are in the order of 80%–100%. Tumor lysis syndrome may complicate initial treatment, particularly in patients with excessive leucocytosis. Once remission is obtained, there are several options for continuing treatment, but no 'best' protocol can be defined at present. Remission consolidation with intensified chemotherapy aiming at destroying minimal residual ALL uses drugs such as methotrexate, cytarabine, given systemically and intrathecally to prevent relapse in the meningeal sanctuary. In contrast to AML, maintenance chemotherapy is still standard in many institutions, although its value has occasionally been challenged. Traditionally, combinations of methotrexate, 6-mercaptopurine, and steroids are given in monthly cycles >1–3 years. Adult ALL patients are at a considerably higher risk of relapse than children, and therefore many young to middle-aged patients are candidates for allogeneic BMT in first remission, particularly those with Philadelphia-positive ALL or precursor B-cell ALL. The role of high-dose chemotherapy with autologous peripheral stem-cell transplantation remains unclear. Philadelphia-positive ALL should also receive imatinib mesylate (Glivec) at some stage. Burkitt-type ALL or mature

B-cell ALL should be treated with repetitive short intensive chemotherapy cycles, and standard ALL protocols are inadequate for this particular type of leukemia. In elderly patients, where intensive treatment is not possible, maintenance regimens may provide clinically satisfactory results with remissions lasting for up to 1–2 years without excessive toxicity. In summary, treatment protocols for adult ALL should aim for risk-adapted therapy, and hence comprise complicated algorithms to guide treatment choice through the different phases the disease may take.

Adult patients with ALL generally fare much worse than children. Although initial remission rates are high, most patients will ultimately relapse with chemotherapy-refractory disease and/or CNS involvement. The best prognostic entities of adult ALL are Burkitt-type ALL and T-cell ALL with long-term cure rates of ~80%. Less than 30%–40% of patients with B-cell precursor-type ALL survive for more than a few years, and Philadelphia-positive ALL patients are not curable with conventional chemotherapy. Their results may be improved by early allogeneic transplantation in younger patients, and possibly by adding imatinib mesylate (Glivec) to the regimen. Older ALL patients usually survive for less than a few years only.

chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world and particularly affects elderly patients. The disease results from accumulation of clonal neoplastic relatively well-differentiated lymphoid cells (mostly of B-cell lineage, rarely T cells) with deranged apoptosis programs. The molecular pathology of CLL is characterized by chromosomal deletions, rather than translocations. Although many of these deletions have been mapped extensively, very few genes have been defined that play a specific role in the molecular pathology of CLL. Clinically and biologically CLL is extremely heterogeneous, despite some common features. After a long indolent clinical course, a minority of CLL patients may transform to more aggressive lymphoid neoplasms, including high-grade B-cell lymphoma (Richter's syndrome). CLL is more often associated with autoimmune phenomena than any other leukemia, particularly immune thrombocytopenia or autoimmune hemolytic anemia.

In many patients, the diagnosis of CLL is made by chance on a peripheral blood count. A minority of patients are symptomatic at diagnosis, mainly presenting with enlarged lymph nodes or recurrent infections, for example, pneumonia or sinusitis. Lymphocytosis on a blood film should reach levels of 5000 lymphoid cells/μl or more for a diagnosis of CLL to be considered, but even at these levels reactive lymphocytosis must be carefully excluded. CLL cells may easily be damaged when a blood smear is prepared, and appear as smudge cells or Gumprecht cells. The most important diagnostic technique to complement morphology is immunophenotyping. B-CLL cells typically express B-cell markers such as CD19, CD20, and CD23, but also CD5, a T-cell antigen. B-CLL cells are mature enough to express surface Igs, albeit at low intensity. Immunophenotyping data have been assembled into diagnostic scores to differentiate CLL from other lymphoid neoplasms that may release neoplastic lymphoid cells into the peripheral blood. The bone marrow, usually examined at presentation, does in fact not add very much essential information. In contrast to all other leukemias, CLL patients require some staging similar to lymphoma, since in addition to cytopenias, lymphadenopathy and splenomegaly are criteria to separate CLL into stages with distinctly differing prognoses (the Rai and the Binet staging systems are still most commonly used). Chest X rays and abdominal ultrasound or computed tomography (CT) scans may therefore be helpful. In contrast to acute leukemias and CML, cytogenetic analysis of CLL has not been widely incorporated into routine, mainly for technical difficulties, but it conveys important prognostic information. As an alternative (if available), chromosomal deletions can be detected by FISH using probes targeting loci of interest. Patients with the relatively frequent deletion at chromosome 13q usually show an indolent course, whereas patients with deletions within chromosome 17 or complex aberrations fare poorly. A number of molecular techniques have become available to break CLL into prognostically distinct subgroups. Direct sequencing of Ig variable chain genes permits one to assess CLL cells for IgV somatic hypermutation, which conveys a much better prognosis than germline IgV genes. Surface markers such as CD38 or ZAP70 may serve as surrogate markers for the IgV gene status, if direct molecular analysis is not possible.

CLL is usually responsive to a variety of chemotherapy agents, but not curable. In early stage CLL, treatment is usually deferred for months or often many years after diagnosis, particularly in good prognosis subgroups. Patients with disease-related symptoms or complications require treatment. Alkylating agents, particularly chlorambucil, have long been the standard front-line treatment, but in many centers have been replaced by fludarabine, given its high remission rate and its advantage in terms of progression-free survival. Treatment is usually given to the point of maximum response, but should not exceed half a year for fear of cumulative toxicity. Combination chemotherapies usually fare no better than single-agent treatment, but may be an option at second or third line. The best use of monoclonal antibodies, particularly rituximab directed against CD20 and CAMPATH-1H targeting the CD52 antigen, remains to be defined in CLL. High-dose chemotherapy with autologous stem-cell transplantation cannot be recommended in routine, and allogeneic stem-cell transplantation is not often performed, since many CLL patients are too old. Response criteria to assess treatment in CLL have been defined by the National Cancer Institute Working Group.

CLL patients with good prognostic features may live for many years, often for long periods without any treatment at all. The median survival for Rai stage 0 patients is 12 years. Patients in adverse prognostic groups, e.g. far-advanced Rai stages, or patients with adverse cytogenetic or molecular markers (for example, IgV gene germline configuration) may show an aggressive clinical course, often fatal within 1–2 years. Treatment and hence the prognosis of CLL are likely to change during the coming few years, as the results of many large trials on risk-adapted treatment are becoming available.

prolymphocytic B-cell leukemia

Prolymphocytic B-cell leukemia (PLL) is a rare disease of the elderly, presenting with advanced-stage disease and an aggressive course. It can be distinguished from classical B-cell CLL by the distinct morphology of prolymphocytes on a blood smear and by its immunophenotype, where in contrast to B-cell CLL, CD5 is negative. Since PLL responds more poorly to treatment than classical B-CLL, the prognosis tends to be much worse.

hairy cell leukemia

Hairy cell leukemia (HCL) also needs to be considered in the differential diagnosis of CLL and other lymphoproliferative disorders with peripheral blood lymphocytosis. The typical HCL patient is an elderly male with peripheral pancytopenia (including notably monocytopenia), atypical lymphoid cells on the blood smear that stain for tartrate-resistant acid phosphatase, and splenomegaly. The immunophenotype shows mature B-cell markers including CD45, a molecular involved in B-cell or T-cell signaling, as well as CD25 (the IL-2 receptor), but also the monocytic antigen CD11c. HCL usually runs an indolent course, but because of marked pancytopenia, treatment is often necessary. HCL shows an interesting 'treatment history'. It was one of the first disorders to be demonstrated to respond to interferons, which, however, were overruled by the purine analogues, particularly cladribine (2-chloro-deoxy-adenosine). A single course of treatment very often brings about lasting remissions. Splenectomy is nowadays reserved for the rare patients with therapy-refractory disease who experience complications of splenomegaly.

multiple myeloma, plasmacytomas, MGUs and Waldenström's macroglobulinaemia

Multiple myeloma (MM), extramedullary and solitary plasmocytomas, monoclonal gammopathy of uncertain significance (MGUS), and Waldenström's macroglobulinaemia (WM) are part of a spectrum of mature clonal B-cell neoplasms where neoplastic plasmacytoid cells accumulate, and produce and often (but not always) excrete a monoclonal Ig molecule detectable on serum or urine immune electrophoresis as monoclonal gammopathy or a paraprotein peak. Paraproteins in MM are of the IgA, IgD, or IgG subclass, or may consist exclusively of Ig light chains. WM by definition shows IgM. Although no consistent genetic abnormality has been found in either MM or WM, a number of karyotype abnormalities (for example, deletions on the long arm of chromosome 13) are found in MM.

Patients may present with symptoms, or the diagnosis may be made by chance, when an excessively high erythrocyte sedimentation rate (ESR) (due to the monoclonal serum protein) is investigated, or when a serum electrophoresis is commissioned for unrelated reasons. Monoclonal gammopathies can occur in diseases other than MM, or WM, particularly in B-cell CLL, indolent non-Hodgkin's lymphomas (NHLs), cold agglutinin disease, or amyloidosis. Symptoms of MM or WM are quite distinct. MM tends to destroy bone, and osteolytic lesions cause pain (particularly back pain) and fractures, or there may be severe osteoporosis. Osteolytic activity may lead to hypercalcemia. Ig paraproteins, particularly Ig λ or κ light chains (also known as Bence-Jones protein), may damage the kidney tubules, and renal failure is therefore frequent. These features are uncommon in WM, where instead, symptoms of anemia and particularly the hyperviscosity syndrome due to hyperproteinemia and excess serum IgM prevail. Erythrocyte transfusions to anemic WM patients may trigger off a formerly silent hyperviscosity syndrome because of an increase in intravascular red-cell volume on top of an expanded plasma protein mass. Both MM and WM infiltrate the bone marrow and lead to cytopenias. Extramedullary and solitary plasmocytoma usually present as tumors in soft tissue or associated with bone, respectively, with or without a paraprotein detectable in the serum or urine.

In MGUS, the number of plasma cells in the bone marrow is normal, and the paraprotein the only abnormality in the work-up of such patients. The diagnosis of MM, WM, and related disorders must be ascertained by biopsy. Often bone marrow aspirates and biopsies are diagnostic, but in some patients extramedullary tumor masses must be biopsied surgically, or through CT scan-guided biopsy. The malignant plasmacytoid cells in MM or the neoplastic cells with lympho-plasmacytoid morphology in WM are usually easy to identify through the microscope. Immune-electrophoretic analysis of serum and urine (collected over 24 h) is essential to identify and quantify the type of paraprotein, and initial measurements are ideal markers for later assessment of treatment. Rarely, patients with MM, however, fail to secrete paraproteins, and their diagnosis can only be made by morphology. Increasingly, karyotype abnormalities (detectable by FISH) have turned out to be of prognostic value. For example, deletions of chromosome 13 imply an adverse outcome. Staging of MM usually requires an assessment of the extent of bone involvement, either by conventional X-ray imaging, CT scans, or magnetic resonance imaging. Bone scans have a high false-negative rate and are therefore not routinely recommended. The β2-microglobulin (i.e. the light chain of the major histocompatibility complex) in the serum is a helpful prognostic marker (provided the serum creatinine is normal), and its increase indicates a large tumor mass and an adverse prognosis. Traditional staging of MM (the Durie–Salmon Staging System) is on the basis of the levels of paraprotein, the degree of anemia, serum calcium levels, and the extent of bone destruction. The presence or absence of renal failure is added as an affix. A new International Staging System (ISS) is being introduced, where serum β2-microglobulin, serum albumin, platelet count, serum creatinine, and age emerged as powerful predictors of survival. The new ISS is simple, on the basis of easy to use variables, and increasingly recommended for widespread use.

Treatment may be deferred in patients with asymptomatic early stage myeloma until disease progression or symptoms occur. However, MM patients presenting with symptoms, or patients with advanced-stage MM at diagnosis, invariably require therapy. Melphalan and prednisone have long been standard treatment of MM, and are probably no less effective in the long run than more toxic traditional standard dose combination chemotherapy. Progress in the therapy for MM has come with the introduction of the VAD induction regimen (incorporating high-dose steroids and suitable for patients in

renal failure), followed in responders by high-dose melphalan. In MM, the benefit of high-dose chemotherapy with autologous stem-cell transplantation is particularly well documented, although it is not curative. Newer clinical data suggest that more progress in MM is on the horizon with the advent (or reintroduction in clinical medicine, as it were) of thalidomide and bortezomib, both very active drugs. Their 'best' place in the therapy for MM still needs to be defined more clearly, but combinations of thalidomide and steroids hold more therapeutic promise than classical VAD. Interferon was hailed for some time as beneficial maintenance treatment, but since no survival benefit could be found, enthusiasm for this toxic and costly drug has dampened. Extensive osteolytic lesions in the bone may require radiotherapy, or surgery to prevent or repair pathological fractures. Osteolytic bone disease requires supportive care with bisphosphonates, which inhibit osteoclast activity. Bisphosphonates are the treatment of choice for patients with MM-associated hypercalcemia and have largely replaced calcitonin. Patients with MM and renal failure may need renal dialysis.

Extramedullary and solitary plasmocytomas should be treated with local radiotherapy, which often results in excellent long-term control of the disease. The role of additional standard chemotherapy in these particular patients is unclear, and the newer agents active in MM have only scarcely been tested in solitary plasmocytoma.

MGUS patients require no treatment, but regular follow-up since some of them eventually progress to MM over many years. The risk of transition from MGUS to frank myeloma is about 1% per year.

WM differs somewhat from MM in the treatment approach. Plasmapheresis is often necessary in patients with excessive IgM paraprotein to treat a symptomatic hyperviscosity syndrome. Chemotherapy with alkylating agents (cyclophosphamide or chlorambucil) and steroids has long been the standard treatment; more recently, it has been replaced by first-line fludarabine (particularly in the United States). The role of high-dose melphalan has been much less well defined in WM than in MM.

The prognosis of MM depends on the stage at presentation and on a number of cytogenetic features (e.g. deletions of chromosome 13). Patients at early stages may live up to a median of several years, whereas patients with far-advanced disease and adverse prognostic factors may survive for <1 year. Prognosis in WM is better in that the median survival for most patients is ~5 years. Patients with extramedullary or solitary plasmocytoma show a remarkably low local relapse rate after radiotherapy, but many of them eventually progress to frank MM after a median lag time of several years.

the malignant lymphomas

The malignant lymphomas are the largest group of hematological malignancies. The vast majority are B-cell Non Hodgkin's lymphomas (NHL), followed by Hodgkin's disease (HD), and more rarely T-cell NHLs. Nodal NHLs are more frequent than extranodal NHLs, with the latter group most prevalent in the gastrointestinal tract, the brain and bone, as well as skin. Lymphomas are clonal neoplastic proliferations derived from transformed lymphoid cells. Virtually each stage of lymphoid maturation, from early lymphoid precursor cells to mature plasma cells, is represented by a particular type of lymphoid neoplasm. Early lymphoid precursor cells give rise to lymphoblastic lymphoma or ALL. Many NHLs are derived from germinal center lymphoid cells, notably follicular lymphoma or diffuse large B-cell lymphoma. Finally, myeloma and WM are the malignant counterparts to plasma cells, which have reached the final B-cell maturation stage. The cell of origin of HD has long been elusive, but is now thought to represent a transformed lymphoid B cell. Most NHLs exhibit chromosomal translocations that are crucial for their molecular pathology. In contrast to leukemias, translocations in NHL usually do not form fusion genes but rather misplace an oncogene present on one partner chromosome into the vicinity of the promoter of a gene residing on the other chromosome. Typically, that latter gene is actively transcribed in lymphoid cells. In B-cell neoplasms, the promoter is usually derived from an Ig gene, whereas in T-cell neoplasms, a T-cell receptor gene promoter is used. Oncogenes placed under the influence of these promoters are, for example, the c-*myc* gene (a transcription factor) in Burkitt's lymphoma (BL), a cyclin gene (involved in cell cycle regulation) in mantle cell lymphoma, the BCL-6 gene (a transcription factor active in germinal centers) in diffuse large B-cell lymphoma, or the BCL-2 gene (encoding a protein important for regulating programmed cell death) in follicular lymphoma. Extranodal lymphomas derived from transformed B cells in the mucosa-associated lymphoid tissue (MALT lymphomas) are an exception to this rule, since they show fusion genes similar to leukemias.

In patients with suspicious lymphadenopathy, a diagnostic biopsy should be obtained before lengthy staging procedures are undertaken. The diagnosis of a lymphoma requires sufficient fresh tumor material. A fine-needle aspirate or a cytological examination is usually not sufficient for definitive lymphoma typing. The basis of lymphoma diagnostics is still morphology of histological sections, complemented by immunohistochemistry (many diagnostic antibodies can be used on formalin-fixed material). Molecular analyses usually require fresh lymphoma tissue, and include immunogenotyping to look for antigen receptor gene rearrangements (to assess clonality) and the detection of typical chromosomal translocations through amplification of specific chromosomal breakpoints by PCR. FISH can be applied for the same purpose. The diagnosis of lymphoma requires an expert hemato-pathologist with special training in this difficult field, and cannot be left to all-round pathologists. The histopathological classification of lymphoma has been a subject of much debate over many years, with controversies between experts at times creating more confusion than light. The taxonomical chaos has largely been overcome with the introduction of the revised European–American lymphoma classification, later amended and issued as the current WHO classification of lymphoid neoplasms. It incorporates histology, immunophenotype data, cytogenetics, and molecular diagnostics to define distinct lymphoma entities with clinical relevance. At the clinical level, NHLs are often lumped as indolent (e.g. follicular lymphoma and other NHLs with a long natural history), intermediate-grade [diffuse large B-cell NHL (DLBCL), mantle cell NHL, and others], and truly

high-grade NHLs (chiefly BL and lymphoblastic lymphoma). DLBCLs are sometimes also referred to as 'high-grade' rather than 'intermediate-grade' NHL.

Once the diagnosis of lymphoma is established, patients require staging and a search for risk factors before treatment decisions are made. An exception are patients with particularly aggressive advanced lymphoma types (such as BL) or patients with lymphoma involving critical anatomical sites, such as patients with spine compression or the upper vena cava syndrome. They may require immediate treatment, before routine staging can be completed. Staging consists of a careful clinical examination to detect the extent of lymphadenopathy, as well as hepato-splenomegaly, and involvement of Waldeyer's ring. In the history, B symptoms (weight loss, unexplained fever, and night sweats) should be specifically recorded. The standard of imaging is still CT scanning, with positron emission tomography increasingly gaining ground. In many lymphomas, a bone marrow aspirate and biopsy are considered compulsory to rule out marrow involvement. Sensitive PCR assays to look for minimal occult marrow involvement cannot be recommended as routine procedure. Since extranodal lymphoma may simultaneously present in Waldeyer's ring as well as in the upper gastrointestinal tract, patients with clinical involvement of Waldeyer's ring require a gastroscopy and vice versa. NHLs are classified according to the Ann Arbor system that extends from stage I (involvement of one lymph node area only) to stage IV (systemic disease with involvement of extranodal tissue or organs). Gastric NHLs are classified according to the Blackledge Staging System, where stages I–III describe lymphoma limited to the gastrointestinal tract with progressive degrees of loco-regional penetration, and stage IV refers to disseminated disease. Specific clinical features and treatment of different NHLs are discussed below.

indolent lymphomas

Indolent (or 'low-grade') nodal B-cell NHLs include follicular lymphoma, small lymphocytic lymphoma (which only differs from B-CLL by exhibiting no particular propensity to spill lymphoid cells into the peripheral blood), and marginal zone lymphoma (which may also present at extranodal sites).

Follicular lymphomas (the most frequent subgroup of indolent lymphomas) arise from germinal center B cells. More than 90% of follicular lymphomas show the translocation t(14;18) which juxtaposes the *bcl-2* oncogene next to an Ig heavy-chain gene promoter. On histology section, these lymphomas should be graded according to the number of lymphoid blasts present (grade 1–3). Patients often have few symptoms, and typically consult a doctor because they themselves have detected waxing and waning lymphadenopathy. In a few patients, B symptoms provide the motif for further clinical investigation. Bone marrow involvement at diagnosis is frequent, but a minority of patients show extensive bone marrow infiltration with clinical sequelae of cytopenias. An International Prognostic Index (IPI) validated in diffuse large B-cell lymphoma (see below) has been adapted to follicular lymphomas to become FLIPI, on the basis of the same parameters plus the hemoglobin level.

In early stage follicular lymphoma, radiotherapy to involved sites is considered as a long-established standard, with a potential for cure or at least long-lasting remission. In most situations, chemotherapy is not recommended, except perhaps for younger patients with adverse prognostic factors, and in patients with grade 3 follicular lymphoma. Optimal treatment choices for patients at advanced stages remain controversial. The common denominator is that today virtually no treatment is truly curative. In patients with few symptoms, in elderly patients, and in patients with stable or slowly progressive disease, therapy may be withheld for many months or sometimes years, and the natural history may be very indolent. General symptoms, progressive lymphadenopathy or splenomegaly, or cytopenias are the main reasons for administering therapy, but the 'best choice' is a matter of debate. No survival advantage can be demonstrated when various single-agent or combination chemotherapies are compared. Typical first-line compounds include alkylating agents, anthracyclines, purine analogues, steroids, and various combinations thereof. In grade 3 follicular lymphoma, it seems advisable to administer combination regimens typically used in intermediate- to high-grade lymphomas. 'Classical' chemotherapy may be complemented by interferon (either concomitantly or to maintain remission), but this is not universally accepted. The addition of an anti-CD20 antibody, rituximab, to chemotherapy increases remission rates, but more importantly it may prolong survival, and is therefore increasingly considered as an adjunct. Conjugated radioactive-labeled antibodies are effective with acceptable non-hematological toxicity profiles, and their use can be considered, provided that the degree of bone marrow infiltration is low. However, their place in clinical routine still needs to be established. Patients in lymphoma relapse may be re-treated with a previously used regimen, if the treatment-free interval is long enough (at least a year as a rule of thumb), or they may be treated with different combinations of cytostatic drugs, topped up with rituximab. The remission duration between second-line to later treatments progressively decreases by about half after each additional regimen used, until patients become truly therapy-refractory. In relapsed follicular lymphoma, radiation therapy is often valuable if progressive tumor causes local problems such as compression of vital anatomical structures. The role of high-dose chemotherapy with autologous stem-cell transplantation in follicular lymphoma is a matter of much debate, mostly because few data from suitably sized phase III trials are available. In first remission, its role has not been established. In relapse, it should be considered (if at all) before patients are heavily pre-treated, since results tend to be better and toxicity more acceptable. *In vitro* purging of harvested stem cells has not consistently been shown to provide a clinical advantage. In younger patients with advanced lymphoma and an HLA-identical sibling, allogeneic stem-cell transplantation, perhaps using non-myeloablative regimens, can be discussed. Its proper role is uncertain, but perhaps its best place is at consolidation when lymphoma mass reduction has been achieved with other means. In early stage FL, two-thirds of patients may still be alive and well at 10 years, and one-third at 20 years of follow-up. Advanced FL patients experience median disease-free survival of one to

several years, and long-term survivor rates are in the range of 10%–20%.

Patients with small lymphocytic B-cell lymphoma (SLBL) typically present with asymptomatic lymphadenopathy, and often have bone marrow involvement, as well as lymphocytosis in the periphery. If so, the separation of small lymphocytic lymphoma from B-cell CLL becomes somewhat blurred. No single typical chromosome or molecular abnormality has been described in this lymphoma. A paraprotein peak may be present, but usually less abundant than that in myeloma. The same treatment recommendations specified for follicular lymphoma or CLL apply. The clinical course of SLBL may be very slow and indolent over many years, and therefore these patients should be managed very conservatively and often must be convinced that observation rather than treatment is in their best interest.

Marginal zone B-cell lymphoma has a particular propensity to present extranodally, although nodal lymphoma is also well known. The marginal zone corresponds to the outer limit of the splenic white pulp and plays a critical role in the immune response to T-cell-independent antigens. Many cases of splenic lymphoma belong to this lymphoma type. Nodal marginal zone NHL may develop in patients with preexisting autoimmune inflammatory disorders, for example, Sjögren's syndrome. Extranodal types of marginal zone NHL comprise the MALT lymphomas and are discussed below. Patients with nodal marginal zone NHL may be treated (or rather not treated!) along the guidelines explained for the other subtypes of indolent lymphoma. In patients with splenic lymphoma (presenting with splenomegaly without lymphadenopathy), splenectomy is often performed and is only for diagnostic purposes. Unless specific clinical reasons are present, such patients usually do not require further treatment. Vaccination against pneumococcal infection is a must before splenectomy.

intermediate-grade NHL

Diffuse large B-cell lymphoma, grade 3 follicular lymphoma (see above), immunoblastic NHL, and to some extent mantle cell NHL can clinically be grouped together as intermediate-grade NHL.

Diffuse large B-cell lymphoma (DLBCL) is most prevalent. DLBCL often arise from transformed germinal center B cells, but gene expression profiling suggests that a prognostically distinct group of DLBCL may be derived from activated B cells. The BCL-6 oncogene is often involved in chromosomal translocations or otherwise mutated in germinal-center-derived DCBCL. BCL-6 is transcriptional repressor, which is crucial to the normal development of germinal centers in lymph nodes. Patients with DLBCL may present (at different age groups) with a wide spectrum of clinical problems, ranging from a single enlarged painless lymph node to severe systemic illness with rapidly progressive organ failure, for example, due to compression of vital structures such as ureters or bile ducts. Constitutional symptoms (B symptoms) may be pronounced. Patients should be tested (with their consent) for HIV infection, since lymphomas in HIV-positive patients often correspond to this category. The IPI separates patients into distinct prognostic categories. It uses simple factors including age (<60 years versus older), Ann Arbor stage I or II versus III or IV, performance status (0 or 1 versus worse), lactate dehydrogenase (LDH) (normal versus high), and the number of extranodal sites (none/one versus more). Regardless of stage at presentation and in contrast to indolent NHLs, immediate systemic therapy is almost always warranted in DLBCL. In early stages, short-term chemotherapy is customarily topped up with involved-field radiotherapy, which improves local control and survival. Longer chemotherapy may yield the same results, obviating the need for local radiation. In advanced disease, front-line chemotherapy typically consists of combinations of alkylating agents, anthracyclines, vinca alkaloids, and steroids (CHOP or CHOP-like regimens). More recent data suggest that the addition of rituximab, an anti-CD20 antibody, improves results and is therefore mandatory. Customarily, six to eight cycles of systemic therapy are given to obtain and consolidate complete remission. In advanced-stage lymphoma, radiotherapy to areas of excessive tumor bulk can be discussed as an adjunct to chemotherapy, for example, in mediastinal sclerosing B-cell lymphoma. The role of consolidation high-dose chemotherapy and autologous stem-cell transplantation in first remission is still a matter of much debate, even in poor-risk patients. Patients in relapse, however, who exhibit chemo-sensitive disease, should receive high-dose chemotherapy. In elderly patients, the feasibility of intensive treatment is often limited, and prognosis therefore less favorable. Cure rates in DLBCL are generally high approaching 80%–90% in patients with favorable limited-stage disease, and hovering ~50%–60% in patients with advanced stages.

Patients with mantle cell lymphoma are mostly elderly males who present with advanced disease, splenomegaly, and bone marrow involvement. The neoplastic cells arise from transformed B cells present in the mantle zone surrounding germinal centers in lymph nodes. Mantle cell lymphoma often shows a translocation t(11;14) joining the *bcl*-1 or cyclin D1 gene to the Ig heavy-chain gene promoter. Overexpression of cyclin D1 can be assessed immunohistochemically. Therapy guidelines in practice do not differ much from those outlined for DLBCL, but the literature is somewhat more controversial, and cure in this specific entity is rare. Median overall survival is about 3 years, and median response duration is typically short, usually in the range of 8–9 months.

aggressive NHL

Truly high-grade aggressive lymphomas include Burkitt's and Burkitt-like NHL [BL], as well as lymphoblastic lymphoma. Concordance between pathologists in differentiating BLs from Burkitt's-like lymphoma on histological examination is low. BLs are B-cell neoplasms characterized by rearrangements of the c-*myc* oncogene, which is sometimes used to separate them from BL-like lymphomas, but this is not quite clear. The epidemic form of BL found in Africa is associated with chronic Epstein–Barr Virus (EBV) infection, but in the Western World, we see the so-called sporadic BL, which is not necessarily linked to EBV. BL patients are typically young adult males, and often present with rapidly progressive widespread disease and at times impressive tumor bulk. Therapy differs from DLBCL. It is on the basis of pulses of high-dose systemic combination

chemotherapy including methotrexate and cytarabine at doses which penetrate the cerebrospinal fluid. Transplantation is advocated early, i.e. shortly after an initial response to chemotherapy.

Lymphoblastic lymphoma is mostly identical to the T-cell variant of ALL. Young adults are mostly likely to be afflicted, and stage at presentation is usually advanced. It should be treated in the same way as ALL (see above).

In highly aggressive NHL (including cases of advanced DLBCL), chemotherapy may initially lead to very rapid and substantial tumor destruction (tumor lysis syndrome). Hyperuricemia, hypocalcaemia, hyperkalemia, hyperphosphatemia, and metabolic acidosis are typical, and renal failure is a real threat. Generous hydration, and suppression of uric acid formation with allopurinol or rasburicase, and at times renal dialysis are essential to overcome this early complication of therapy.

T-cell NHL

Peripheral T-cell lymphoma is rare. The term refers to a heterogeneous group of T-cell neoplasms that arise from postthymic mature T-lymphoid cells, which must be distinguished from immature or thymic T-cell neoplasms, for example, T-cell lymphoblastic lymphoma or T-cell ALL. Peripheral T-cell lymphomas include mycosis fungoides, which predominantly involves the skin, but spreads to lymph nodes or other organs at later stages. Rare (at times ill defined) entities are angioimmunoblastic T-cell lymphoma, hepato-splenic T-cell lymphoma of the $\tilde{\alpha}\beta$- or the $\tilde{\gamma}\delta$ type, angiocentric T-cell lymphoma, and others. T-cell lymphomas often present with systemic symptoms, that may be severe, and with inflammatory tissue alterations, such as skin vasculitis, granulomas in various organs, lung infiltrates. The diagnosis is often very difficult, both clinically and histologically. Once it is established, staging procedures are performed as in the B-cell lymphomas. Few trials exist to establish optimal treatment. Usually, T-cell lymphomas are treated according to the guidelines established for intermediate-grade B-cell NHL, but obviously without rituximab, since T-cell NHLs do not express any CD20. Many patients with T-cell lymphomas have a very poor outcome, with the notable exception of patients with mycosis fungoides, where disease may be limited to the skin for many years and responds well to treatment (even if not curative in the long run).

extranodal NHL

The management of extranodal lymphomas requires special considerations. The three most frequently involved sites of extranodal NHL are the gastrointestinal tract, the skin, and the brain.

In patients with non-bulky early stage gastric MALT lymphoma, antibiotics suitable to eradicate *Helicobacter pylori* infection may suffice to induce lymphoma remission. Restaging gastroscopy is required to document that *H. pylori* infection has been eliminated and lymphoma has significantly regressed. The role of chemotherapy in these patients has not been established. In patients with advanced MALT lymphoma, the same strategies of selecting treatment (or not) apply as for advanced indolent nodal NHL. High-grade gastric MALT lymphomas are usually treated with same regimens used in intermediate-grade nodal NHL, followed by local radiation. This approach has largely replaced surgery and conserves gastric function. Patients with long-standing gluten-sensitive celiac disease are at risk of developing enteropathy-type T-cell lymphoma, which carries a poor prognosis despite aggressive chemotherapy.

Primary cutaneous lymphomas often pose difficult diagnostic problems, since chronic inflammatory skin lesions may mimic clonal lymphoma. At least half of indolent B-cell lymphomas of the skin do not spread to other organs and show a benign clinical behavior, often obviating the need for therapy. Extensive lesions can be controlled by local radiation if necessary. Cutaneous T-cell lymphomas mostly present as the Sézary syndrome or mycosis fungoides (see T-cell lymphomas). Large T-cell lymphomas may be CD30+ with a favorable prognosis, or CD30− with a poor outcome.

Primary CNS lymphomas (virtually always of B-cell origin) are most often seen in men in their fifties or sixties. A biopsy should preferably be obtained before patients are given steroids, since rapid response may obscure a histological diagnosis. The histology almost always corresponds to a DLBCL type of lymphoma. Systemic high-dose methotrexate has become established, since it penetrates the blood-brain barrier, as does high-dose cytarabine. The sequential use of high-dose chemotherapy followed by radiation may perhaps improve outcome, although it is often not well tolerated.

lymphoma and immunosuppression

Severely immunosuppressed patients, notably patients with active HIV infection and organ-transplant recipients, are particularly prone to developing lymphoma, mainly B-cell lymphoma, presenting either as nodal lymphoma or as CNS lymphoma. In HIV-positive patients, histology almost always indicates intermediate- to high-grade disease, usually at an advanced stage in nodal NHL. Organ-transplant recipients under immunosuppression may show posttransplant lymphoproliferative disease evolving through different steps ranging from early polyclonal B-cell proliferation to full-blown malignant monoclonal high-grade B-cell lymphoma. The same treatment recommendations outlined for immunocompetent NHL lymphoma patients would apply, but the feasibility of intensive chemotherapy regimens is often jeopardized by an excessive risk of infectious complications. In HIV-positive patients, highly active anti-retroviral therapy is mandatory in parallel with chemotherapy. In organ-transplant recipients, immunosuppression should be tailored down to the minimum level required to guarantee proper functioning of the transplanted organ. In patients with posttransplant lymphoproliferative disease, which has not yet fully progressed to the point of becoming a monoclonal malignant lymphoma, this important measure may suffice to induce remission. Unless the degree of immunosuppression can be successfully reduced, and full treatment given, the prognosis of these patients is poorer than that in their immunocompetent counterparts.

Hodgkin's disease

HD is traditionally discussed separately from the NHLs, since HD entails a fair number of specific aspects, both in terms of biology and treatment. The cell of origin is most likely to be a transformed B cell. No consistent chromosomal or molecular abnormalities have been described in HD, but deletions of genetic material seem to be much more frequent than chromosomal translocations. On histological examination, the separation of nodular lymphocyte-predominant Hodgkin's lymphoma (NLP-HD) from classical Hodgkin's lymphoma is essential. The latter is split into the frequent nodular-sclerosis and the mixed-cellularity subtypes, while lymphocyte-rich classical HD is rare. Many cases formerly classified as lymphocyte-depletion HD can nowadays be identified as NHL, particularly T-cell NHL and T-cell-rich B-cell NHL, or undifferentiated carcinomas, although true lymphocyte-depletion HD patients do exist. Histologically, lesions contain the pathognomonic Reed–Sternberg cells in classical HD, and atypical B cells ('popcorn cells') in NLP-HD. Staging procedures in HD are not much different from NHL. Staging laparotomy with splenectomy has been abandoned, since it provides no clinical advantage over modern imaging. In contrast to NHL, HD spreads via neighboring lymph node areas in an orderly fashion (Kaplan's rule) and rarely skips adjacent lymph node regions. In younger patients, as a rule of thumb, lymph node areas above the diaphragm are most frequently involved, while in elderly patients HD lesions tend to cluster below the diaphragm. The Cotswold staging system for HD is similar to the Ann Arbor staging used in NHL, with the absence (A) or presence (B) of constitutional symptoms specified. Prognostic factors overlap to some extent with those identified in NHL, with B symptoms, stage, and age being important. A prognostic score from the German Hodgkin Study Group has identified a number of additional parameters as being discriminatory, such as the degree of anemia, low albumin, but (somewhat surprisingly) not the ESR or LDH.

Treatment of HD offers high chances of cure throughout, perhaps higher than in any other type of lymphoma. The choice of treatment depends much on the stage at diagnosis, but no truly international consensus exists as to the 'best' modalities. Early stage HD with favorable prognostic features may be treated with radiotherapy alone. Radiotherapy can be given to clinically/radiologically involved areas (i.e. 'involved field') or extended to include neighboring lymph node areas (i.e. 'extended field'). Mantle fields more or less involve all lymph nodes above the diaphragm, while an 'inverted Y field' encompasses para-aortic, pelvic, iliacal, and inguinal regions. Extensive radiotherapy is increasingly being abandoned, and trends favor short-pulse chemotherapy combined with limited radiotherapy even for stage I–II patients. In advanced stage, HD radiation can be limited to tumor bulk with a particularly high risk of local relapse. In patients with advanced HD stages, and those at early stages with risk factors, chemotherapy is mandatory. A number of chemotherapy regimens have been reported to be active in HD, such as MOPP, ABVD, and their hybrid combinations, as well as BEACOPP (dose escalated), and others. Their common denominator is that they combine alkylating agents, anthracyclines, and steroids. In BEACOPP and some hybrid regimens, etoposide is added. Optimal duration and number of cycles are not strictly defined, but for best results patients generally require several months or up to half a year of therapy. The combination of extensive radiotherapy and prolonged administration of alkylating agents increases the likelihood of secondary AML and solid neoplasms. Long-term survivors of HD may also suffer from late cardiac or pulmonary toxicity, or hypothyroidism, which should be considered at late follow-up visits. Current treatment protocols are therefore geared not only toward improving cure rates (high anyway) but also toward limiting such late toxicity. Patients with HD in relapse may expect a renewed chance of cure, but they usually require more intensive treatment, and many of them are candidates for high-dose chemotherapy with autologous stem-cell transplantation. A minority of patients experience second or later relapses, and in these chances of cure tend to dwindle. Palliative treatment may nevertheless be valuable, but should be cautiously used to limit toxicity. Cure rates in early stage HD approach 90%–95% of patients. Patients with far-advanced HD exhibiting adverse prognostic factors represent the other end of the spectrum, but may still hope for cure in about 50%.