22.3.3 Acute myeloid leukaemia 5205 Nigel Russell

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myelodysplastic syndromes or myeloproliferative neoplasms. Clinical features—these are of marrow failure, with anaemia, bleeding (petechiae, purpura, from mucous membranes), and infection. Acute promyelocytic leukaemia should be viewed as a medical emergency characterized by disseminated intra- vascular coagulation which requires urgent treatment to avoid haemorrhagic death. Diagnosis relies on examination of periph- eral blood and bone marrow for blast cell infiltration, with clas- sification and prognosis of disease depending on morphology, immunophenotyping, karyotyping, and definition of particular molecular mutations. General approach to treatment—aside from providing appropriate supportive care, the first clinical decision to be made is whether to give conventional intensive chemotherapy aiming for disease eradica- tion, or to adopt a more palliative approach. Intensive chemotherapy is the norm up to age 65 to 70 years. Above this age, the biology of the disease tends to be less favourable and patients may have significant comorbidities limiting treatment tolerance. A decision about embarking on conventional intensive therapy in older patients should be made only after a careful medical assessment. Initial chemotherapy—(1) intensive chemotherapy—this typically in- volves the combination of daunorubicin (or other anthracycline-like drug) and cytosine arabinoside (cytarabine, ara-C), which achieves complete remission in 50 to 80% of cases depending on age. This is followed by consolidation chemotherapy (a second course of in- duction treatment and then further ara-C with or without additional agents). (2) Less-intensive chemotherapy—has most often com- prised of hydroxycarbamide (hydroxyurea), low doses of ara-C, or a demethylating agent such as azacitidine. (3) Acute promyelocytic leukaemia is exquisitely sensitive to all-trans-retinoic acid (ATRA) or arsenic trioxide (ATO), each of which can be given concurrently with chemotherapy. Recent data demonstrate that the combination of ATRA and ATO alone is highly effective, at least in low-risk cases. In patients under 60 years, 75 to 80% will achieve initial remission and about 45 to 50% will survive. In older patients given intensive treatment, 50 to 60% will enter remission but only 15 to 20% will sur- vive 2 years. With nonintensive treatments, remissions are seen in 15 to 25% with the median survival being 6 to 9 months. Relapsed disease—more than 50% of patients will ultimately relapse and their overall outcome is generally very poor. The best curative option is allogeneic stem cell transplantation if a second complete remission can be achieved with reinduction chemotherapy. Prospects for the future Increasing knowledge of the underlying molecular characteristics of acute myeloid leukaemia may permit more targeted therapy; how- ever, most cases have more than one of the many mutations which can occur and the resulting small patient groups will be a challenge for therapy development in what is already a relatively rare disease. Currently available treatments may be improved in some patients using minimal/measurable residual disease assessment to determine risk on a more individualized basis. Epidemiology and causation The median age at presentation is 68 to 70 years. Acute myeloid leukaemia (AML) occurs at all ages, ranging in frequency from 3 per million up to 12 to 15 per million patients in their 70s and 80s (Fig. 22.3.3.1). This age range has implications for treatment. In most cases there is no obvious cause; however, it is known that chemical and ionizing radiation exposure can be leukaemogenic. Chemotherapy for other cancers may be leukaemogenic, and the development of AML represents a late complication of treatment of some solid tumours, which is being seen more frequently as chemo- therapy becomes more successful. In many cases, AML in older pa- tients evolves from the related disorder myelodysplastic syndrome or other myeloproliferative disease, and indeed the boundary be- tween the diseases is sometimes hard to define. The current inter- national consensus defines AML as over 20% blast cells in the bone marrow. At this level, marrow function is usually compromised re- quiring intervention.

 At the molecular level, it is believed that AML is an example of multi-hit pathogenesis, with mutations which promote growth or inhibit apoptosis arising in association with mutations that inhibit differentiation. Dysregulation of gene expression by methylation is also involved. Molecular abnormalities that have such effects are being increasingly recognized. Diagnosis The heterogeneity of morphology which reflects the ability of the leukaemic blast to achieve some degree of differentiation gave rise to a commonly accepted morphological classification known as the French–American–British (FAB) classification. With the increasing availability of high-quality monoclonal antibodies, immunophenotypic confirmation gave some objectivity to the diag- nostic process. Over 30 years ago it was being recognized that various chromosome abnormalities were present in the blast cells. These were nonrandom and comprised balanced translocations, deletions, and trisomies. In about 40% of cases only, a normal karyotype could be found. Some of these abnormalities corresponded to the morpho- logical subtype. It took a number of years for the clinical community to feel that this was useful knowledge. However, it is now recognized that the karyotype is the strongest predictor of response to therapy, and is now an essential part of the diagnostic process. Since some of the cytogenetic breakpoints have been cloned, they have revealed targets for therapy or sensitive disease monitoring. Currently a similar awakening is underway with the recognition that molecular abnormalities are often found. The most common are mutations of the FMS receptor FLT3, NPM1, DNMT3A, IDH1, IDH2, CEBPα, RAS, and c-KIT. These represent in some cases add- itional strong independent prognostic factors, but may become the target of a new generation of molecular-based therapies. There is increasing interest in the role of noncoding DNA and epigenetic abnormalities Prognostic factors Several characteristics independently predict how a patient with AML will respond to treatment. Most apply to the prospect of initial treatment achieving complete disease remission, and to overall survival. Performance score is mainly useful for predict ing response to induction treatment. It should be mentioned here that these factors have been defined in the setting of large clinical trials, into which poor performance patients may not be entered. The key factors are shown in Box 22.3.3.1. Cytogenetics has been most widely adopted, and can guide treatment decisions such as who should be subjected to allogeneic transplant. Grouping the more favourable abnormalities (t(8;21), inv(16), and t(15;17)) and the poorer group abnormalities (of chromosomes 5 or 7, 3q–, complex) leaves about 60% of patients as at standard risk. As can be seen in Fig. 22.3.3.2, this subdivision has a major impact on survival. One of the reasons that older patients respond less well to the same chemotherapy is that older patients tend to have a high proportion of adverse features, in contrast to younger patients. Some molecular abnormalities may provide prognostic informa- tion particularly in normal karyotype AML, for example, the asso-ciation with an NPM1 mutation in the absence of a FLT3 mutation or biphenotypic mutation of CEBPα are generally regarded as having a favourable prognosis with chemotherapy, and as such can avoid stem cell transplant as part of initial treatment. Molecular findings are continuously influencing prognostic estimates. This is highly complex because of the coexistence of mutations which may modulate each other’s impact compared with when they occur alone. Furthermore, the allelic burden of a mutation can impact on its prognostic importance. Treatment of acute myeloid leukaemia General considerations Because of the variation of disease and patient biology, treatment and the assessment of treatment is complex. Treatment outcomes have improved over the years in children and adults under 60 years 0 25 75 50 100 20 15 10 5 0 age rate per 100 000 Median age: 65–70 years Fig. 22.3.3.1 Age-specific incidence of acute myeloid leukaemia (AML). Data from Wingo PA, et al. (1995). Cancer statistics, 1995. CA Cancer J Clin, 45, 8. Box 22.3.3.1 Prognostic factors • Age • Cytogenetics • Presenting WCC • Secondary disease •

Performance score • FLT3/NPM1 mutation status • Expression of resistance phenotype • Marrow response to first chemotherapy course 100 75 50 25 0 0 1 2 3 4 5 years from randomization 68% 44% 18% 2P <0.00001 % still alive Good Standard Poor Fig. 22.3.3.2 Survival from complete remission (CR) by the Medical Research Council (MRC) risk group.

22.3.3 Acute myeloid leukaemia 5207 (Fig. 22.3.3.3), but progress in older patients is much less clear. Chemotherapy has been relatively unchanged over the years in terms of drugs used, and it is easy to attribute the better outcomes to improved supportive care, which in turn has allowed treatment to be given in a more intensive way. Definition of remission The standard definition of 'remission' is that the bone marrow should show evidence of trilineage activity with less than 5% blasts, and peripheral blood counts should have returned to at least 100 × 109/litre for platelets and 1.0 × 109/litre for neutrophils. Molecular and other markers of residual disease may still indicate the presence of the leukaemic clone, and it is well established that failure to deliver further courses of treatment to consolidate the response will result in rapid regrowth of disease. It is increasingly likely that the application on minimal residual disease detection by flow cytometry or polymerase chain reaction (PCR) may refine these definitions as is the case in other haematological malignan- cies. The first clinical decision to be made in an individual patient is whether to undertake conventional intensive chemotherapy aiming for disease eradication, or to adopt a more palliative ap- proach. The aim of intensive chemotherapy is to kill off the leu- kaemic population, which then enables normal haematopoiesis to re-establish itself. This will inevitably mean several days of pan- cytopenia, a high risk of gut toxicity, and extreme vulnerability to infections of microbiological, fungal, or viral causation. Chemotherapeutic regimens The combination of the anthracycline daunorubicin and the nucleo- side analogue cytosine arabinoside (cytarabine, ara-C) has been the mainstay of treatment of AML for nearly 40 years with the intention of inducing complete remission (CR) and curing the disease. Such a combination is extremely myelosuppressive and is associated with a significant risk of infection and severe systemic toxicity. Among younger patients, there is a risk of death during induction therapy of almost 10%, usually due to infection or bleeding. Such toxicity may limit the applicability of such a regimen to the treatment of older adults who constitute the majority of patients with AML. Patients who achieve CR will continue with further courses of chemotherapy, at approximately monthly intervals, to consolidate the remission and reduce the risk of relapse. In the United Kingdom, initial induction therapy for younger people (<60 years of age) comprises 3 days of daunorubicin at doses of 60 mg/m2 (usually given on days 1, 3, and 5) with 10 days of ara-C at 200 mg/m2 daily. In the United States of America, this is usually shortened to a 7-day continuous infusion of ara-C, the so-called 3+7 approach. Recent studies have shown a dose effect of daunorubicin, with 90 mg/m2 being superior to 45 mg/m2. However a large recent study showed that 60 mg/m2 was equivalent to 90 mg/ m2. Similarly higher doses of ara-C have been tested in induction without convincing evidence of improving survival. There are other apparent differences in treatment preferences between the United States of America and the United Kingdom. Comparison of large national trials has not shown convincing evidence that the addition of a third drug, usually etoposide or thioguanine, improves the out- come of induction treatment in younger adults since the additional leukaemia cell kill is potentially offset by increased toxicity. Equally, attempts to improve outcomes with alternative anthracyclines (idarubicin or mitoxantrone) have shown no advantage. The United Kingdom Medical Research Council (MRC) AML12 trial compared MRC AML Trials: overall survival age 0–14 MRC AML Trials: overall survival age 15–59 100 75 73% 63% 63% 54% 46% 24% 3% 50 % still alive 25 0 100 75 53% 43% 35% 0 5 10 15 20 25 years from entry 29% 23% 15% 5% 50 %

still alive 25 0 0 5 10 years from entry (a) (c) (b) 15 20 25 MRC AML Trials: overall survival age 60+ 100 75 23% 10% 7% 4% 2% 1% 50 % still alive 25 0 0 5 10 years from entry 15 20 25 2%
Fig. 22.3.3.3 Medical Research Council (MRC) trial results by patient ages. (a) 0 to 14 years (n = 1096); (b) younger adults, 15 to 59 years (n = 7704); (c) older patients, 60+ years (n = 3541).

 mitoxantrone with daunorubicin, in combination with either etoposide or thioguanine, and found no overall difference in long- term outcome. In recent years, it has become feasible to conjugate chemothera peutics with antibodies as a means of targeting the antileukaemic potential without increasing toxicity. The archetypal agent in AML is gemtuzumab ozogamicin, which is a CD33-targeted immuno conjugate of the anthracycline-like drug, calicheamicin. CD33 is a transmembrane protein expressed on the cells of 95% of patients with AML. On binding antibody, it is rapidly internalized, and free calicheamicin is released causing genotoxic damage. A recent meta- analysis of five large trials in over 3000 patients where gemtuzumab ozogamicin was combined with induction chemotherapy reported that this provides a significant survival benefit for patients without adverse cytogenetic characteristics. Cytarabine remains one of the most active drugs in the treatment of AML. Several groups have increased the dose up to 3 g/m2 in in- duction with mixed results. At these high doses there is significant skin, renal, and central nervous system toxicity. However, certain subsets of AML, particularly the core binding factor leukaemia as- sociated with t(8;21) and inv(16), are particularly sensitive to ara-C and may benefit from this approach. Newer analogues of cytarabine such as cladribine are now entering randomized trials. The combin- ation of fludarabine/ara-C/granulocyte-colony stimulating factor (G-CSF) and idarubicin (FLAG-Ida) is a very effective induction combination capable of producing high remissions with one in- duction course, but results in profound myelosuppression, and may limit the ability to deliver consolidation treatment. Outcomes of treatment Between 40 and 80% of patients, depending on age, will achieve CR with this approach and over 70% will do so after a single course of induction. Factors influencing the chance of CR include age at diag- nosis, cytogenetic abnormalities, and expression of multidrug resist- ance genes (e.g. p-glycoprotein). For example, 75 to 80% of patients aged less than 60 years will achieve a CR, compared with 45 to 55% of older patients given the same treatment schedule. Consolidation of chemotherapy Patients who achieve CR will require further consolidation chemo- therapy. This may take the form of a second course of the initial induction treatment, followed by two or three further courses of al- ternative drugs. High doses of ara-C (1.5 g/m2 or 3.0 g/m2) are com- monly used particularly in patients with favourable and standard risk disease. There are probably better treatments for consolidation of adverse risk patients such as FLAG-Ida, but such patients should proceed to an allogeneic stem cell transplant. It is not clear how many courses of treatment is optimal pretransplant or in total if a transplant is not feasible. Treatment of older patients Age is a major factor determining CR rates and long-term outcome. Older age is associated with the onset of significant comorbidities such as hypertension, lung disease, or renal or cardiac impairment, which limit chemotherapy delivery. Similarly, the biology of leu- kaemia is more adverse in older people: there is a higher incidence of unfavourable genetic changes and multidrug resistance, and AML in this age group more frequently results from secondary disease. Consequently, older people tend to do less well than younger pa- tients with AML given the same treatment. The age of 60 years is frequently taken as an arbitrary threshold for the use of the term ‘older’, but this is arbitrary. Up to this age there is little doubt that intensive chemotherapy should be the norm; however, with increasing age, patients develop comorbidities and become less generally fit. This makes intensive treatment more risky particularly in patients older than 70 years. In addition, the

biology of the disease is less favourable, with a higher proportion of patients with secondary AML, more with leukaemia that has associated resistance proteins within the leukaemic population, and a higher proportion with an adverse risk karyotype. A number of epidemiological studies indicate that at least 40% of older pa- tients are not treated with intensive chemotherapy and receive supportive care only with hydroxycarbamide (hydroxyurea) or some other low-intensity treatment. There has been much recent interest in the development of treatments for this patient group. A major national trial in the United Kingdom was able to demon- strate that low doses of ara-C given subcutaneously (20 mg twice daily for 10 days) repeated at 4- to 6-week intervals is superior to hydroxycarbamide. Indeed, one in six patients will gain CR with this approach, although these remissions tend to be less durable than those seen in younger patients treated with conventional doses of chemotherapy. Demethylation treatments, azacitidine or decitabine, are more widely used and are approved in Europe for this patient group. These agents do not improve the rate of remission compared with low-dose ara-C, but seem capable of maintaining those who do not enter remission in a stable haematological condition. Such ran- domized data as are available do not show a significant difference in survival between these treatment options. Azacitidine also has activity in AML, particularly in patients with unfavourable cytogen- etics or myelodysplasia-related changes although randomized trials did not result in a significantly better survival compared with low- dose cytarabine. What these studies show is that overall the outlook for older pa- tients with AML remains very poor but that the majority of older patients should be considered for specific chemotherapy as well as optimal supportive care with prophylactic antibiotics, antifungals, and blood product support. Treatment of relapsed AML Despite 60 to 80% of patients with AML attaining CR with induction chemotherapy, more than 50% of these will ultimately experience a relapse of their disease. Reinduction with intensive chemotherapy remains an option for these patients, but the overall outcome is gen- erally very poor. Remission rates with reinduction are lower than in first presentation, and remissions are generally of shorter duration. The factors which predict outcome, irrespective of what treatment is used, are patient age, the risk group based on cytogenetics and other factors at the original presentation, the duration of first remis- sion, and whether or not a stem cell transplant has already been per- formed. The only curative option is to proceed to an allogeneic bone marrow transplantation when in second complete remission (CR2). No randomized trial has shown a superiority of one reinduction regimen over another, but the combination of fludarabine (a purine analogue) with ara-C and idarubicin with G-CSF support is one favoured regimen.

22.3.3 Acute myeloid leukaemia 5209 Targeted therapy In recent years the molecular heterogeneity of AML has become better understood and has opened an era of targeted treatments, some of which have received regulatory approval. None is a ‘cure- all’ for the particular subset targeted. Gentuzumab ozogamicin has been mentioned and because its addition to induction chemo- therapy has reduced the risk of relapse it can improve the survival of intermediate and favourable, but not adverse risk groups. The first molecularly targeted treatment has been midostaurin against FLT3 mutated disease which occurs in 30% of younger patients and about 15% of older patients. The survival benefit is significant but still less than 10% at 5 years when added as part of first line treatment. More recently a second FLT3 inhibitor (gilteritinib) has been approved for relapsed disease, and there are other FLT3 inhibitors in devel- opment. More recently mutations of the iso-citrate dehydrogenase (IDH) genes have been found in 10–15% of cases. There are now IDH inhibitors of IDH1 (ivosidenib) and IDH2 (enasidenib) which have been approved for relapsed disease. It has been recognized that one reason why AML treatment is less

successful in older patients is that the cells more frequently express anti-apoptotic proteins such as BCL2. Previous efforts to target BCL2 have not been successful, however venetoclax has caused great interest in other haemato- logical malignancies and preliminary studies in older patients with AML in combination with low dose cytaribine or azacitidine or dectibine have led to its regulatory approval. A development, which was surprising to some, was that by com- bining daunorubicin and cytarabine in a fixed 1:5 ratio in a lipo- some, showed superior survival when compared with daunorubicin and cytarabine alone. However the benefit was restricted to patients with secondary AML or adverse cytogenetics. This drug, Vyxeos, provides a new option for poor risk patients. These new agents which have become available in the last two years, provide many opportunities to further refine treatment. Maintenance chemotherapy and DNA methylation Traditionally, maintenance therapy using lower doses of chemo- therapy has had no or only marginal benefit, and has dropped out of use. There has been interest over the years in immunomodulation using interleukin-2 (IL-2). This agent did not show benefit in ran- domized trials and was associated with toxicity. However, efforts were made to find treatments which could be combined with IL- 2 which could retain the efficacy, but with lower doses of IL-2 and thereby less toxicity. Studies with the combination of histamine dichloride and low-dose IL-2 validated this approach, but confirma- tory studies are lacking. There is emerging interest as to whether maintenance therapy with a demethylation agent could be effective, arguably through an immunomodulatory mechanism. Bone marrow transplantation Having entered remission, the main challenge is to prevent re- lapse. There is no doubt that the most effective approach is to ad- minister myeloablative chemoradiotherapy followed by infusion of donor haematopoietic stem cells. These have been obtained from an HLA-matched sibling donor as bone marrow or mobilized stem cells collected from the peripheral blood. This approach reduces the risk of disease relapse from 40 to 50%, to 10 to 15%. This powerful antileukaemic effect is partly due to the myeloablation and partly due to the associated ‘graft versus leukaemia’ mediated by donor T lympho- cytes in the graft. Unfortunately, it has not been possible to fully realize the antileukaemic potential of allogeneic transplantation due to the associated risks of graft-versus-host disease and immunosuppression which usually involve a life-threatening risk of up to 30%. The risks increase with advancing age and the presence of comorbidities particu- larly when intensive myeloablative conditioning is used. The develop- ment of large donor banks has made the finding of a matched unrelated donor a practical possibility for the majority of patients, and the results of this approach are now equivalent to those using a matched sibling. Allografting involving reduced-intensity conditioning (RIC) has become well developed. Here the mechanism is primarily im- munological, mediated by a graft-versus-leukaemia effect. Data now emerging from the National Cancer Research Institute AML 15 and 16 trials suggest that this is also a feasible approach which can im- prove survival compared to chemotherapy in older patients up to the age of 70 years who have few comorbidities. As discussed previously, once patients enter remission, they are at differing risks of relapse based on their cytogenetic group. It is unlikely that patients with favourable cytogenetics will benefit from allogeneic transplant, because the additional reduction in relapse risk is more than outweighed by the treatment risks. For patients at intermediate risk, there are mixed opinions, but no convincing evidence of overall survival benefit in United Kingdom prospective trials. Most would accept that patients with bad risk disease should undergo a transplant as soon as the risk is known. Such patients will have a higher risk of relapse after the transplant, but they have a very poor outcome with chemotherapy alone. The debate about who should receive a transplant, and of which type if the option is avail- able, has been going on for many years. The debate centres on the 60% of younger patients who have intermediate risk. It is generally accepted that any benefit from a

myeloablative transplant is limited to patients less than 40 years of age. As well as cytogenetics and the other risk factors mentioned previously, the various molecular abnormalities can now be taken into account. For example, many investigators use the presence of a FLT3 mutation as an indication for transplant because of the high relapse risk. However, the results from transplantation in these patients is less good than expected, and furthermore the prognosis of a FLT3 mutated patient can be affected by the alleleic ratio of the mutation and whether or not its adverse effect is neutralized by the coexistence of a nucleophosmin 1c (NPM1c) mutation. Studies from the United Kingdom currently suggest that for patients aged less than 40 years a matched (related or unrelated) myeloablative transplant is beneficial in patients with adverse risk and those with intermediate risk who have a FLT3 mutation-positive/NPM1c mutation-negative genotype. For older patients, a RIC allograft is beneficial for intermediate risk patients who have a matched sibling donor. There is a lack of evidence for benefit for a RIC in intermediate risk with an unrelated donor, or patients with adverse risk. These observations are subject to change as novel preparative schedules for RIC transplants are developed. For patients who relapse following chemotherapy and enter a second remission, the prospects for cure are poor and are largely dictated by the length of their first remission. It is axio- matic that second remissions will be shorter than first remissions. Transplantation is the only treatment that can change this and is indicated for all patients who relapse, where it offers a 30 to 40% chance of salvage.

SECTION 22 Haematological disorders 5210 Supportive care in AML The steady but significant improvements seen in disease survival rates over the last 30 to 40 years have been facilitated by the de- velopment of better supportive care strategies which have allowed the safer intensification of chemotherapy regimens. There is clear evidence that the 30- and 60-day mortalities have dropped over recent years. Following diagnosis of AML, early mortality can result either dir- ectly from presenting complications of the disease, from the direct consequences of treatment initiation, or from problems arising during the 3 to 4 weeks of profound pancytopenia that inevitably follow remission-induction chemotherapy. Effective supportive care during this period requires close coordination between special- ists from a number of disciplines including haemato-oncologists, microbiologists, radiologists, intensivists, specialist nurses, phar- macists, and dieticians working in facilities dedicated to the care of this type of patient. Clear written standards should be adhered to, including local policies for infection prophylaxis and treatment, national guideline documents, and, where appropriate, clinical trial protocols. Supportive care at the initiation of therapy The presenting clinical features of AML vary according to both the depth of bone marrow failure and the rate of turnover of the leu- kaemic clone. Prompt chemotherapeutic intervention is required in cases with high rates of blast proliferation but, paradoxically, rapid cell kill may lead to life-threatening metabolic disturbances. Hyperleucocytosis Although a feature of only a minority of cases, a high presenting white cell count (WCC) is a well-established poor prognostic factor in AML. Patients with hyperleucocytosis (WCC >100 × 109/litre) are at a threefold greater risk of early mortality (15%) than those with lower counts. Hyperleucocytosis predisposes to hyperviscosity and leucostasis. ‘Sludging’ in the microvasculature, particularly of the lungs and brain, clinically manifests most frequently as hyp- oxia and central nervous system dysfunction and carries significant risks of both thrombotic and haemorrhagic sequelae. The effects of hyperviscosity may be partially offset at presentation by the pres- ence of concurrent anaemia: red cell transfusion should thus be delayed, unless absolutely unavoidable, until the WCC has been re- duced. Oral hydroxycarbamide may be of practical value in reducing the WCC prior to the commencement of formal induction chemo- therapy. Leucapheresis is generally safe and, although evidence is

lacking, may be considered in patients presenting with symptomatic hyperleucocytosis. However, leucapheresis may fatally exacerbate the presenting coagulopathy of APL and should be avoided in this setting. Tumour lysis syndrome and metabolic complications Acute tumour lysis syndrome describes a collection of metabolic abnormalities including hyperuricaemia, hyperphosphataemia, hypocalcaemia, and hyperkalaemia that result from the release of nuclear and cytoplasmic degradation products from malignant cells and may precipitate acute kidney injury. It is vital that treating phys- icians are aware of the risks of acute tumour lysis syndrome, par- ticularly when instituting cytoreductive therapy in AML patients with hyperleucocytosis or bulky extramedullary disease. Emergency haemodialysis may be required in the event of acute kidney injury, rising potassium levels, or recalcitrant hyperphosphataemia. Standard measures to prevent acute tumour lysis syndrome prior to the commencement of chemotherapy include use of the xanthine oxidase inhibitor allopurinol (300 mg daily) coupled with vigorous intravenous hydration and with meticulous monitoring of fluid balance and electrolyte levels as induction therapy commences. Alkalinization of the urine using intravenous bicarbonate has been used historically to reduce tubular uric acid crystal deposition, but it remains controversial as it carries the potential for both reducing tubular xanthine solubility and exacerbating calcium pyrophosphate deposition in organs including the heart. The recombinant urate oxi- dase enzyme rasburicase is able to rapidly reverse hyperuricaemia by promoting the breakdown of uric acid into allantoin. It is now the treatment of choice in patients with hyperleucocytosis at pres- entation, renal failure, or early evidence of evolving acute tumour lysis syndrome. Rasburicase also avoids any need for urinary alkalinization. Hypokalaemia is also frequently encountered in AML patients, both at presentation (due to high serum lysozyme levels particu- larly in monocytic subtypes M4 and M5) or later as a consequence of prolonged diarrhoea or the renal tubular effects of amphotericin. Vigorous intravenous electrolyte supplementation is frequently required. Other supportive measures prior to starting cytotoxic therapy Secure central venous access is usually established through inser- tion of a tunnelled Hickman line or temporary central line, allowing safe administration of vesicant drugs, blood products, and intra- venous antibiotics, as well as facilitating frequent blood-sampling procedures. Young men should be counselled regarding potential loss of fertility and, whenever possible, offered the opportunity to store sperm. Loss of fertility due to chemotherapy is less common in women: in vitro preservation of unfertilized ova is not yet under- taken routinely. There is a high risk of severe emesis with intensive chemotherapy, and strenuous efforts should be made to prevent this distressing complication. Serotonin antagonists (ondansetron or granisetron) are a standard first choice, although combination therapy is often necessary. Supportive care during chemotherapy-induced pancytopenia Clearance of leukaemic blasts by induction chemotherapy is achieved at the expense of 3 to 4 weeks of severe pancytopenia, and similar cytopenic episodes will follow subsequent courses of con- solidation therapy. During these periods, patients remain at high risk: prompt access to blood product support and robust procedures to prevent and manage neutropenic infections are vital. Blood product support By the time of initial disease presentation, the ability of most patients to produce red cells and platelets is severely impaired. Due to the often rapid onset of anaemia, there may be little time for haemo- dynamic compensation making many patients symptomatic due to acute impairment of oxygen-carrying capacity. In the absence of hyperleucocytosis, red cells should be transfused promptly. Following intensive chemotherapy, patients will inevitably be de- pendent on regular transfusion support until bone marrow recovery.

22.3.3 Acute myeloid leukaemia 5211 Although there is no firm evidence to support a particular red cell transfusion threshold, many units operate a policy of transfusing as required to maintain haemoglobin levels in excess of 80 g/litre. Patients treated with cytotoxic regimens containing purine ana- logues (fludarabine or clofarabine) should receive irradiated blood products to minimize the risk of transfusion-associated graft- versus-host disease. In general, one adult therapeutic dose of platelets should be transfused whenever the platelet count falls to below 10 × 109/litre. Platelet survival may be further compromised by sepsis or the use of concurrent intravenous antibiotics, and in these situations or in the presence of additional haemostatic abnormalities a higher transfu- sion threshold of 20 × 109/litre is usually observed. Antifibrinolytic agents such as tranexamic acid may be useful for local mucosal bleeding but are contraindicated in the presence of haematuria due to the potential for ureteric clot formation. Infection The risk of infection in AML is influenced by both the degree and duration of neutropenia and increases markedly during episodes of chemotherapy-induced bone marrow aplasia. Changes to the bac- terial flora as a consequence of broad-spectrum antibiotic use, and poor nutritional status following prolonged periods of hospitaliza- tion also contribute significantly. The vast majority of AML patients will become febrile at some point, although only a minority of these episodes will be accompanied by symptoms or signs of localizing infection. Sepsis should be suspected in the presence of any sudden nonspecific clinical deterioration; inflammatory responses may be muted in the neutropenic setting and may be associated with hypothermia, declining mental status, myalgia, or increasing leth- argy. Potential portals of bacterial entry include indwelling lines and chemotherapy-induced breaches in the integrity of the bowel mucosa. Neutropenic patients should be advised to pay particular atten- tion to personal hygiene and dental care. Careful hand-washing and decontamination before patient contact is mandatory for healthcare workers. The role of prophylactic antibiotic therapy remains con- tentious. Data from studies of adults with leukaemia, and stem cell transplantation, suggest that prophylaxis with fluoroquinolone anti- biotics reduces the risk of neutropenic sepsis and this approach is recommended in National Institute for Health and Care Excellence guidance but with the corollary that rates of antibiotic resistance and infection patterns within individual institutions should be monitored. Patients should be made aware of their susceptibility to infection and provided with emergency contact details to allow rapid clin- ical assessment. In the presence of neutropenic sepsis, the prompt institution of broad-spectrum antibacterial therapy is potentially life-saving. Patterns of infection and pathogen isolation will vary between hospitals, and clear written guidelines for the emergency management of patients with febrile neutropenia should be decided in discussion with local microbiologists. Examples of empirical antibiotic regimens include monotherapy with a third-generation cephalosporin or carbapenem, or combination therapy with a broad-spectrum antipseudomonal penicillin and aminoglycoside. Vancomycin or teicoplanin may be added to broaden Gram- positive coverage if there are particular clinical concerns regarding indwelling line infection. Mandatory investigations include central and peripheral blood cultures, cultures of urine and stool, and a chest radiograph. Further modifications to the initial antibiotic regimen should be based on culture results and regular clinical examination, although surveys demonstrate that the rate of proven bacteraemia during episodes of febrile neutropenia has remained between 20 and 25% for many years. Persistent infection or blood culture isolation of Gram-negative organisms or candida should prompt indwelling central line removal. The risk of invasive fungal infection is high in AML patients re- ceiving intensive chemotherapy, and its incidence increases with the severity and duration of neutropenia, often occurring in the aftermath of bacterial sepsis. Established fungal infections carry a high mortality. The diagnosis of invasive fungal infection should be confirmed wherever possible,

and there is an increasing move away from the empirical use of antifungal agents as treatment of fever of unknown origin. High-resolution CT scanning of the chest in pa- tients with persistent pyrexia refractory to antibiotic therapy, and screening of patients using the sandwich enzyme-linked immuno- sorbent assay (ELISA) for Aspergillus galactomannan aid the early detection of invasive pulmonary aspergillosis, allowing the tar- geted implementation of antifungal therapy with agents including liposomal amphotericin B and caspofungin. Azole antifungal agents are widely prescribed prophylactically during neutropenia in AML. Posaconazole is the drug of choice in this setting and has activity against a broader spectrum of fungal organisms than fluconazole which is inactive against moulds including aspergillus species. A modest reduction in duration (but not depth) of neutropenia may be achieved with the use of recombinant growth factors (G- CSF or granulocyte–macrophage colony-stimulating factor) fol- lowing induction and consolidation chemotherapy. Large controlled trials show variable effects on the incidence of severe infection and no clear overall survival benefit. Routine growth factor use is not recommended, although there may be cost–benefit advantages in terms of reduction in both antibiotic usage and the duration of hos- pital admissions. Acute promyelocytic leukaemia APL is a medical emergency characterized by bleeding and dis- seminated intravascular coagulation. It usually presents with pan- cytopenia rather than a raised WCC. The diagnosis is made on morphology with a typical hypercellular marrow with characteristic heavily granulated promyelocytes. Immunophenotyping by flow cytometry may provide supportive data, and PML body staining shows a characteristic perinuclear speckled pattern on staining for PML. The diagnosis is confirmed by cytogenetic or molecular studies for the PML-RARα rearrangement of the t(15;17) translocation. Treatment of APL This disease is exquisitely sensitive to treatment with all-trans- retinoic acid (ATRA), a vitamin A analogue normally present in blood. The translocation renders cells resistant to physiological con- centrations of ATRA, but sensitive to pharmacological doses. APL is particularly sensitive to anthracyclines so ATRA is given con- currently with idarubicin. Whether other anthracyclines could be equally effective is not clear. Whether other chemotherapy drugs are need is a matter of debate, in particular the need for any ara-C,

 and the requirement for maintenance is now in doubt. The disease is also highly sensitive to arsenic trioxide. High rates of CR and an excellent long-term prognosis with 5-year disease-free survival rate of greater than 80% are now expected. However, treatment is associ- ated with an increased risk of bleeding in these patients, particularly in the first 3 or 4 weeks of treatment, and intense support of the coagulation system is required with blood products. Once a patient reaches 1 month into treatment, the prognosis is greater than 90% survival, and the risk of relapse is lower with APL than with other types of AML. Due to the specific nature of the molecular lesion in APL, moni- toring of minimal residual disease by PCR allows very sensitive de- tection of any impending relapse. Restarting treatment at the time of molecular detection of disease recurrence improves overall out- come. For relapsed APL the treatment of choice is arsenic trioxide which induces degradation of PML-RARα. In recent years, the aim of most clinical trials has been to de- escalate treatment and the most recent randomized data impres- sively show that the ‘chemo-free’ combination of ATRA and arsenic trioxide is highly effective, giving an overall survival of higher than 90%. In these studies, the risk of disease relapse is very low once in molecular remission, which raises the question of the need for rou- tine minimal residual disease monitoring in the context of that treat- ment, although it probably has benefit if the ATRA/anthracycline chemotherapy is used. Supportive care issues specific to treatment initiation in APL Although abnormalities of coagulation may contribute to a bleeding tendency at presentation in any subtype of AML, APL, and more es- pecially its hypogranular variant (M3v), are

particularly associated with a high risk of early haemorrhagic death due to a combination of disseminated intravascular coagulation and increased fibrin- olysis. Eighty per cent of APL patients have clinically significant coagulopathy: this condition constitutes a genuine haematological emergency that requires rapid diagnosis and prompt initiation of therapy. There is now considerable evidence that the early introduc- tion of ‘differentiation therapy’ with ATRA alongside anthracycline- based chemotherapy improves the coagulopathy associated with APL. The platelet count and coagulation profile should be checked at least twice daily during the early stages of treatment. By using an ag- gressive transfusion policy, the platelet count should be maintained above 50 × 109/litre, and coagulation times kept within the normal range using fresh frozen plasma replacement. Cryoprecipitate or fi- brinogen concentrates should be used to maintain a fibrinogen level close to 2 g/litre. The use of heparin is no longer recommended. Complications of treatment in APL Retinoic acid syndrome (also known as differentiation syndrome) is a potentially life-threatening complication of the use of ATRA or arsenic trioxide therapy in APL. It is caused by cytokine release from differentiating APL cells and characterized by a rising WCC with ac- companying features of fluid retention and capillary leak including pulmonary infiltrates, pleural and pericardial effusions, peripheral oedema, hypoxia, and progressive respiratory failure. Standard treat- ment on first suspicion of retinoic acid syndrome is dexamethasone 10 mg intravenously twice daily, with interruption of ATRA therapy and provision of respiratory support until all symptoms and signs have resolved. Minimal/measurable residual disease measurement Techniques for sensitive measurement of residual disease beyond the sensitivity of the microscope or cytogenetics are developing in haematological cancer and in some circumstances are approved as a surrogate endpoint for testing new treatments. There are several molecular targets for which semi-quantitative reverse transcription PCR methods have been developed. However, they are only suitable for 50 to 60% of patients. Aberrant phenotypes can also be defined at diagnosis by immunophenotyping using several antibodies. This is demanding technology requiring a high level of standardization, but it is ap- plicable to most patients depending how many antibodies are in the panel. There is little doubt that tests on marrow which is clearly in morphological remission will detect residual disease at a level of 1 cell per 1000. This is usually a reliable predictor of imminent re- lapse thus enabling pre-emptive treatment to be given. While this approach is attractive for individualizing patient choices, at present it may not be ready for routine practice. It is prognostic, probably adding additional information to what is already known to enable refinement of current treatments, but the predictive value will re- quire prospective confirmation. FURTHER READING Appelbaum FR, et al. (2006). Age and acute myeloid leukemia. Blood, 107, 3481–5. Burnett A, Wetzler M, Löwenberg B (2011). Therapeutic advances in acute myeloid leukemia. J Clin Oncol, 29, 487–94. Burnett AK (2012). Treatment of acute myeloid leukemia: are we making progress? Hematology Am Soc Hematol Educ Program, 2012, 1–6. Cancer Genome Atlas Research Network (2013). Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med, 368, 2059–74. Dohner H, et al. (2010). Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood, 115, 453–74. Estey E, Dohner H (2006). Acute myeloid leukaemia. Lancet, 368, 1894–1907. Grimwade D, Freeman SD (2014). Defining minimal residual disease in acute myeloid leukemia: which platforms are ready for ‘Prime Time’? Blood, 124, 3345–55. Grimwade D, et al. (1998). The importance of diagnostic cytogenetics on outcome in AML: Analysis of 1,612 patients entered into the MRC AML:10 Trial. Blood, 92, 2322–3. Grunwald MR, Levis MJ (2013). FLT3 inhibitors for acute myeloid leu- kemia: a review of their efficacy and mechanisms of resistance. Int J Hematol, 97, 683–94. Milligan DW, et al. (2006). Guidelines on the management of acute myeloid leukaemia in adults. Br J Haematol, 135, 450–74. Sanz MA, et al. (2009). Management of acute

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