Acute myeloid leukaemia

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Abstract

For several decades, few substantial therapeutic advances have been made for patients with acute myeloid leukaemia. However, since 2017 unprecedented growth has been seen in the number of drugs available for the treatment of acute myeloid leukaemia, with several new drugs receiving regulatory approval. In addition to advancing our therapeutic armamentarium, an increased understanding of the biology and genomic architecture of acute myeloid leukaemia has led to refined risk assessment of this disease, with consensus risk stratification guidelines now incorporating a growing number of recurrent molecular aberrations that aid in the selection of risk-adapted management strategies. Despite this promising recent progress, the outcomes of patients with acute myeloid leukaemia remain unsatisfactory, with more than half of patients ultimately dying from their disease. Enrolment of patients into clinical trials that evaluate novel drugs and rational combination therapies is imperative to continuing this progress and further improving the outcomes of patients with acute myeloid leukaemia.

Introduction

Acute myeloid leukaemia is a malignant disorder of haemopoietic stem cells characterised by clonal expansion of abnormally differentiated blasts of myeloid lineage. Consequences of this proliferation of immature myeloid cells include accumulation of immature progenitors (blasts) with impairment of normal haemopoiesis, leading to severe infections, anaemia, and haemorrhage. Some patients might also present with extramedullary disease, including involvement of the CNS.[1] Prompt diagnosis and initiation of acute myeloid leukaemia directed therapy is imperative, especially when rapid proliferation of malignant blasts is accompanied by tumour lysis syndrome or disseminated intravascular coagulation, both of

which can be rapidly fatal without aggressive supportive management and treatment of the underlying acute myeloid leukaemia.[2]

This Seminar provides an overview of the most recent advances in genomics, prognostication, and therapeutics for acute myeloid leukaemia. We aim to provide an understanding of the complex interactions of disease-related and patient-related factors that both affect outcomes of patients with acute myeloid leukaemia and help to guide therapeutic decisions. In light of recent regulatory approval of several promising new drugs for acute myeloid leukaemia, we focus on how they have altered the therapeutic algorithm for patients with acute myeloid leukaemia and on their therapeutic strategies.

Epidemiology

Acute myeloid leukaemia is the most common acute type of leukaemia in adults, accounting for 1·3% of new cancer cases in the USA and affecting an estimated 0·5% of the population at some point in their lifetime.[3] Although acute myeloid leukaemia can occur in any age group, acute myeloid leukaemia is predominantly a disease in older adults, with a median age at diagnosis of 68 years. The incidence of acute myeloid leukaemia is rising, partly due to an increasing prevalence of therapy-related acute myeloid leukaemia as more patients with cancer treated with cytotoxic chemotherapy are cured of their primary malignancy.[4] Several genetic and environmental risk factors have been identified that predispose individuals to the development of acute myeloid leukaemia (appendix). Germline predisposition to acute myeloid leukaemia might be more common than previously thought, although, despite a robust history and genomic testing, most patients still do not have a clear predisposing factor for acute myeloid leukaemia.[5] History of antecedent haematological disorders, including the myelodysplastic syndromes or myeloproliferative neoplasms, is also associated with a substantially increased likelihood of progression of acute myeloid leukaemia.[6,7]

Pathogenesis

Advances in stem cell biology and large, comprehensive genomic analyses have greatly improved our understanding of the mechanisms by which acute myeloid leukaemia develops. Although leukaemogenesis is still incompletely understood, acute myeloid leukaemia is believed to originate from the oncogenic transformation of a haemopoietic stem cell or of progenitors that have reacquired stem cell-like properties of self-renewal.[8] The resultant self-renewing leukaemic stem cell is capable of maintaining the malignant clone. These leukaemic stem cells are both rare and quiescent, making them particularly resistant to cytotoxic chemotherapy and contributing to relapse.[9] Progenitors from leukaemic stem cells undergo further genetic events, leading to karyotypic and molecular heterogeneity of the bulk leukaemic population, with multiple coexisting, competing clones present at the time of diagnosis.[10–12] However, of note, the pathogenesis of acute myeloid leukaemia is probably quite different between subtypes of acute myeloid leukaemia;[13] therefore, no singular model of pathogenesis is likely to account for all cases.

Specific mutations occur early in leukaemogenesis and might provide a selective advantage for clonal expansion of haemopoietic stem cells and eventual progression to acute myeloid leukaemia. In particular, epigenetic mutations of *DNMT3A, TET2,* and *ASXL1* have been identified in preleukaemic haemopoietic stem cells decades before the development of acute myeloid leukaemia, suggesting that these are early founder events that precede leukaemogenic transformation.[14,15] Expanded clones containing these somatic mutations can be identified in the peripheral blood or bone marrow of patients without evidence of overt haematological malignancy. This is a newly defined entity called clonal haemopoiesis of indeterminate potential (CHIP).[16] CHIP has been identified in 10% of patients older than 65 years of age, with an incidence that increases with age, and predisposes to acute myeloid leukaemia and other haematological malignancies, including myelodysplastic syndromes.[17,18] Notably, the rate of transformation of CHIP into overt haematological disease is about 0·5–1% per year.[16] Through incompletely understood mechanisms, CHIP is also associated with an increased risk of atherosclerotic cardiovascular disease.[18,19]

In roughly 10% of patients with acute myeloid leukaemia, the development of the disease is preceded by exposure to cytotoxic chemotherapy (particularly alkylating agents or topoisomerase inhibitors) or ionising radiation, usually as treatment for a primary malignancy.[4] In some cases, direct genotoxic effects from chemotherapy or irradiation can serve as the leukaemogenic event, directly leading to the development of acute myeloid leukaemia. However, emerging data suggest that some patients harbour CHIP before treatment for their primary malignancy and that these patients are at increased risk for the development of therapy-related myeloid neoplasms such as acute myeloid leukaemia.[20,21] Some somatic mutations associated with these clones (eg, *TP53* mutations, which are present in up to 37% of therapy-related myeloid neoplasms[22]) are relatively resistant to chemotherapy and, therefore, have a competitive advantage over healthy haemopoietic stem cells when exposed to cytotoxic drugs. These mutations have been hypothesised to be enriched in the post chemotherapy bone marrow and, in the case of *TP53* mutations, contribute to genomic instability and the acquisition of new leukaemogenic mutations during regenerative haemopoiesis.[23]

Genomics

Acute myeloid leukaemia is characterised by several recurrent mutations that affect disease biology and phenotype, response to therapy, and risk of subsequent relapse (table 1).[24] Great strides have been made in understanding the genomic diversity of acute myeloid leukaemia and how these various aberrations interact to affect disease phenotype and prognosis.[25,26] Although the number of mutations per acute myeloid leukaemia genome or exome is lower than for most other cancers,[27] with an average of only five recurrent mutations per acute myeloid leukaemia genome,[11] at least one driver mutation can be identified in 96% of patients with de-novo acute myeloid leukaemia, and 86% of patients have two or more driver mutations.[26] Tremendous diversity exists in the overlap of these mutations and the subclonal genomic architecture of the disease. In addition to informing prognosis, some of these mutations serve as potential targets for acute myeloid leukaemia directed therapies.[28]

As conventional cytogenetics have an established prognostic impact for acute myeloid leukaemia, consideration of both karyotype and mutations is necessary, to classify acute myeloid leukaemia subtypes in a clinically meaningful way. To further refine prognostication of acute myeloid leukaemia, a large, comprehensive analysis of acute myeloid leukaemia genomics was done using targeted sequencing of 1540 patients with acute myeloid leukaemia.[26] By incorporating cytogenetic analysis into genomic profiling, 11 mutually exclusive subtypes of acute myeloid leukaemia were identified, unambiguously classifying 80% of patients into distinct disease subgroups. In addition to eight well established acute myeloid leukaemia subsets, defined by gene fusions or the presence of an *NPM1* mutation or biallelic *CEBPA* mutations, three new heterogeneous subtypes of acute myeloid leukaemia were defined. These groups included acute myeloid leukaemia with mutations of genes regulating RNA splicing (eg, *SRSF2* and *SF3B1*), chromatin (eg, *ASXL1*), or transcription (eg, *RUNX1*), acute myeloid leukaemia with mutation of *TP53* or cytogenetically visible copy number alterations, and, provisionally, acute myeloid leukaemia with *IDH2*[R172] mutation. Further studies are needed to confirm the prognostic significance of these novel acute myeloid leukaemia subgroups and their justification as distinct disease entities.

Diagnosis

A diagnosis of acute myeloid leukaemia requires identification of 20% or more myeloid blasts (eg, myeloblasts, monoblasts, or megakaryoblasts) with morphological assessment of the peripheral blood or bone marrow. Exceptions to this blast cutoff, in which acute myeloid leukaemia can still be diagnosed, include isolated extramedullary acute myeloid leukaemia (ie, myeloid sarcoma) or the presence of recurrent karyotypic or molecular aberrations that are pathognomonic for acute myeloid leukaemia. These acute myeloid leukaemia-defining genomic changes consist of t(8;21) forming the *RUNX1-RUNX1T1* fusion and inv(16) or t(16;16) forming *CBFB-MYH11*, which define core-binding factor acute myeloid leukaemia, and the t(15;17) fusion gene *PML-RARA*, which defines acute promyelocytic leukaemia.

In addition to morphological assessment of peripheral blood and bone marrow, immunophenotyping by flow cytometry[39] is used at the time of diagnosis to confirm the myeloid origin of malignant blast populations and to aid in further categorisation of acute myeloid leukaemia subtype. Cytogenetic analysis and screening for commonly occurring gene mutations and rearrangements should also be done. Such screening is necessary, because, although some myeloid neoplasms are characterised primarily by morphological and immunophenotypic assessment, the 2016 WHO update recognises 11 acute myeloid leukaemia subgroups defined by the presence of specific recurrent genetic abnormalities, including balanced translocations, gene fusions, or single molecular mutations.[40] Further to testing for *NPM1, CEBPA*, and *RUNX1*, which each define specific acute myeloid leukaemia subtypes, additional genomic testing for *FLT3*-internal tandem duplication (ITD), *TP53*, and *ASXL1* should also be done, as mutations in these genes have prognostic importance and have been incorporated into consensus risk stratification guidelines.[41]

Risk stratification

The outcome of acute myeloid leukaemia is heterogeneous, with both patient-related and disease-related factors contributing to an individual patient's likelihood of achieving response to therapy and long-term survival. Accurate prognostication of acute myeloid leukaemia is imperative, as postremission therapies (eg, consolidation chemotherapy *vs* haemopoietic stem cell transplantation [HSCT] for patients in first remission) are assigned largely according to a patient's anticipated risk of relapse in the absence of HSCT and their anticipated risk of non-relapse mortality with HSCT.[42] Of note, the risk categories established by the consensus guidelines are not fixed and might evolve with emerging therapies, requiring continued reassessment of their prognostic importance. In addition to pretreatment characteristics, such as cytogenetics or molecular mutations, depth of response (ie, presence or absence of minimal residual disease) achieved with initial therapy is emerging as a powerful factor in assessing relapse risk.[43]

Pretreatment factors

Pretreatment factors that affect prognosis for patients with acute myeloid leukaemia can be divided into those related to the patient's ability to tolerate therapy and those related to the inherent chemosensitivity or chemoresistance of the disease itself, although some overlap between these two features exists. Patient-related variables that affect a patient's ability to receive adequate antileukaemic therapy include advanced age, poor performance status, and the presence of clinically significant medical comorbidities. Patients with these risk factors have higher treatment-related mortality when treated with intensive chemotherapy.[44] Due, in part, to their poor tolerance of intensive treatment, the outcomes of many older patients (particularly those patients 60 years of age and older) are significantly worse than their younger counterparts (<60 years).[45] However, less intensive therapies might not be adequate to result in long-term remission.[46] Although higher treatment-related mortality could account for some of the differential outcomes observed between older and younger patients with acute myeloid leukaemia, older patients have more adverse-risk cytogenetic and molecular abnormalities, which also contribute to their poorer outcomes.[36,47] Similarly, the presence of an antecedent haematological disorder (eg, myelodysplastic syndromes or myeloproliferative neoplasms) or previous treatment with cytotoxic chemotherapy or irradiation are historical factors that are associated with poorer response to acute myeloid leukaemia directed therapy and shorter survival.[48]

Genetic analyses, including both karyotyping and screening for recurrent gene fusions and molecular mutations, provide important information about disease biology and strongly inform prognostic assessment, which in turn is used to guide decisions about postremission therapy (table 2).[41] Based on karyotypic analysis, the favorable risk group includes patients with core-binding factor acute myeloid leukaemia—eg, t(8;21) or inv(16)—whereas the adverse risk group includes patients with complex karyotype (defined as three or more cytogenetic abnormalities) or specific chromosomal aneuploidies (eg, −5/−5q, −7, and −17/17p).[49] However, cytogenetics cannot effectively risk stratify many patients with acute myeloid leukaemia, as up to 50% of adult patients present with cytogenetically normal acute myeloid leukaemia.[50] Historically, the majority of patients with a normal karyotype,

in whom outcomes are particularly heterogeneous, were classified into an intermediate-risk group.[50] In this large subset of patients with cytogenetically normal acute myeloid leukaemia and in patients without a well established prognostic karyotypic abnormality, identification of recurrent gene mutations is especially important for risk stratification. The presence of biallelic mutations of *CEBPA* defines an acute myeloid leukaemia subset with relatively favorable prognosis,[51,52] whereas mutations of *RUNX1, ASXL1,* or *TP53* are associated with a high risk of relapse and are classified as adverse risk.[24,37,53]

Mutations of different genes frequently interact in complex ways to affect prognosis, associations that are just beginning to be elucidated on the basis of analyses with large annotated genomic databases.[26] Thus, in many cases, the prognostic impact of a specific gene mutation can only be understood in the context of the other genomic aberrations. For example, *NPM1* and *FLT3*-ITD mutation status interact to affect prognosis, and knowledge of the mutational status of both of these genes, as well as the *FLT3*-ITD allelic ratio, are required to fully assess relapse risk in an individual patient.[41] Data have suggested that *DNMT3A* mutation status could in part mediate the effect of this prognostic association between *NPM1* and *FLT3*-ITD.[26] Prognostic gene–gene interactions have also been described with respect to mutation status of *NRAS, DNMT3A,* and *NPM1,* and *DNMT3A* and *IDH2*[R140], further adding to the complexity of devising a comprehensive genomics-based risk stratification algorithm for acute myeloid leukaemia.[26]

Post-treatment factors

A patient's response to acute myeloid leukaemia directed therapy is a strong determinant of future outcomes. Achievement of a complete remission requires bone marrow assessment showing less than 5% blasts with recovery of peripheral blood elements (ie, neutrophil count >1000 per μL and platelet counts >100 000 per μL) and no evidence of extramedullary disease. Less stringent criteria for response, in which blasts decrease to less than 5% but with incomplete peripheral blood recovery, are associated with less favourable outcomes than in patients achieving complete remission, but better than non-responders.[54]

More sensitive tests for minimal (also called measurable) residual disease, allow for better discrimination of relapse than does morphological assessment alone.[55] The two methods in routine clinical practice for minimal residual disease detection are multiparameter flow cytometry (MFC) and quantitative real-time PCR, which both have their own advantages and disadvantages.[56] MFC-based minimal residual disease assessment relies on comparison of leukaemia-associated immunophenotypes (ie, aberrant patterns of antigen expression found on leukaemic blasts) between diagnostic and remission samples. In the absence of a baseline sample, flow cytometric analysis of the remission sample evaluating different than normal immunophenotype can also be used to detect minimal residual disease.[57] By contrast, real-time PCR requires the presence of a defined target (eg, fusion transcripts, such as *PML-RARA*, or gene mutations, such as *NPM1*) at diagnosis that can be monitored with high sensitivity in follow-up remission peripheral blood or bone marrow samples. Both MFC-based and real-time PCR-based minimal residual disease measurements are highly prognostic for long-term survival in acute myeloid leukaemia.[33,58–61] In one study of patients with acute myeloid leukaemia undergoing HSCT, those in complete remission

but with detectable minimal residual disease by MFC had similar post-transplant relapse and overall survival to those individuals transplanted when not in morphological remission.[62] These studies have supported the development of a new acute myeloid leukaemia response criterion: complete remission without minimal residual disease.[41]

Treatment

General approach

With the approval of several new drugs in 2017, the frontline management of acute myeloid leukaemia is rapidly changing, and rapid, targeted genomic analysis is becoming increasingly necessary to identify genomic and molecular changes that inform the selection of appropriate upfront therapy (table 3).[63] Another important consideration in designing a treatment plan for a patient with newly diagnosed acute myeloid leukaemia is to determine whether they are suitable candidates to receive intensive chemotherapy (figure 1). Such assessment is based largely on the anticipated treatment-related mortality of this approach,[64] which defines the patient's fitness for a given anti-leukemic therapy. Thus, fitness is primarily influenced by patient-related factors such as advanced age, performance status, and pretreatment co-morbidities. Although the predicted mortality can be affected by patient age, it is important to consider all patient-related and disease-related factors when designing an appropriate treatment plan. Owing to better supportive care measures and better selection of patients for intensive versus less intensive acute myeloid leukaemia directed therapies, treatment-related mortality with intensive therapy in large clinical trials has declined over the past two decades from 15–20% to less than 5% in many studies.[65]

For patients who achieve remission with induction therapy, appropriate selection of postremission therapy is essential.[66] Postremission therapies are generally selected by balancing the treatment-related mortality and morbidity associated with HSCT in first remission with the patient's risk of relapse. Patients with an increased risk of relapse in the absence of HSCT (eg, >35%) are usually considered for HSCT in first remission. Various models exist to help determine a patient's candidacy for HSCT, accounting for both non-relapse mortality associated with transplantation and the relapse risk with and without HSCT.[67] Patients with favourable disease-related features generally receive postremission consolidation chemotherapy, whereas those individuals with adverse-risk disease are usually offered HSCT in first remission.[42] For those patients with intermediate-risk disease, no consensus exists regarding the optimal postremission therapy, and treatment should be individualised on the basis of full assessment of relapse risk, patient fitness, adequacy of a suitable donor, and patient preference.

Induction therapy

For over four decades, a combination of cytarabine and an anthracycline has been the standard induction regimen for patients deemed suitable for intensive acute myeloid leukaemia therapy.[68,69] With the 7+3 regimen of 7 days of infused cytarabine (100–200 mg/m^2 daily) plus 3 days of an anthracycline (eg, daunorubicin or idarubicin), complete remission of 60–85% was achieved in patients younger than 60 years and 40–60% was achieved in patients aged 60 years or older, respectively.[70] In an attempt to increase these

responses, various studies have evaluated the optimal dosing of the anthracycline and cytarabine for acute myeloid leukaemia induction, as well as whether the addition of a third drug to this backbone can further improve long-term outcomes (appendix).[71]

Gemtuzumab ozogamicin is an anti-CD33 antibody-drug conjugate that carries calicheamicin, a potent DNA-damaging toxin. In a meta-analysis of five randomised clinical trials enroling patients 15 years of age and older with newly diagnosed acute myeloid leukaemia, the addition of gemtuzumab ozogamicin to induction chemotherapy was shown to improve overall survival at 6 years compared with standard induction chemotherapy (6-year overall survival 34·3% *vs* 30·6%; odds ratio 0·90, 95% CI 0·82–0·98; p=0·01).[78] This beneficial effect is most pronounced among patients with favourable-risk or intermediate-risk cytogenetics. Notably, gemtuzumab ozogamicin initially gained regulatory approval in the USA in 2000, but was subsequently withdrawn from the market in June, 2010, after one randomised trial of intensive chemotherapy with or without gemtuzumab ozogamicin in patients 18–60 years of age with acute myeloid leukaemia found an excess of early mortality, which reduced the clinical benefit in the gemtuzumab ozogamicin containing group. However, owing to promising results from several subsequent randomised trials, gemtuzumab ozogamicin was again approved by the US Food and Drug Administration in September, 2017, for treatment of adults with either newly diagnosed or relapsed or refractory CD33-positive acute myeloid leukaemia. The approval includes single-drug use, as well as combined (in a fractionated dosing schedule) with standard chemotherapy, and, importantly, includes paediatric patients.

Few effective treatments are available for patients with acute myeloid leukaemia who harbour adverse risk features. CPX-351 is a liposomally encapsulated formulation of cytarabine and daunorubicin that preserves a 5:1 molar ratio and has several theoretical advantages over the standard 7 + 3 regimen, including delivery of the drugs at a more sustained synergistic ratio, bypassing drug efflux pumps, and prolonged drug exposure in the bone marrow.[79] Initial randomised phase 2 studies in both the frontline and relapsed or refractory settings showed improved proportions of patients who achieved an objective response compared with conventional therapies, especially in patients with poor-risk features, including secondary acute myeloid leukaemia (ie, arising from a preceding haematological disorder or therapy related).[80,81] A subsequent randomised phase 3 trial was done in older patients (aged 60–75 years) with secondary acute myeloid leukaemia or de-novo acute myeloid leukaemia with myelodysplastic syndromes related cytogenetic abnormalities.[74] Compared with standard 7 + 3 induction, CPX-351 resulted in higher proportions of patients with an objective response and longer survival (median overall survival 9·6 months *vs* 6·0 months; hazard ratio [HR] 0·69; p=0·005), without an increase in early mortality or toxicity, although data on absolute survival benefit are still awaited. CPX-351 therefore represents a reasonable treatment option for patients with secondary acute myeloid leukaemia who are considered suitable for intensive acute myeloid leukaemia therapy.

Mutations of the *FLT3* gene are present in about 30% of patients with newly diagnosed acute myeloid leukaemia.[24,82] Many FLT3 inhibitors have been developed. When used by themselves in patients with *FLT3* mutations, they induce a rapid decrease in peripheral

blood and bone marrow blasts in a substantial percentage of patients.[83,84] However, most responses are partial or without full haemopoietic recovery, and typically of short duration. Thus, FLT3 inhibitors have been combined with chemotherapy in patients harbouring *FLT3* mutations.[85,86] Midostaurin is an oral multitargeted kinase inhibitor that is active against FLT3. In a large, multicenter phase 3 study, patients younger than 60 years of age with newly diagnosed *FLT3*-positive acute myeloid leukaemia (either ITD or a point mutation in the tyrosine kinase domain) received standard induction followed by consolidation chemotherapy (or HSCT, if indicated) and were randomly assigned to receive either midostaurin or placebo.[72] Midostaurin was given with induction and consolidation, followed by up to an additional year of maintenance midostaurin. Compared with the placebo group, the midostaurin group had a significant improvement in overall survival, both in patients with *FLT3*-ITD and those with *FLT3* kinase domain mutations (4-year overall survival 51·4% *vs* 44·3%; median overall survival 74·7 months *vs* 25·6 months; HR 0·78; 95% CI 0·63–0·96; p=0·009]). Based on these results, midostaurin was approved in the USA and is now standard therapy for patients with a *FLT3* mutation in combination with conventional therapy.

Postremission therapy

Consolidation chemotherapy with a cytarabine-based regimen is standard of care for patients who achieve remission after induction chemotherapy and in whom HSCT is not recommended, owing to favourable disease-related factors, high expected transplant-related mortality, or lack of suitable donor availability.[66] In patients who were given cytarabine and were younger than 60 years of age, the decreased relapse and prolonged survival appeared to be dose dependent.[87] Therefore, in younger patients with acute myeloid leukaemia, single-drug high-dose cytarabine, typically at a dose of 3 g/m^2 every 12 h over 3 days of each cycle, is the most commonly used consolidation strategy, although multiple variations of the dose and schedule have been reported, and such high doses of cytarabine are unlikely to be required for optimal antileukaemic activity.[88] Four consolidation cycles are generally administered, although the optimal number of consolidation cycles has not been firmly established. With this high-dose cytarabine consolidative regimen, long-term survival of about 50% has been achieved in patients younger than 60 years of age who achieve complete remission with induction chemotherapy.[87] The benefit of high-dose cytarabine consolidation is largely limited to those with favourable-risk or cytogenetically normal acute myeloid leukaemia, which represent subtypes of acute myeloid leukaemia that are generally more chemosensitive.[89] Older patients (60 years) are less likely to benefit from or tolerate intensive cytarabine, except perhaps the small proportion of those with favourable-risk cytogenetics.

The addition of other drugs to the cytarabine backbone for consolidation might also be beneficial in some acute myeloid leukaemia subgroups. For example, midostaurin should be given with consolidation for patients with *FLT3*-mutated acute myeloid leukaemia.[72] In one study of younger patients (18–59 years) with intermediate-risk or adverse-risk cytogenetics, the addition of the purine nucleoside analogue clofarabine to intermediate-dose cytarabine significantly prolonged relapse-free survival, although no overall survival benefit was observed.[90] After consolidation chemotherapy, no role for further maintenance

in the management of acute myeloid leukaemia has been established. However, several maintenance strategies, such as targeted drugs (eg, FLT3 inhibitors) and immune approaches (eg, checkpoint inhibitors and monoclonal antibodies), are being investigated.

Several variables are part of the considerations for HSCT, in addition to proper patient selection, including the optimal preparative regimen, donor, and stem cell source (appendix). The mechanistic role of allogeneic HSCT in acute myeloid leukaemia is in two parts: the high-dose preparative conditioning regimen provides antileukaemic cytoreduction, and, perhaps more importantly, engrafted donor T cells exert an immunological graft-versus-leukaemia effect to further eliminate residual leukaemic cells.[91] Allogeneic HSCT improves outcomes of patients with both poor-risk and intermediate-risk acute myeloid leukaemia, although the magnitude of benefit in patients with intermediate-risk disease is lower, probably due to the substantial heterogeneity of this group and because chemotherapy is generally more effective than in patients with poor-risk disease.[92–94] For these intermediate-risk patients, minimal residual disease status might have a particularly informative role in defining the risk-benefit ratio of HSCT for a given patient, although the optimal use of minimal residual disease to inform such decisions remains controversial.[95] Although HSCT for high-risk patients with acute myeloid leukaemia consistently decreases the frequency of relapse compared with chemotherapy alone, many patients still relapse. In an effort to improve outcomes for these high-risk patients, several studies have evaluated the use of post-HSCT maintenance with mixed results.[96] Studies evaluating post-HSCT hypomethylating agents, lenalidomide, and FLT3 inhibitors are in progress.

Patients unfit for intensive therapy

As almost half of patients with acute myeloid leukaemia are older than 70 years of age at the time of diagnosis, frequently with comorbidities and poor performance status, many are considered unfit for intensive chemotherapy.[64] Of note, this assessment is often subjective and some older patients can still benefit from intensive chemotherapy.[97] Several less intensive therapies are commonly used for these unfit patients, including low-dose cytarabine and hypomethylating agents.[45] Although these regimens are associated with lower treatment-related mortality than intensive chemotherapy, long-term outcomes for older patients (60 years) with acute myeloid leukaemia remain dismal, with a median survival of about 6–9 months. Therefore, enrolment in a clinical trial should always be considered for these patients.

In patients deemed unfit for intensive chemotherapy, low-dose cytarabine (eg, 20 mg subcutaneously twice daily for 10 days administered every 4 weeks) is associated with a complete remission of 15–25% and improves overall survival compared with hydroxyurea plus best supportive care.[98] However, response to low-dose cytarabine is minimal in patients with adverse karyotype. Given the potential for haematological toxicity with low-dose cytarabine and the high proportion of older adults with poor-risk cytogenetics, low-dose cytarabine is a suboptimal strategy for the majority of older patients with acute myeloid leukaemia.

The hypomethylating agents azacitidine and decitabine are epigenetic therapies that inhibit DNA methylation and are believed to lead to re-expression of silenced tumour suppressor

genes, which can, in part, explain their efficacy in both myelodysplastic syndromes and acute myeloid leukaemia.[99] In a randomised study comparing azacitidine (75 mg/m^2 subcutaneously daily for 7 days administered every 4 weeks) with conventional care regimens (eg, standard induction chemotherapy, low-dose cytarabine, or supportive care only) in patients with acute myeloid leukaemia aged 65 years or older, azacitidine significantly improved survival (median overall survival 12·1 months *vs* 6·9 months, HR 0·76; 95% CI, 0·60–0·96; p=0·019), an effect that was seen across subgroups, including in patients with poor-risk cytogenetics.[100] A randomised trial comparing decitabine (20 mg/m^2 intravenously daily for 5 days administered every 4 weeks) with low-dose cytarabine or supportive care in a similar population of older patients (65 years) with acute myeloid leukaemia showed a modest overall survival benefit for patients treated with decitabine.[101] The proportion of patients who achieve an objective response with hypomethylating agents is 20–30%, which is lower than that observed with intensive chemotherapy.[70] However, overall survival is similar or possibly superior compared with what can be expected with intensive chemotherapy in these older patients with acute myeloid leukaemia, probably driven by lower treatment-related mortality with these less intensive strategies.[102,103] Of note, epigenetic therapy could be particularly beneficial in patients harbouring *TP53* mutations, which confer resistance to traditional cytotoxic chemotherapy.[104]

In several studies, gemtuzumab ozogamicin alone has been shown to be effective in older adults (>60 years), including those who are deemed unfit for intensive chemotherapy. In a randomised study of gemtuzumab ozogamicin treatment versus best supportive care, low-dose gemtuzumab ozogamicin (6 mg/m^2 on day 1 and 3 mg/m^2 on day 8 of induction, followed by monthly doses of 2 mg/m^2 as consolidation) resulted in a response of 27% and improved overall survival compared with the control group, without an increase in adverse events.[76]

The benefit of gemtuzumab ozogamicin was seen across most subgroups, especially patients with high CD33 expression status and those with favourable or intermediate-risk cytogenetics. With the reapproval of gemtuzumab ozogamicin, future studies evaluating its optimal use in older patients with acute myeloid leukaemia, including combination strategies, are needed.

Relapsed or refractory acute myeloid leukaemia

With standard chemotherapy, long-term survival for patients with acute myeloid leukaemia is achieved in only 35–45% of those younger than 60 years of age and 10–15% of those aged 60 years and older.[41] Relapsed disease and the associated leukemia-associated complications are the most common causes of death. Acute myeloid leukaemia relapse is associated with a substantial increase in molecular complexity, with multiple new subclones and mutations identified at the time of relapse, contributing to increased resistance to cytotoxic chemotherapy.[15,105–107] For patients in first relapse, the median survival is roughly 6 months with only about 10% of patients achieving long-term survival.[108,109] Predictors for poorer outcomes in patients with first acute myeloid leukaemia relapse include a duration of first remission of 6 months or less, unfavourable karyotype, previous HSCT, and advanced

age.[108] Patients with primary induction failure or multiply relapsed disease have especially poor outcomes.

For patients with primary induction failure or who develop relapsed disease, the goal of further antileukaemic therapy is to achieve remission and proceed to allogeneic HSCT, which offers the best chance of cure.[110] For older (>70 years) or unfit patients with relapsed or refractory disease and in whom allogeneic HSCT is not feasible, further treatment is largely palliative. For patients with a first remission duration longer than 1 year, retreatment with an intermediate-dose or high-dose cytarabine-containing regimen should be considered, as this subset of patients often relapse with somewhat chemosensitive disease.[108] This regimen should still be followed by HSCT whenever feasible. However, for patients with a shorter first remission duration or with primary induction failure, there is no consensus reinduction regimen. In a large, multicenter trial of 381 patients with relapsed or refractory acute myeloid leukaemia, most of whom had multiply relapsed disease, patients were randomly assigned to the experimental therapy (elacytarabine) or investigator's choice of one of seven commonly used acute myeloid leukaemia salvage regimens, including high-dose cytarabine, multidrug chemotherapy, hypomethylating agents, hydroxyurea, or supportive care.[111] Overall survival did not differ among any of the therapies administered. The proportion of patients who achieved an objective response to salvage therapy was 20–25% and the median survival was 3–4 months regardless of the regimen received, highlighting the need for more effective therapies for patients with relapsed or refractory acute myeloid leukaemia and the necessity of enrolling these patients in clinical trials.

As knowledge of the genomic landscape of acute myeloid leukaemia continues to grow, therapies targeting specific pathogenic mutations are likely to have an increasing role in the management of acute myeloid leukaemia and improve outcome. One such example is enasidenib, an oral, selective inhibitor of mutant IDH2. When mutated, IDH2 has pro-leukaemic properties mediated by epigenetic phenomena; the use of enasidenib reverts these effects and induces differentiation of malignancy myeloblasts.[112] *IDH2* mutations are identified in 10–20% of patients with acute myeloid leukaemia.[113,114] In a phase 1/2 trial of patients with *IDH2*-mutant relapsed or refractory acute myeloid leukaemia, enasidenib was associated with overall response of about 40%, complete remission of about 20%, and median survival of 9·3 months.[73] In August, 2017, enasidenib was approved in the USA for use in patients with relapsed or refractory acute myeloid leukaemia harbouring an *IDH2* mutation. As retrospective studies suggest that intensive chemotherapy is also effective in patients with *IDH2* mutations,[115] future combinations of IDH2 inhibitors with chemotherapy might improve these outcomes. Clinical trials of other targeted therapies for relapsed or refractory acute myeloid leukaemia are continuing, including drugs targeting mutant FLT3, IDH1, and RAS.[63] Incorporation of several of these drugs into frontline acute myeloid leukaemia management is also being investigated.

Acute myeloid leukaemia in the paediatric patient

Acute myeloid leukaemia in childhood accounts for 20% of paediatric leukaemias, with 5·1% of patients with acute myeloid leukaemia being diagnosed at younger than 20 years of age.[3] Several genetic syndromes have been associated with the development of acute

myeloid leukaemia in childhood (appendix). As paediatric acute myeloid leukaemia is a relatively rare entity, much of the approach regarding prognostic factors and treatment are derived from data and studies in adult patients. Risk stratification for paediatric acute myeloid leukaemia is, therefore, largely based on the same genetic categories that have been established in adult acute myeloid leukaemia.[41] However, some notable differences exist in the prevalence of different karyotypic and molecular abnormalities between adult and paediatric populations. For example, acute myeloid leukaemia that presents in childhood is associated with higher rates of t(8;21), inv(16), and rearrangements of 11q23 (*KMT2A*).[116] By contrast, mutations of *NPM1* and *FLT3*-ITD appear to be less frequent in children than in their adult counterparts.[117] As in adults, flow cytometric minimal residual disease response to acute myeloid leukaemia directed therapy is a powerful prognostic factor in the paediatric population.[118–120]

Treatment of paediatric acute myeloid leukaemia uses a multidrug cytarabine and anthracycline-based induction, followed by either post-remission consolidative chemotherapy or HSCT.[121] Similar to the approach in adults, HSCT in first remission is generally reserved for patients with high-risk disease features, including poor response to induction chemotherapy or poor-risk cytogenetics, although proper patient selection remains controversial.[122] With contemporary treatment, the proportion of patients cured in some subgroups of paediatric acute myeloid leukaemia can approach 70%.[123] The anti-CD33 antibody-drug conjugate gemtuzumab ozogamicin has shown particular promise in further improving these outcomes. A randomised phase 3 study in children and young adults (29 years) with newly diagnosed acute myeloid leukaemia showed that the addition of gemtuzumab ozogamicin to standard chemotherapy was associated with a significant improvement in 3-year event-free survival (53·1% *vs* 46·9%; HR 0·83; 95% CI 0·70–0·99; p=0·04), although no overall survival benefit was observed.[124] In a subsequent analysis, this benefit was primarily restricted to the around 50% of patients who have the CC genotype of a CD33 splicing polymorphism.[125] As with adult acute myeloid leukaemia, supportive care has an essential role in improving outcomes in paediatric acute myeloid leukaemia.[126]

Future directions

Despite progress in recent years, with several new drugs gaining regulatory approval for the treatment of adults with acute myeloid leukaemia since 2017, many important questions remain. Ongoing efforts to understand the genomic background of acute myeloid leukaemia, including the mechanisms by which each mutation drives the disease phenotype and how these mutations interact with one another to affect risk of relapse, will be crucial, not only in risk stratification of acute myeloid leukaemia, but also in developing novel targeted therapies and rational combinations. The development of novel minimal residual disease assays might also further refine selection of patients with HSCT in first remission.[127] For example, mutation clearance using next-generation sequencing of recurrent myeloid gene mutations done on remission bone marrow has been associated with improved survival, but is still a research tool.[128,129] Ultrasensitive methods for minimal residual disease detection with digital droplet PCR to target low amounts of residual gene mutations are also being developed.[130] Ultimately, comprehensive prognostic models are needed that incorporate both pretreatment prognostic factors (eg, karyotype and molecular mutations) with minimal

residual disease status to improve assessment of relapse risk. Furthermore, whether a reliable measure of minimal residual disease could serve as a surrogate endpoint for regulatory drug approval is also an area of active investigation and controversy.[43,131]

The development of future therapies for acute myeloid leukaemia must be informed by an increased understanding of the biology of acute myeloid leukaemia, including its heterogeneity and subclonal nature, as well as an appreciation of the presence of leukaemic stem cells that are generally chemoresistant and serve as an important reservoir of disease that can lead to relapse after initial response to therapy (figure 2). Many compounds with novel and diverse mechanisms of action are actively being tested in clinical trials, including drugs such as monoclonal antibody constructs against CD33 or CD123, bromodomain and extra terminal protein inhibitors, and B-cell lymphoma 2 (BCL-2) inhibitors, all of which are capable of targeting and potentially eliminating leukaemic stem cells.[9] Given the substantial advances made with immunotherapy in the field of solid oncology, efforts are also ongoing to investigate immune-based therapies in acute myeloid leukaemia, including the use of checkpoint inhibitors (eg, anti-CTLA-4 and anti-PD1 monoclonal antibodies) and novel chimeric antigen receptor T-cell therapies that target epitopes highly expressed on acute myeloid leukaemia blasts.[132] Several novel epigenetic therapies are in clinical trials, including guadecitabine (SGI-110), an oral formulation of azacitidine (CC-486), and IDH1 inhibitors (eg, AG-120; table 4). Because the role of the microenvironment is increasingly recognised as being protective, allowing leukaemic cells to survive the effect of therapy, treatment strategies directed at reversing this protective effect are actively being pursued.

We have outlined the ongoing phase 3 trials enrolling patients with newly diagnosed acute myeloid leukaemia or those who have achieved remission with standard therapy (ie, maintenance trials; table 4). Most of these studies combine investigational drugs with chemotherapy or hypomethylating agents, an approach that is most likely to maximise the benefit of these novel drugs.[133] Multi-arm, biomarker-driven trials (such as the BEAT AML study[134]) offer a novel way to rationally select therapies for patients on the basis of specific genomic alterations present at diagnosis and for testing multiple compounds within a single umbrella trial. However, given the genomic complexity of acute myeloid leukaemia, whether single drugs targeting a specific genomic alteration will be sufficient to eradicate the disease is unclear. Therefore, strategies targeting more universal pathways (eg, immune-based therapies) might be a more successful therapeutic strategy. Beyond mutation-driven or antigen-driven drug selection, the use of in-vitro drug screening or functionality testing (eg, BH3 profiling to predict sensitivity to BCL-2 inhibitors) or the individualised study of induced pluripotential stem cells derived from primary acute myeloid leukaemia cells could further personalise acute myeloid leukaemia directed therapy.[135,136] To evaluate the growing list of promising drugs for acute myeloid leukaemia, increased enrolment of patients with acute myeloid leukaemia into clinical trials will be needed to rapidly investigate the safety and efficacy of these promising therapies and ultimately bring them to the general population so that all patients can benefit. However, as data accumulate from rigorously monitored trials, in which patients are carefully selected for enrolment, we must be judicious in extrapolating these results to general practice.[137] As we now have improved tools to approach these complex tasks, the work is ready to be done.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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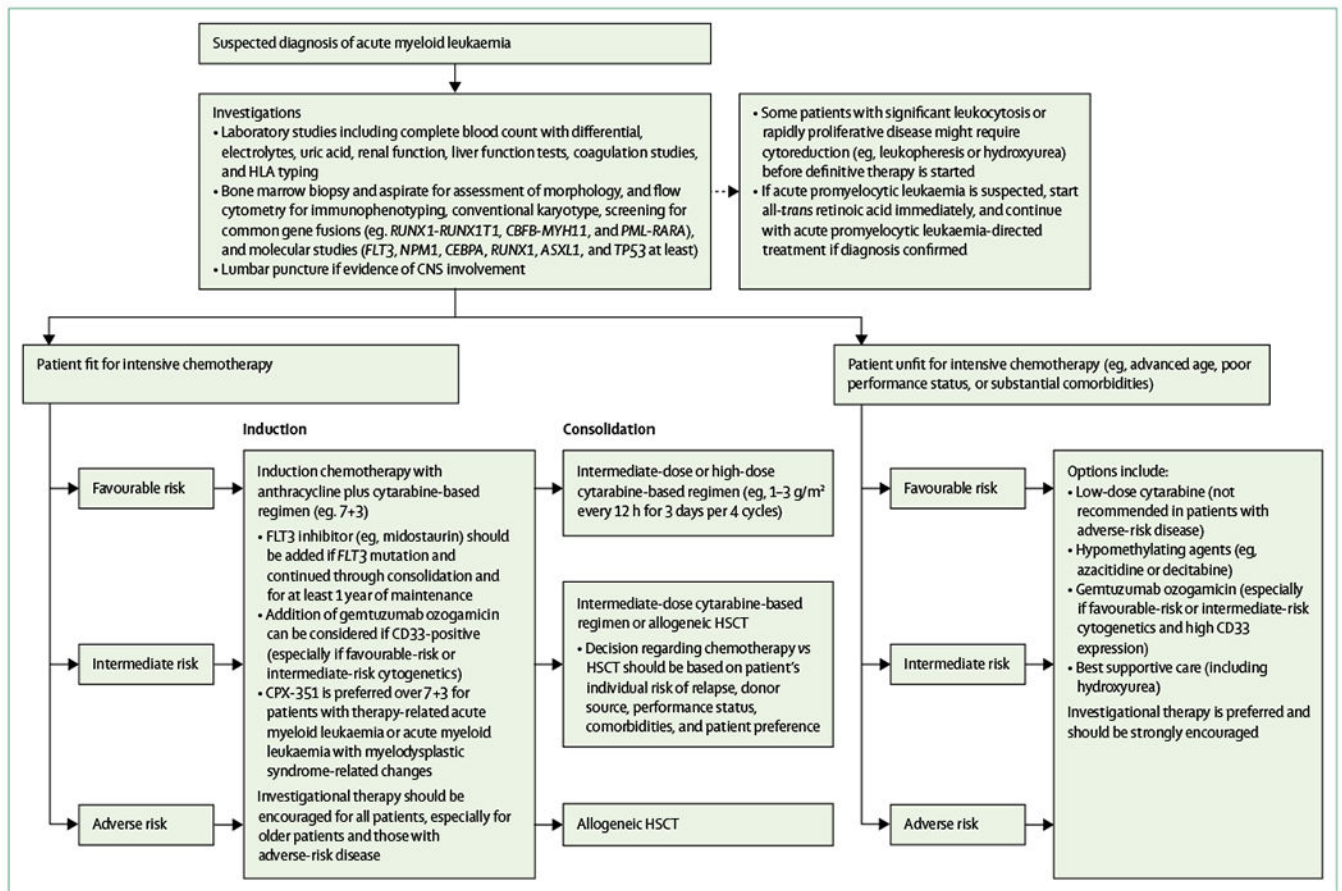
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Search strategy and selection criteria

We searched the Cochrane Library and PubMed for relevant randomised trials and other high-quality studies (eg, systematic reviews and meta-analyses) published in English between Jan 1, 2007 and Oct 1, 2017. We used the search terms "acute myeloid leukaemia" or "AML" in combination with the terms "genomics", "outcomes", "prognosis", and "treatment". We largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we deemed relevant. Our reference list was modified based on comments from peer reviewers.
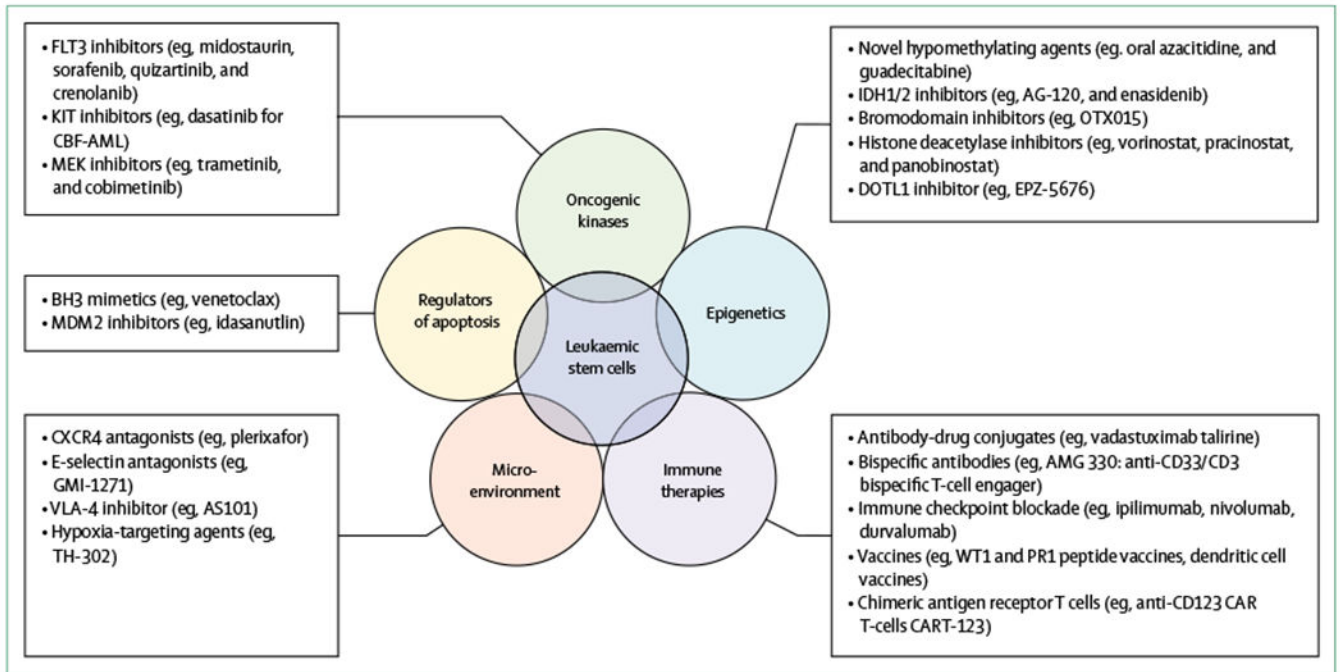
Figure 1: Management of acute myeloid leukaemia in adults
HLA=human leukocyte antigen. HSCT=haemopoietic stem cell transplant.

Figure 2: Examples of selected novel therapeutic strategies in acute myeloid leukaemia

Five therapeutic targets being developed for the management of acute myeloid leukaemia are highlighted, as well as representative compounds that are in clinical trials. These examples are not intended to be all inclusive. Strategies that eliminate leukaemia stem cells, which are generally chemoresistant and serve as a reservoir for relapse, are needed to achieve cure.

Table 1:

Recurrent genomic mutations in newly diagnosed acute myeloid leukaemia in adults

	Frequency	Impact on prognosis	Comments
FLT3	20–25% (ITD) and 5–10% (D835 TKD)	Inferior survival for ITD mutations and prognostic significance of D835 TKD mutations unclear	More common in NK acute myeloid leukaemia (<35% for ITD mutations), *FLT3*-ITD mutation with high allelic burden (ie, 0·5) associated with worse prognosis[29,30] than lower allelic burden, prognosis affected by concomitant *NPM1* mutation status, and prognostic significance not fully established with widespread use of *FLT3* inhibitors
NPM1	About 30%	Superior survival in the absence of high allelic burden *FLT3*-ITD mutation	More common in NK acute myeloid leukaemia (<60%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in younger patients, coexisting chromosomal abnormalities do not affect prognosis[31,32], substantial association with concomitant *FLT3*, *IDH1/2*, and *DNMT3A* mutations,[26] and can be used to monitor for minimal residual disease[33]
CEBPA	About 10%	Superior survival (only if biallelic)	More common in NK acute myeloid leukaemia (<20%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in younger patients, coexisting chromosomal abnormalities do not affect prognosis,[34] and germline mutations with familiar predisposition to acute myeloid leukaemia have been described[35]
KIT	About 10%	Inferior survival in CBF acute myeloid leukaemia	More common in CBF acute myeloid leukaemia (present in 25–35%) than in non-CBF, poor prognosis more notable in acute myeloid leukaemia with t(8;21) than with inv(16), KIT inhibitors (eg, dasatinib) are being evaluated in clinical trials of CBF acute myeloid leukaemia
DNMT3A	About 20%	Conflicting reports on impact on survival	More common in NK acute myeloid leukaemia (<35%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in older adults, CHIP mutation[18], inferior prognosis particularly when present with other mutations (eg, *IDH2*[R140])[26], prognosis affected by type of *DNMT3A* mutation (ie, R882 *vs* non-R882) and patient age
IDH1 and *IDH2*	5–15% (*IDH1*) and 10–20% (*IDH2*)	Conflicting reports on impact on survival	More common in NK acute myeloid leukaemia (<30%) than in acute myeloid leukaemia with cytogenetic abnormalities, *IDH1* and *IDH2*[R172] are associated with concomitant *NPM1* mutations, *IDH2*[R172] can represent distinct acute myeloid leukaemia disease subtype,[26] enasidenib (IDH2 inhibitor) has been approved for use in relapsed or refractory *IDH2*-mutated acute myeloid leukaemia, and IDH1 inhibitors are in clinical development
NRAS	About 15%	Conflicting reports on impact on survival	Associated with *NPM1* and biallelic *CEBPA* mutations, and with inv(16) or t(16;16) and inv(3) or t(3;3), superior outcomes with *NRAS*[G12/G13] mutation in presence of *NPM1* and *DNMT3A* mutations,[26] and RAS pathway inhibitors are in clinical development
TET2	5–20%	Conflicting reports on impact on survival	More common in NK acute myeloid leukaemia (<25%) than in acute myeloid leukaemia with cytogenetic abnormalities, increased incidence in older adults, CHIP mutation,[18] mutually exclusive with *IDH1* and *IDH2* mutations
ASXL1	5–15%	Inferior survival	Increased incidence in older adults, CHIP mutation,[18] associated with secondary acute myeloid leukaemia that has progressed from antecedent haematologic malignancy[36]
RUNX1	5–20%	Inferior survival	Increased incidence in older adults, associated with secondary acute myeloid leukaemia that has progressed from antecedent haematologic malignancy,[37] and germline mutations with familiar predisposition to acute myeloid leukaemia have been described[38]
TP53	5–20%	Inferior survival	Increased incidence in older adults, and associated with complex karyotype, monosomal karyotype, and secondary acute myeloid leukaemia (from antecedent haematological malignancy or therapy related)

ITD=internal tandem duplication. TKD=tyrosine kinase domain. NK=normal karyotype. CBF=core-binding factor. CHIP=clonal haemopoiesis of indeterminate potential.

Table 2:

Genomic risk stratification of acute myeloid leukaemia

		Favourable	Intermediate	Adverse
Cytogenetic		t(8;21)(q22;q22.1) for *RUNX1-RUNX1T1*, and inv(16)(p14.1q22) or t(16;16) (p13.1q22) for *CBFB-MYH11*	t(9;11)(p21.3;q23.3) for *MLL3-KMT2A* [*], and cytogenetic abnormalities not classified as favourable or adverse	t(6;9)(p23;q34.1) for *DEK-NUP214*; t(v;11q23.3) for *KMT2A* rearranged; t(9;22)(p34.1;q11.2) for *BCR-ABL1*; inv(3)(q21.3q26.2) or t(3;3) (q21.3;q26.2) for *GATA2* and *MECOM* (*EVI1*); −5 or del(5q); −7, and −17/ abn(17p); complex karyotype[†]; and monosomal karyotyped[‡]
Molecular		Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low] [§], and biallelic mutated *CEBPA*	Mutated *NPM1* and *FLT3*-ITD[high] [§], and wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low] [§] (without adverse-risk genetic lesions)	Wild-type *NPM1* and *FLT3*-ITD[high] [§], mutated *RUNX1*[¶], mutated *ASXL1*[¶], and mutated *TP53*[‖]

Table is adapted from Dohner and colleagues,[41] the European LeukemiaNet 2017 recommendations. Prognostic impact of a marker is treatment-dependent and might change with new therapies. ITD=internal tandem duplication.

[*] The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

[†] Three or more unrelated chromosomal abnormalities in the absence of one of the WHO-designated recurring translocations or inversions—ie, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3) for acute myeloid leukaemia with *BCR-ABL1*.

[‡] Presence of a single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosomal abnormalities (excluding core-binding factor acute myeloid leukaemia).

[§] Low and high allelic ratios are defined as less than 0·5 and 0·5 and higher, respectively; semiquantitative assessment of *FLT3*-ITD allelic ratio (with DNA fragment analysis) is determined as the ratio of the area under the *FLT3*-ITD curve divided by area under the *FLT3*-wild type curve. Studies[29,30] indicate that acute myeloid leukaemia with NPM1 mutation and FLT3-ITD low allelic ratio might also have a more favourable prognosis and patients should not be routinely assigned to allogeneic haemapoietic stem cell transplant.

[¶] Should not be used as an adverse prognostic marker if they co-occur with favourable-risk acute myeloid leukaemia.

[‖] *TP53* mutations are significantly associated with acute myeloid leukaemia with a complex and monosomal karyotype

Table 3:

Drugs approved for acute myeloid leukaemia by the US Food and Drug Administration in 2017

	Drug class	Approved indication	Clinical outcomes
Midostaurin	Multi-targeted kinase inhibitor (FLT3, VEGFR2, PDGFR, and KIT)	Newly diagnosed *FLT3*-mutated acute myeloid leukaemia in adults (given in combination with chemotherapy)	Chemotherapy and midostaurin *vs* chemotherapy alone: median overall survival 74·7 months *vs* 25·6 months (HR 0·78; p=0·009)[72]
Enasidenib	IDH2 inhibitor	Relapsed or refractory *IDH2*-mutated acute myeloid leukaemia	Overall response rate 40·3%, complete remission 19·3%, and median overall survival 9·3 months[73]
CPX-351	Cytotoxic chemotherapy (liposomal 5:1 molar ratio of cytarabine and daunorubicin)	Newly diagnosed therapy-related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes in adults	CPX-351 **vs** 7 + 3 regimen: median overall survival 9·6 months *vs* 6·0 months (HR 0·69; p=0·005)[74]
Gemtuzumab ozogamicin	Anti-CD33 antibody-drug conjugate	Newly diagnosed CD33-positive acute myeloid leukaemia in adults and relapsed or refractory CD33-positive acute myeloid leukaemia in adults or paediatric patients aged 2 years and older	For newly diagnosed, chemotherapy plus gemtuzumab ozogamicin *vs* chemotherapy alone: median event free survival 15·6 months *vs* 9·7 months (HR 0·58; p=0·0003),[75] and gemtuzumab ozogamicin *vs* best supportive care: median overall survival 4·9 months *vs* 3·6 months (HR 0·69; p=0·005).[76] For relapsed or refractory, overall response rate 33·3%, complete remission 26·3%, and median overall survival 8·4 months[77]

HR=hazard ratio.

Table 4:

Selected ongoing randomised, phase III frontline trials for adults with acute myeloid leukaemia

	Specific inclusion criteria	Trial identifier
Patients eligible for intensive chemotherapy		
Dasatinib (multitargeted kinase inhibitor) plus chemotherapy *vs* chemotherapy alone	Core-binding factor acute myeloid leukaemia	NCT02013648
Quizartinib (FLT3 inhibitor) plus chemotherapy *vs* chemotherapy alone	Acute myeloid leukaemia with *FLT3*-ITD mutation	NCT02668653
Patients not eligible for intensive chemotherapy		
Venetoclax (BCL-2 inhibitor) plus azacitidine *vs* azacitidine alone	NA	NCT02993523
Venetoclax (BCL-2 inhibitor) plus low-dose cytarabine *vs* low-dose cytarabine alone	NA	NCT03069352
Pracinostat (histone deacetylase inhibitor) plus azacitidine *vs* azacitidine alone	NA	NCT03151408
Ivosidenib (IDH1 inhibitor) plus azacitidine *vs* azacitidine alone	Acute myeloid leukaemia with *IDH1* mutation	NCT03173248
Guadecitabine (novel hypomethylating agent) *vs* treatment choice	NA	NCT02348489
Patients in remission after induction and consolidation		
Gilteritinib (FLT3 inhibitor) *vs* placebo	Acute myeloid leukaemia with *FLT3*-ITD mutation in first remission	NCT02927262
Oral azacitidine *vs* placebo	NA	NCT01757535

ITD=internal tandem duplication.