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Acute Myeloid Leukaemia:

Optimal Management and Recent Developments

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Abstract

The current treatment of patients with acute myeloid leukaemia yields poor results, with expected cure rates in the order of 30–40% depending on the biological characteristics of the leukaemic clone. Therefore, new agents and schemas are intensively studied in order to improve patients' outcomes. This review summarizes some of these new paradigms, including new questions such as which anthracycline is most effective and at what dose. High doses of daunorubicin have shown better responses in young patients and are well tolerated in elderly patients. Monoclonal antibodies are promising agents in good risk patients. Drugs blocking signalling pathways could be used in combination with chemotherapy or in maintenance with promising results. Epigenetic therapies, particularly after stem cell transplantation, are also discussed. New drugs such as clofarabine and flavopiridol are reviewed and the results of their use discussed. It is clear that many new approaches are under study and hopefully will be able to improve on the outcomes of the commonly used ‘7+3’ regimen of an anthracycline plus cytarabine with daunorubicin, which is clearly an ineffective therapy in the majority of patients.

Acute myeloid leukaemia (AML) can be divided into two subtypes: *de novo*, when it is not caused by chemotherapy or another preceding haematological condition, and secondary, when it is derived from such a condition. AML is a group of neoplastic disorders characterized by an increase in the number of immature myeloid cells in the bone marrow with or without involvement of the peripheral blood. As a consequence, a bone marrow failure syndrome, producing anaemia, granulocytopenia and thrombocytopenia, with its clinical manifestations characterized by dyspnoea and weakness, infections and bleeding, is seen.^[1,2] If untreated, AML is usually fatal within weeks from the time of diagnosis.^[1–3]

AML is more frequently seen in older adults. The incidence in the US is 3.5 cases per 100 000, being higher in patients over the age of 65 years compared with younger patients (15.9 vs 1.7, respectively), and causes approximately 2.1% of all cancer deaths in the US, with an annual death rate of 3.2 per 100 000 in 2007.^[4,5]

Clinical evaluation, including new biomarkers, therapy and prognosis in patients with AML, has changed dramatically over the last two decades. The clinician's challenge is to improve

response and survival, especially in patients over the age of 65 years, where the incidence and chemoresistance are higher than in other patient groups.

We searched MEDLINE/PubMed, EMBASE, Web of Science and one trial registry (www.clinicaltrials.gov). Key words searched were 'AML', 'acute myeloid leukaemia', 'anthracyclines', 'clinical trials in AML', 'blocking signaling pathway treatments' and 'monoclonal antibodies'. Thus, this article discusses novel therapies for the treatment of patients with AML, but without discussing the role of transplantation, as that has been reviewed elsewhere.^[6]

1. Approach to Patients with Acute Myeloid Leukaemia (AML)

Classical factors predicting response to induction chemotherapy or relapse are age >60 years, unfavourable karyotype, secondary AML, poor performance status and white blood cell count (WBC) >20 000/mm³.^[1,7–13] New biomarkers such as Fms-like tyrosine kinase 3 receptor-internal tandem duplication (*FLT3*/ITD, related to leukocytosis), nucleophosmin mutations (NPM1) and CCAAT/enhancer-binding protein alpha (CEBPA) status have been proposed and suggested to be related to new subtypes of AML.^[2,14–20]

Our approach to treatment is based on clinical findings, flow cytometry and cytogenetics (characteristic mutations as translocations or deletions), where we can subdivide the condition by risk groups.^[6] The four risk groups are (i) acute promyelocytic leukaemia; (ii) low-risk core binding factor AML [Inv(16), t(16;16), t(8;21)]; (iii) intermediate group (normal karyotype or other different to low- or high-risk cytogenetics); and (iv) high-risk [del(5q), del(11q), monosomy 7, and complex karyotype – more than three abnormalities]. Unfortunately, metaphase cytogenetics detect an abnormal karyotype in only half of patients with AML. Thus, another approach to consider in the evaluation of these patients, especially in those with normal karyotype, is genetic profiling.^[21]

This genetic profile includes NPM1, CEBPA and *FLT3*/ITD. The *NPM1* mutation was discovered in 2005 and is included as a provisional entity in the 2008 WHO classification of leukaemias.^[18,22] This genetic mutation is important because the biological and clinical features of *NPM1* mutated AML do not seem to be significantly influenced by concomitant chromosomal aberrations or multilineage dysplasia (MLD). Patients with *NPM1* mutations have a 'good' outcome using only chemotherapy.^[23–26] CEBPA is a transcription factor that it is in charge of regulating proliferation and differentiation in myeloid cells.^[27,28] Patients with AML and normal karyotype who also have a double (biallelic) mutation have a better risk AML.^[29,30] Unfortunately, this double mutation is observed in less than 15% of patients.^[30] NPM1 and CEBPA are used as good prognostic biomarkers in patients receiving 'standard' chemotherapy. *FLT3* expression is necessary for normal haematopoiesis and the development of the immune system. In 1996, the *FLT3*/ITD mutation was described in AML by Nakao et al.^[31] and is seen in approximately 30% of young adult AML patients.^[32] The *FLT3*/ITD mutation is associated with a worse prognosis due to an increased risk of relapse and therefore reduced survival.^[14,20,31–33] Gale et al.^[20] evaluated the presence of none, one or both biomarkers (NPM1 and *FLT3*/ITD) in a cohort of patients with AML and created a stratification with three prognostic groups identified: good (*FLT3*/ITD[−]NPM1⁺), intermediate (*FLT3*/ITD[−]NPM1[−] or *FLT3*/ITD⁺NPM1⁺), and poor (*FLT3*/ITD⁺NPM1[−]). The authors concluded that patients with high *FLT3*-ITD mutation levels (>50%) or *FLT3*/ITD⁺ in the absence of an *NPM1* mutation may be good candidates for more experimental therapeutic approaches.^[20]

2. Standard Treatment for AML

2.1 Is There a Standard Treatment for Induction in AML?

We do not think there is a standard treatment for induction in AML. We have to keep in mind the principal objectives of treatment: (i) to achieve complete remission (CR); and (ii) to maintain response (intent to cure).

‘Conventional therapy’ is ‘traditionally’ based on an anthracycline plus cytarabine. Since 1980, daunorubicin administered in doses of 45 mg/m² for 3 days plus cytarabine 100–200 mg/m² by continuous infusion for 7 days is considered the ‘most common’ induction regimen (so called ‘7+3’). This regimen achieves CR in 56–76% of younger patients (<60 years old) and 38–45% of older patients (>60 years old).^[34,35] In attempts to achieve a better outcome, other anthracyclines have been used; however, there is no consensus about which type of anthracycline is most effective.^[36–40]

Some systematic reviews have tried to answer this question. The British AML Cooperative Group evaluated 1052 patients in five clinical trials comparing daunorubicin versus idarubicin.^[41] They observed that early induction failures were similar with the two treatments (20% idarubicin vs 18% daunorubicin; $p = 0.4$), but after day 40, induction failures were fewer with idarubicin (17% vs 29%; $p < 0.0001$). Therefore, CR rates were higher with idarubicin (62% vs 53%; $p = 0.002$). It is important to mention that patients aged <40 years who received idarubicin had higher CR and overall survival (OS) rates at 5 years than those in the daunorubicin group.^[41] The Swedish Council of Technology Assessment in Health Care reviewed 129 scientific articles: one meta-analysis, 51 randomized trials, 39 prospective and 18 retrospective studies, and 20 other articles. The total number of analysed patients was 39 557 and the authors concluded that there is no evidence to prove that either idarubicin or mitoxantrone is superior to daunorubicin.^[42] Unfortunately, most of those studies were heterogeneous in age, combination with other drugs at induction (i.e. etoposide, thioguanine or tretinoin), consolidation therapy and maintenance.

There have also been attempts to achieve higher CR and survival rates by being more ‘aggressive’, using higher doses of anthracyclines at induction, intensified with autologous or allogeneic stem cell transplant (SCT). Recently, two trials reported on using high doses of daunorubicin and another randomized study used three different anthracyclines plus cytarabine as induction, later intensified if they obtained CR with autologous or allogeneic SCT.^[43–45] Fernandez et al.^[43] compared daunorubicin 45 mg/m² versus 90 mg/m² in young patients, and they reported a higher CR rate in the high-dose daunorubicin group compared with the standard-dose group (70.6% vs 57.3%, respectively; $p < 0.001$), and there were no differences in haematological and non-haematological toxicities. When they analysed survival depending on cytogenetic subgroups, they observed that the greatest difference between standard versus high doses was in the intermediate risk group, with a median survival of 17.8 and 32.3 months (hazard ratio [HR] = 0.64; $p < 0.02$), respectively.^[43] Löwenberg et al.^[44] compared standard versus high-dose daunorubicin in older patients (median age 67 years, 21% >71 years), where they reported a better CR in the high-dose group than in the standard-dose group (64% vs 54%, respectively; $p < 0.002$). OS was not different between these groups. However, there was a significant improvement in OS in patients aged 60–65 years who received the higher dose of daunorubicin compared with the conventional dose (73% vs 51%, respectively).^[44]

The advantage of high doses of daunorubicin could be explained by the hypothesis of ‘the inoculum effect’, where the cellular uptake and cytotoxicity of anthracyclines plus cytarabine decreases with an increase of tumour cell density *in vitro*.^[46] Bogason et al. described this phenomenon *in vivo*.^[47] The authors observed a clear but weak inverse

relationship between the baseline WBC and plasma levels of daunorubicin ($r^2 = 0.11$; $p < 0.05$) at 1 hour after infusion of drugs. Furthermore, a clear relationship between baseline WBC and daunorubicin central volume distribution using population pharmacokinetic modelling was also noted, and they concluded that leukaemic cell burden influences the plasma daunorubicin level.^[47] Mandelli et al.^[45] reported the outcome of the AML-10 trial, which included 2157 younger patients who received intensive induction-consolidation chemotherapy containing daunorubicin (50 mg/m²), idarubicin (10 mg/m²) or mitoxantrone (12 mg/m²) plus cytarabine (200 mg/m²).^[45] After achieving CR, patients underwent either allogeneic or autologous SCT, depending on the availability of a sibling donor. The CR rate was similar in the three groups, but disease-free survival at 5 years was lower in the daunorubicin arm (29%) than in the other arms (mitoxantrone 37% and idarubicin 37%).^[45] This difference was lost in patients who underwent allogeneic SCT (34% vs 34% vs 31%, respectively). These results are similar to other studies reported.^[16,48]

2.2 Influence of Genetic Profile in Response to Anthracycline-Based Therapy

We need to keep in mind that the genetic profile is useful in patients with a 'normal' karyotype (intermediate risk group). Schnittger et al.^[23] reported the outcome in 401 patients, 52% of whom had the *NPM1* mutation (all of them were heterozygous). These patients were treated with an 'intensive' approach: thioguanine, cytarabine and daunorubicin, followed by high doses of cytarabine. The *NPM1*-mutation group had a higher CR rate (70.5% vs 54.7%; $p = 0.003$), a trend to a longer OS (median 1012 vs 549 days; $p = 0.076$) and significantly longer event-free survival (median 428 vs 336 days; $p = 0.012$).^[23] Falini et al. demonstrated that MLD in *NPM1*-mutation patients did not influence the CR rate and survival.^[24] The *NPM1* mutation was detected in 318 patients from three series (GIMEMA [Italian Group for Adult Hematologic Disease] LAM99P, GIMEMA/EORTC [European Organisation for Research and Treatment of Cancer] AML12, and the German group [Munich Leukemia Laboratory]) with 74 patients affected by MLD.^[24] The first two reports ($n = 110$) used the same therapy (daunorubicin, etoposide and cytarabine) and the German group series ($n = 208$) used mitoxantrone and cytarabine at high doses. The 110 patients included from LAM99P and AML12 did not show differences in CR rate between *NPM1* mutation with and without MLD (83.3% vs 80.9%; $p = 0.99$). No differences were observed for either OS or event-free survival in *NPM1* mutation AML cases with normal karyotype (19 with MLD, 79 without MLD).^[24] The Barcelona group confirmed this observation.^[25]

The *NPM1* mutation has also been shown to confer a favourable outcome after therapy in elderly patients. Becker et al. described 148 older patients from three clinical trials developed by the Cancer and Leukemia Group B (CALGB).^[49] The CR rate in patients with the *NPM1* mutation was better than in wildtype-*NPM1* patients (84% vs 48%; $p < 0.001$); disease-free survival rates were also higher in the *NPM1* mutation patients.^[49]

FLT3/ITD has a negative outcome in survival. Fernandez et al.^[43] reported outcomes using daunorubicin in standard or high doses in young patients with the *FLT3*/ITD mutation. They did not observe any positive impact on survival using standard or high doses of daunorubicin. Besides, *FLT3*/ITD showed a similar median survival to the unfavourable cytogenetic group (15.2 vs 11 months, respectively).^[43]

2.3 Therapy in Elderly Patients

Unfortunately, there has been no improvement in AML treatment in older patients in recent years.^[8,10,44,50–54] However, we need to redefine our position on whether or not to offer 'elderly' patients intensive therapy at induction. Why? Because the reticence to treat older adults with standard doses of induction chemotherapy has often been based on a sometimes

mistaken perception that such therapy cannot be tolerated. Low-dose chemotherapy will not reduce the toxicity and is more likely to lead to ineffective therapy with a similar degree of myelosuppression.^[55,56] Löwenberg et al. reported the same grade of toxicity in AML patients treated with daunorubicin in standard and high doses.^[44] The problem is still that many of these patients cannot achieve remission. This could be related to negative prognostic factors (independent of age), such as pre-treatment cytogenetics, presence of myelodysplastic syndrome, genetic profile and, of course, associated co-morbidities.^[11–15,57,58]

The older AML patient population is very heterogeneous, usually with poor prognosis, and both patient-specific and leukaemia-specific factors must be taken into consideration when choosing the therapy that will most benefit each patient with the fewest adverse events. Thus, patients in this special group are candidates for new approaches with new drugs, such as monoclonal antibodies, intracellular signal blocking, epigenetic modulator drugs, flavopiridol or clofarabine.

3. Monoclonal Antibody Therapy in AML

3.1 Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin was the first monoclonal antibody approved for treatment of relapsed or refractory CD33+ AML in older patients. With gemtuzumab ozogamicin monotherapy, the overall response was 14% in relapsed/refractory AML patients.^[59] The gemtuzumab ozogamicin or GO ‘fever’ subsided when some groups reported on ‘sinusoidal obstructive syndrome’ (SOS) or veno-occlusive disease characterized by hyperbilirubinaemia, painful hepatomegaly, ascites and sudden weight gain developing at a median of 10 days following gemtuzumab ozogamicin administration for patients who did not undergo an allogeneic SCT, and 13 days following a transplant for patients who had previously received gemtuzumab ozogamicin.^[60–65] The Research on Adverse Drug Events and Reports (RADAR) group mentioned that SOS incidence was 3% at doses $\leq 6 \text{ mg/m}^2$ if administered as monotherapy or in combination with non-hepatotoxic agents versus 28% if administered with thioguanine and 15% when administered as monotherapy at a dose of 9 mg/m^2 . Observational studies identified SOS rates between 15% and 40% if an SCT is performed within 3 months of gemtuzumab ozogamicin administration.^[66]

Recently, some reports using combined gemtuzumab ozogamicin and ‘conventional’ drugs in AML as first-line therapy in young or older patients have had varied outcomes (see table I).^[67–71] However, the best prognosis continues to be observed in the cytogenetic low-risk group, with a dismal outcome in the high-risk group,^[68] including patients with *FLT3*/ITD.^[72] In the US, gemtuzumab ozogamicin is no longer available, as Pfizer voluntarily withdrew the drug from the market. The action was at the request of the US FDA after results from a recent clinical trial raised new concerns about the drug’s safety profile and also failed to demonstrate clinical benefit.^[73]

3.2 New Monoclonal Antibodies in AML

3.2.1 Lintuzumab (HuM195)—HuM195 is a recombinant humanized IgG1 monoclonal antibody anti-CD33 and is capable of mediating antibody-dependent cellular cytotoxicity.^[74] It has also been combined with interleukin-2 based on its ability to enhance the activation of natural killer cells and its cytotoxic activity against leukaemic cells.^[75] HuM195 has been labelled to $^{111}\text{Indium}$ and named lintuzumab. Feldman et al.^[76] evaluated the efficacy of lintuzumab in a phase III randomized trial. They compared lintuzumab (12 mg/m^2) $\pm$ mitoxantrone, etoposide and cytarabine (high doses) in 199 relapsed/refractory AML patients. Their outcome showed no difference in CR rates or OS.^[76]

4. Blocking Signalling Pathways as Therapy in AML

Progress in biological knowledge of normal and malignant myeloid cells has permitted the development of ‘magic bullets’ against specific receptors (e.g. receptor tyrosine kinases [RTKs]) or intracellular pathways.^[77–81] The targets and different pathways that can be blocked with these molecules are shown in figure 1 and a summary of clinical outcomes with drugs blocking these pathways in table II.

4.1 Tipifarnib

Tipifarnib is a methyl-quinolinone derivative that acts as a potent and selective nonpeptidomimetic farnesyltransferase inhibitor (FTI) both *in vitro* and *in vivo* in haematological diseases.^[93] In phase I–II studies, it was demonstrated that tipifarnib (the most extensively investigated FTI) had antileukaemic activity.^[82–84] The rates of CR, partial response and/or CR with incomplete platelet recovery (CRp) in patients with refractory/poor-risk AML were 7–14%.^[82–84] A phase III study comparing tipifarnib (as monotherapy) with best supportive care, including hydroxyurea in patients with untreated AML 70 years old showed no survival benefit in the tipifarnib arm. A two-gene classifier (*RASGRP1:APTX* gene expression ratio) predicted response and survival, indicating that a two-gene expression assay may help to select patients with AML who would benefit from tipifarnib.^[85] Karp et al. reported two studies using tipifarnib. The first one reported that a combination of etoposide and tipifarnib for 14 days can produce CR rates of 50% in elderly patients who are not candidates for intensive chemotherapy.^[86] The second study was using tipifarnib as maintenance in poor-risk AML after obtaining CR with chemotherapy. Median disease-free survival was 13.5 months (range: 3.5 to 59+ months), achieving a 30% disease-free survival of >2 years.^[87]

4.2 Sorafenib

Sorafenib was developed for solid tumours and its action produces multiple pathway blockade, especially in RAF kinase, vascular endothelial growth factor receptor (VEGFR)-2, c-KIT and FLT3.^[94] There is evidence that it inhibits AML cells.^[95] In a phase I trial, Crump et al.^[88] evaluated the use of sorafenib in AML patients with poor-risk features. They concluded that sorafenib 300 mg twice daily continuously (for 28 days) can produce responses in AML patients. Other authors have observed the same responses in *FLT3/ITD*⁺ patients, before or after allogeneic SCT,^[89] or in combination with idarubicin and cytarabine.^[90]

4.3 Lestaurtinib and Midostaurin (Selective FLT3 Inhibitors)

Lestaurtinib (CEP701) and midostaurin (PKC412) are two small orally bioavailable molecule inhibitors of FLT3 that have shown encouraging activity, both preclinically and in relapsed AML.^[91,92,96] There is an ongoing a phase III clinical trial.^[97] Knapper et al.^[96] studied the effects of both molecules on 65 AML blast samples. Both agents induced concentration-dependent cytotoxicity in most cases, although responses to midostaurin required higher drug concentrations. Importantly, lestaurtinib induced cytotoxicity in a synergistic fashion with cytarabine, particularly in *FLT3*-mutant samples. Both lestaurtinib and midostaurin caused inhibition of FLT3 phosphorylation in all samples.^[96] Fischer et al.^[91] treated 95 patients with relapsed/refractory AML or MDS (*FLT3*-wild type [63%], *FLT3*-mutated [37%]) with midostaurin. The bone marrow response was higher in *FLT3*-mutated than in *FLT3*-wild type patients (71% vs 42%); only one patient presented partial response while receiving 100mg.^[91] In another phase II trial using lestaurtinib as monotherapy in untreated older patients with AML not considered fit for intensive chemotherapy, irrespective of *FLT3* mutation status, the drug was administered orally for 8 weeks, initially at a dose of 60 mg twice daily, escalating to 80 mg twice daily, and was well

tolerated. Clinical activity was measured in bone marrow and peripheral-blood blasts or longer periods of transfusion independence. The authors observed response in 3 (60%) of 5 patients with *FLT3* mutation and 5 (23%) of 22 evaluable wild-type *FLT3* patients.^[92]

4.4 PI3K/Akt/mTOR Pathway as Possible Target

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signalling pathway plays a central role in cell growth, proliferation and survival, not only under physiological conditions but also in a variety of tumour cells. Therefore, the PI3K/Akt/mTOR axis may be a critical target for cancer therapy. Some studies have shown data about outcome in proliferation and differentiation *in vitro* and *in vivo*. Everolimus and 1,25-dihydroxyvitamin D₃ or cytarabine are capable of inducing growth inhibition.^[98,99]

5. Epigenetic Approach to Treatment in AML

The pathogenesis of AML involves complex molecular events triggered by diverse alterations of genomic DNA.^[3] A limited number of initiating lesions, such as chromosomal translocations generating fusion genes, are constantly being identified in specific forms of leukaemia and are critical to leukaemogenesis. Leukaemia fusion proteins derived from chromosomal translocations can mediate epigenetic silencing of gene expression. Epigenetic dysregulation of the DNA methylation status and of the chromatin 'histone code' at specific gene sites cooperates in the pathogenesis of leukaemias. One such mechanism that has received considerable attention with potential therapeutic impact is DNA cytosine methylation, which can modify gene expression. Abnormal methylation patterns have been recognized in AML by genome-wide analysis.^[100,101]

5.1 Epigenetic Modifiers

Epigenetic mechanisms include DNA methylation and histone tail modifications. Classical hypomethylation drugs are DNA methyltransferase inhibitors such as 5-azacytidine (azacitidine) and 5-aza-2'-deoxycytidine or decitabine. Azacitidine is prescribed routinely in myelodysplastic syndrome with acceptable outcomes.^[102–105] The action of azacitidine and decitabine has been proven in AML cell lines. Both drugs produced DNA methyltransferase-1-depletion, DNA hypomethylation and DNA damage induction, thus reducing cell viability and increasing the sub-G1 fraction and apoptosis markers in AML cell lines.^[106] Fenaux et al.,^[105] in a prospective, randomized phase III trial, demonstrated that use of azacitidine is better than 'conventional care regimens' (low-dose cytarabine, intensive chemotherapy or best supportive care) in patients with 20–30% bone marrow blasts. Azacitidine increased median OS (24.5 vs 16 months; *p* = 0.005), and was associated with shorter hospital stays for patients treated (*p* < 0.001).^[105] Patients relapsing after bone marrow transplant may even benefit from these drugs^[107–109] (table III).

6. Other Regimens for AML

Other regimens for AML include two new drugs with high potential: flavopiridol and clofarabine.

6.1 Flavopiridol

Flavopiridol (alvocidib) is a serine-threonine kinase inhibitor that inhibits cell cycle progression by targeting multiple cyclin-dependent kinases, inducing checkpoint arrest and interrupting transcriptional activity.^[111] This drug has been used in a group of relapsed/refractory or *de novo* AML patients with a combination regimen named FLAM (flavopiridol, high doses of cytarabine and mitoxantrone), with promising outcomes and low toxicity.^[112–114]

6.2 Clofarabine

Clofarabine (2-chloro-2'-fluoro-deoxy-9-β-D-arabinofuranosyladenine) is a nucleoside analogue and was designed to incorporate the beneficial properties of fludarabine and cladribine.^[115] This new drug could be very important for the treatment of older patients or those unfit for conventional induction treatment with *de novo* AML. Burnett et al.^[116] analysed two trials in older patients and those with poor performance status. Their series obtained a 48% CR rate with clofarabine as monotherapy; interestingly, poor-risk cytogenetic profile was not a negative factor (CR rate: 44%). The authors compared their cohort with another (the UK Leukaemia Research Fund AML14 trial) and observed that CR rate and OS were superior in the clofarabine arm.^[116] A similar outcome was reported by the MD Anderson group, who observed a 46% CR rate.^[117]

7. Experience in Developing Countries

The majority of English language manuscripts reported on MEDLINE and EMBASE are from developed countries. Nonetheless, we think that is important to report outcomes in developing countries, where the difference in resources is evident.^[118]

The induction outcomes obtained in AML patients treated in developing countries is similar to developed countries when using '7+3' or similar regimens.^[119–121] Unfortunately, information about novel agents is minimal. Candelaria et al.^[110] reported preliminary results using hydralazine and valproic acid as an epigenetic modifier in ten patients with refractory cytopenias with MLD in Mexico. Overall response was observed in 50% (one CR, one partial response and four haematological improvements), and toxicity was mild and tolerable.

8. Conclusion

The treatment of AML continues to evolve. There is no question that current strategies using the so-called '7+3' regimens yield unsatisfactory results. Therefore, the use of newer schemas and drugs targeting specific pathways provides an exciting possibility to improve the outcome for patients, particularly those with poor-risk disease, such as those with complex cytogenetics or *FLT3/ITD*⁺ mutations. Patients with AML should be enrolled, whenever possible, in clinical trials exploring these new agents.

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Fig. 1.

Pathways involved in proliferation and suppression of apoptosis in acute myeloid leukaemia. Fms-like tyrosine kinase 3 receptor (FLT3) inhibitors: midostaurin and lestaurtinib, PI3K/Akt/mTOR pathway inhibitor: everolimus. **ERK** = extracellular signal regulated kinase; **FTI** = farnesyltransferase inhibitor; **Grb2** = growth factor receptor-bound protein 2; **IκB** = inhibitor of kappa B; **Mad** = nuclear transcription factor protein as part of the basic helix-loop-helix leucine zipper (bHLHZ); **MAPK** = mitogen-activated protein kinase; **Max** = nuclear transcription factor protein as part of the basic helix-loop-helix leucine zipper (bHLHZ); **MEK** = mitogen extracellular kinase; **MEKK** = MEK kinase; **Mt** = metallothionein protein; **mTOR** = mammalian target of rapamycin; **NF-κB** = nuclear factor kappa B; **PI3K** = phosphatidylinositol 3-kinase; **PKC** = protein kinase C; **RTK** = receptor tyrosine kinase; **SOS** = sinusoidal obstructive syndrome.

Table I

Gemtuzumab ozogamicin treatment in young and older patients

Study (y)	Median age (y)	AML clinical characteristics	Dosage [mg/m ²] (no. of infusions)	CR rate [%](CR/CRp)
Roboz et al. (2002) ^[59] <i>a</i>	62	Relapse/refractory	9 (1–3)	14 (9/5)
Leopold et al. (2003) ^[60] <i>a</i>	NR	First relapse	9 (1–3)	38 (NR/NR)
Apostolidou et al. (2003) ^[62] <i>a</i>	37	Refractory	9 (4)	18 (9/9)
Chevallier et al. (2005) ^[63] <i>a</i>	NR	Relapse/refractory	9 (4)	82 (76/6)
Larson et al. (2005) ^[65] <i>a</i>	61	First relapse	9 (2)	26 (13/13)
Amadori et al. (2010) ^[67] <i>a</i>	77	<i>De novo</i>	Arm A: 3 (3) Arm B: 6 (1), 3 (2)	38 (NR/NR) 63 (NR/NR)
McHayleh et al. (2010) ^[68] <i>a</i>	77	<i>De novo</i>	9 (2)	14 (NR/NR)
Candoni et al. (2008) ^[69] <i>a</i>	53	<i>De novo</i>	3 (1)	90 (NR/NR)
Amadori et al. (2004) ^[70] <i>b</i>	68	<i>De novo</i>	9 (3)	54.4 (35.1/19.3)
Eom et al. (2007) ^[71] <i>b</i>	64	<i>De novo</i>	6 (1)	78.4 (75/3)

^aMonotherapy.

^bGemtuzumab ozogamicin plus ‘intensive’ or sequential chemotherapy.

AML = acute myeloid leukaemia; **CR** = complete remission; **CRp** = complete remission without platelet recovery (<100 000); **NR** = not reported.

Table II

Drugs that block signalling pathways used in clinical research phases

Study (y)	Median age (y)	AML clinical characteristics	Dosage	CR rate [%](CR/CRp)
Karp et al. (2001) ^[82] <i>a</i>	65	<i>De novo</i> /refractory/relapsed after two therapies	Tipifarnib 100 mg →1200 mg twice each 21 days (PO)	8.3 (NR)
Hausseuseau et al. (2007) ^[83] <i>a</i>	62	Refractory/relapsed	Tipifarnib 600 mg twice a day for 21 days (PO)	4.39 (3.6/<1)
Lancet et al. (2007) ^[84] <i>a</i>	74	<i>De novo</i>	Tipifarnib 600 mg twice a day for 21 days (PO)	14 (NR)
Harousseau et al. (2009) ^[85] <i>a</i>	76	<i>De novo</i>	Tipifarnib 600 mg twice a day for 21 days (PO)	8 (NR)
Karp et al. (2009) ^[86] <i>b</i>	77	<i>De novo</i> /secondary MDS	Etoposide 100 mg days: 1–3 and 8–10 (PO) Tipifarnib 300 mg →600 mg twice a day for 14 or 21 days (PO)	25 (NR)
Karp et al. (2008) ^[87] <i>b</i>	63	<i>De novo</i> poor risk factors	Tipifarnib 400 mg twice a day for 14 days after CR (PO)	31 (remaining in CR)
Crump et al. (2010) ^[88] <i>a</i>	71	Refractory/relapsed	Sorafenib 100 mg →400 mg twice a day for 14 or 28 days (PO)	2.4 (NR)
Metzelder et al. (2009) ^[89] <i>a</i>	50	Refractory/relapsed	Sorafenib 400 mg twice a day (PO)	0 (NR)
Ravandi et al. (2010) ^[90] <i>b</i>	53	<i>De novo</i>	Sorafenib 400 mg twice a day for 7 days (PO) Cytarabine 1.5 g/m ² IV 4 days Idarubicin 12 mg/m ² IV 3 days	75 (25.5/49.4)
Fischer et al. (2010) ^[91] <i>a</i>	NR	Refractory/relapsed	Midostaurin 100 mg →200 mg twice daily (PO)	0 (NR) ^c
Knapper et al. (2006) ^[92] <i>a</i>	73	<i>De novo</i>	Lestaurtinib 60 mg →80 mg twice a day	0 (NR) ^c

^aMonotherapy.

^bSignalling pathway-blocking drug plus chemotherapy or maintenance after chemotherapy.

^cThe response was haematological and partial.

AML = acute myeloid leukaemia; **CR** = complete remission; **CRp** = complete remission without platelets recovery (<100 000); **IV** = intravenous; **MDS** = myelodysplastic syndrome; **NR** = not reported; **PO** = oral; → indicates escalating doses.

Table III

Clinical outcomes in epigenetic modifier treatment in acute myeloid leukaemia (AML)

Study (y)	Median age (y)	AML clinical characteristics	Dosage	CR rate [%](CR/CRp)
Silverman et al. (2006) ^[103] ^a	NR	Secondary AML (WHO criteria) in three trials	5-AZA 75 mg/m ² /d for 7 days. IV or SC, each 28 days	9–12 (NR)
Fenaux et al. (2009) ^[105] ^b	69	MDS high risk (32% AML WHO criteria)	5-AZA 75 mg/m ² /d for 7 days IV, each 28 days Intensive chemotherapy IV Low-dose AraC SC	NR ^c
Bolaños-Meade et al. (2011) ^[107] ^a	55	Relapsed after stem cell transplantation	5-AZA 75 mg/m ² /d for 7 days IV, each 28 days	60
Czibere et al. (2010) ^[108] ^a	50	Relapsed after stem cell transplantation	5-AZA 100 mg/m ² /d for 5 days IV, each 28 days + DLI	23
Candelaria et al. (2011) ^[110] ^a	53	<i>De novo</i>	Hydralazine + valproic acid 30 mg/kg/d	8

^aMonotherapy.

^bEpigenetic modifiers plus chemotherapy or after chemotherapy.

^cThe authors' endpoints were survival and hazard risk factors.

5-AZA = 5-azacytidine (azacitidine); **AraC** = cytarabine; **CR** = complete remission; **CRp** = complete remission without platelet recovery (<100 000); **DLI** = donor lymphocyte infusion; **IV** = intravenous; **MDS** = myelodysplastic syndrome; **NR** = not reported; **SC** = subcutaneous; **WHO criteria** = blast in bone marrow or peripheral blood 20%.