bjh review

How we treat older patients with acute myeloid leukaemia

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Summary

After decades when intensive chemotherapy remained the only effective anti-acute myeloid leukaemia (AML) treatment, a torrent of novel, less toxic agents are about to revolutionise AML therapy. Prolonged remissions with good quality of life become achievable for many patients previously considered only for palliative care because they could not tolerate intensive therapy. As treatment options multiply, the importance of genetic profile is recognised, even for advanced-age patients for whom cure is unlikely. With lack of randomised comparative trials for most treatment regimens, one can only extrapolate data from existing studies to make evidence-based decisions. We herein present seven common clinical scenarios illustrating the complexity of treating older AML patients and describe our approach to their management. In each case, up-to-date data on relevant agents to be offered to a particular patient are discussed. The current review is limited to the drugs, available and approved in the Western world and many promising agents, still under investigation, are not discussed.

Keywords: acute myeloid leukaemia, older adults, molecular profile, intensive chemotherapy, novel agents.

Acute myeloid leukaemia (AML) is the most prevalent acute leukaemia in adults, with a median age at diagnosis of 68 years. For decades, the main treatment option for newly-diagnosed AML patients has been intensive chemotherapy, which optimally offers a complete remission (CR) rate of 70% and a long-term survival of about 40%.[1] Specifically for patients with advanced age, not only is the remission rate significantly inferior, but also toxicity and treatment-related mortality are excessive compared to younger patients. Fortunately, in recent years, novel, effective and less toxic drugs have become available. Moreover, improvements in supportive care, and better tools for risk stratification and patient selection for allogeneic stem cell transplantation (allo-SCT), have all contributed to an improved outcome. Choosing wisely from the many treatment options available for AML patients with advanced age is currently a common clinical dilemma with no simple textbook answer. It is challenging to translate the accumulating but limited data regarding the effectiveness of each drug into a reliable, effective and evidence-based approach. We herein, with the use of six vignettes, present common treatment options and discuss a few case scenarios, aiming to apply principles that can be used in common clinical practice.

Case 1: Is there still a role for intensive chemotherapy for elderly AML patients?

A previously healthy 72-year-old woman is referred because of increased fatigue. Her complete blood count (CBC) shows a white blood cell (WBC) count of 1,300/μl with 6% blasts, 32,000/μl platelets and haemoglobin of 6·5 g/dl. Her marrow is infiltrated with myeloid blasts, and molecular mutation analysis is negative for NPM1, FLT3-ITD mutations and for core binding factor (CBF) aberrations. Her echocardiogram demonstrates normal left systolic and diastolic functions without pulmonary hypertension or wall motion abnormalities. She has normal renal and liver functions. Cytogenetic results will be available within a week. What is the optimal approach for this patient? Should cytogenetics impact the chosen strategy?

This is a case of an apparently fit patient who, had she been 10 years younger, would have been considered for intensive chemotherapy by most physicians. The question therefore is whether intermediate- and/or adverse-risk patients should be treated differently in an advanced age. To answer this question, it is prudent to consider both the immediate treatment plan and post-remission therapy. It has been well-known for decades that achieving CR in the end of induction is a prerequisite but insufficient condition for long-term remission. A substantial number of patients will relapse early after achieving CR, if no consolidation therapy

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is prescribed.[2,3] Thus, an immediate/induction treatment plan should be such as to allow optimal post-remission therapy, particularly in fit patients, preserving the option for allo-SCT.

Following intensive chemotherapy, fit patients aged 70–80 years with intermediate-risk AML have about 60–65% probability to achieve CR, with a 10–15% early death risk.[1,4] It should be noted that in the large prospective study by the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group (ECOG-ACRIN, E2906) exploring intensive chemotherapy in patients with advanced age, minimal residual disease (MRD) negativity was achieved in 58/147 (39·5%) of patients who achieved remission. These MRD-negative patients have an excellent long-term survival rate.[5] Further improvement of intensive regimes in older patients is challenging. The addition of gemtuzumab ozogamicin (GO) in induction, known to improve CR and survival in younger patients, is probably too toxic for patients over 70 years.[6,7] As GO increases induction toxicity by prolonging the time to bone marrow recovery[8] and increasing early mortality,[9] its use in combination with intensive chemotherapy for older patients cannot be recommended.

For long-term remission in fit older patients, allo-SCT remains the most effective post-remission strategy, with 38% 2-year overall survival (OS) in CR1 for patients older than 69 years and a 3-year OS of 49% for patients older than 60 years.[10,11]

A novel alternative for this patient, considered by some, is using venetoclax with hypomethylating agents (HMA) or low-dose cytarabine (LDAC; discussed later in case 2). Although data from phase Ib/II studies reported CR + CR with incomplete blood count recovery (CRi) rates as high as 73% and low early mortality rates, early results from the phase III trial studying the LDAC and venetoclax combination found a much lower response rate of 47% and a median OS of 7·2 months only. Furthermore, updated results of using an HMA + venetoclax combination in both NPM1 and IDH2 wildtype AML patients demonstrated a 2-year OS of 26·6%.[12] Of note, given SCT ineligibility of most patients included in the phase Ib/II trials, data about the outcome of patients fit to be transplanted are insufficient. Interestingly, in 21 patients (out of 145) initially treated with HMAs and venetoclax combination and then transplanted,[13,14] the median OS is reported to be as high as 24·4 months. However, the required depth of response and optimal timing for SCT after induction with a venetoclax combination still need to be assessed.

Therefore, as long-term data are lacking, and in the absence of prospective comparisons between intensive chemotherapy and venetoclax combinations, it seems that for fit intermediate-risk AML patients, outcomes are better when intensive chemotherapy rather than venetoclax combinations is used.

Assuming that our patient has AML with adverse-risk cytogenetics would lead to complicated decision-making. Available data in patients with advanced age suggest that, for patients presenting with a monosomal/complex karyotype, the CR rates with intensive chemotherapy are as low as 30–35% and become even lower if TP53 is mutated/deleted.[4,15,16] Moreover, early death rates are higher, presumably because of prolonged cytopenia and the need for additional chemotherapy.

Novel agents (e.g., venetoclax + azacytidine) offer at least the same CR with reduced early death rates. However, as discussed earlier, to achieve a long-term outcome, the feasibility and efficacy of allo-SCT after these novel therapies need to be demonstrated in prospective studies.

Older patients who are not candidates for allo-SCT but are in remission after chemotherapy are commonly offered at least one cycle of intermediate-dose cytarabine. The overall results, however, remain disappointing, with a relapse-free survival (RFS) of only 16% after 4 years.[2]

Historically, maintenance therapy with various agents consistently failed to demonstrate OS advantage. Exceptions are three early studies showing an event-free survival (EFS) benefit with LDAC[17,18] and with IL-2 and histamine combination,[19] but this has not been adopted in clinical practice, particularly in the U.S. Recently, the Haemato-Oncology Foundation for Adults in the Netherlands (HOVON) published a phase III trial where patients >60 years who received intensive chemotherapy and achieved remission were randomised to azacytidine maintenance or observation alone. This study reported an EFS benefit without OS prolongation.[20] Other studies established an OS benefit for azacytidine maintenance, but with some limitations. Oliva *et al.* presented at the 23rd European Hematology Association Congress a phase III trial where azacytidine maintenance, preceded by intermediate-dose cytarabine consolidation, led to improved OS compared to non-maintenance.[21] Notably, the number of patients participating in that study was relatively small. A phase II ECOG-ACRIN trial as an ancillary to the large prospective E2906 study included a randomisation for patients who achieved CR1 with intensive chemotherapy. One year of decitabine maintenance was shown to improve OS in the FLT3-ITD-negative subgroup.[22] Finally, the most exciting breakthrough confirming the value of HMA maintenance therapy is in the results of the phase III randomised placebo-control QUAZAR AML-001 study. In this trial, CC-486, an oral formulation of azacytidine, was tested as maintenance therapy for both *de novo* and secondary AML patients aged 55 and older. The drug was given until relapse or allo-SCT, and was reported to double EFS and OS.[23,24]

Our suggestion is to treat this patient with a curative intent, comprising intensive chemotherapy and, if possible, an allo-SCT. If a decision to consolidate her with chemotherapy is taken, at least 1 year of post-remission maintenance with HMAs should also be considered.

Case 2: Initial therapy in an unfit older patient

An active 74-year-old male presents with AML. His ECOG performance status (PS) is 1. He is known to have type II diabetes and hypertension, a prior cerebrovascular accident (CVA) from which he recovered with no sequelae and chronic obstructive pulmonary disease (COPD) with moderate pulmonary hypertension. His WBC count is 60 000/μl, he has no disseminated intravascular coagulation (DIC) and no evidence of end-organ injury on admission. Two months previously, his blood counts were within normal limits. He has a normal karyotype and molecularly is FLT3-ITD-negative/NPM1-positive. Is there a preferred targeted approach for this patient?

Older patients with comorbidities have lower CR rates and higher mortality with intensive chemotherapy than younger patients. Assessing fitness for intensive induction is problematic and biased by considerable subjectivity; thus, published data need to be carefully scrutinised. In general, truly unfit patients have an early mortality rate of approximately 30% with standard chemotherapy, as reported by real-world data from the Swedish registry.[1]

Despite the good PS, his comorbidities, which can be evaluated using either Hematopoietic Cell Transplantation Comorbidities Index or Charlson Comorbidities Index, are predictive of early mortality.[25,26] Thus, treatment with intensive chemotherapy should to be discouraged.

Few low-intensity options are currently approved for unfit newly-diagnosed AML patients. These regimens have not been directly compared; thus, recommending a particular regimen for this patient is based on a careful review of the available data.

Venetoclax

BCL2 superfamily proteins regulate mitochondrial apoptotic signalling, with BCL2, MCL1 and BCL_{XL} proteins being the key anti-apoptotic members. Venetoclax is a potent oral specific BCL2-inhibitor which has only a modest activity against AML blasts as a single agent, possibly due to MCL1-dependent apoptosis evasion.[27] However, based on phase I-II trials, the combination of venetoclax with either HMA or LDAC was approved by the FDA (though not the European Medicines Agency) for newly-diagnosed older or unfit AML patients.

DiNardo *et al.*[13,14] demonstrated that a combination of venetoclax with HMA in newly-diagnosed patients (median age 74 years) who were HMA-naïve induced CR/CRi rates of 67%, compared with the historic rates of 20–25% CR/CRi for azacytidine or decitabine when used as monotherapy.[28,29] Moreover, high response rates were reported even in patients with poor cytogenetics or P53 mutations, with 60% and 47% CR/CRi rates, respectively. With a median follow-up of 15 months, the median OS was not reached in NPM1-mutated AML patients. With the same duration of follow-up, the median OS was not reached if isocitrate dehydrogenase (IDH) 1/2 was also mutated. Early mortality rates were as low as 3% in the first 30 days and 8% in 60 days. Interestingly, MRD-negativity was defined using a low-sensitivity threshold of 10^{-3} and was reached in 30% of responsive patients. An optimal venetoclax dose, when prescribed in combination with HMA, was determined to be 400 mg/day, with no additive value for 800 mg/day and excessive toxicity in the 1200 mg/day dose.

Another phase II trial examined the combination of LDAC (20 mg/day for 10 days) with 600 mg venetoclax. This study also included patients who failed previous treatment with HMA (about a third of the patients). The CR/CRi rates were 26 and 28% respectively, but were dramatically influenced by presence of secondary AML or prior HMA treatment. For patients without prior HMA treatment the CR/CRi rates were 62%, and the median OS was 13·5 months. Of note, patients with NPM1 mutation had favourable response to this combination, with 89% CR/CRi rates.[24]

Retrospective observations report encouraging results of venetoclax combinations even in the relapse setting. Studies demonstrate a response spectrum of 21–64%, emphasising the heterogeneity of these select reports, with higher responses in IDH1/2-mutated AML, intermediate-risk cytogenetics and RUX1-mutated AML.[30–32]

The kinetics of response in the newly-diagnosed AML and relapse settings are similar. The vast majority of the patients who respond to venetoclax-containing regimens do so in the first two cycles.[13,14,24,30] It is therefore rational to assess response after two cycles.

Venetoclax-containing regimens have a few important limitations. The major haematologic toxicity is neutropenia, which may often be profound. If severe neutropenia is evolving while the patient is in remission, granulocyte-colony stimulating factor (GCSF) support provides a short and minimal benefit; therefore, reducing or withholding doses is advised. Detailed dose modification varies and relies on minimal data. Published recommendations include withholding venetoclax administration until neutrophil recovery and then resuming treatment in lower dose (50–75% full dose), reducing the HMA/LDAC doses or extending intervals between treatment cycles.[33] The two latter might be advised when marrow hypocellularity or pancytopenia is evident. Such recommendations are based on clinical experience/observation of dose modifications that lead to peripheral count recovery in some patients. Experience in the practical use of venetoclax is crucial, and precise data regarding the long-term effect of any modifications on survival and relapse are lacking.

Venetoclax is metabolised via CYP3A4, and thus strong CYP3A4 inhibitors, commonly used for other indications in AML patients, may increase venetoclax blood levels. Commonly used azoles, particularly voriconazole and posaconazole, and quinolone antibiotics may have a strong interaction

with venetoclax. It is recommended to reduce the venetoclax dose by 75% when co-administering strong CYP3A4 inhibitors, like the aforementioned azoles, and by 50% for moderate CYP3A4 inhibitors.[24,34] However, as previously noted, these recommendations are based on limited pharmacokinetic data with no clinical evidence supporting the long-term effect of these dose modifications.

A major limitation for venetoclax-containing regimens is venetoclax resistance, as lack of response to venetoclax-based treatment is usually associated with prolonged cytopenias. Moreover, as other options for first-line treatment are available, prediction of response to venetoclax-based therapy will become very important. Venetoclax resistance is driven mainly by overexpression or mutations in MCL1 and BCL-X_L, the two other anti-apoptotic proteins of the BCL-2 family.[35] Recent studies suggested that high BCL2 expression or BCL2/MCL1 ratio can predict for good response to venetoclax. It was also shown that HMA and chemotherapy suppress MCL1 expression and thus synergise with venetoclax.[36,37] A few recently-published articles demonstrate that AML cells with monocytic differentiation respond poorly to venetoclax, possibly because of low BCL2/MCL1 ratio, and that CD14 can serve as a marker for venetoclax sensitivity.[37–40] Other pathways/mechanisms which confer venetoclax resistance are currently being actively investigated, as are other venetoclax combinations, such as those with MEK inhibitor, MDM2 inhibitor and FLT3-ITD inhibitors.[41–44]

Glasdegib

Glasdegib is a specific inhibitor of Smoothened (SMO), a receptor regulating the hedgehog pathway. SMO inhibition in cell lines is found to reduce the percentage of G0 cells, especially in leukaemic stem cells, and to abrogate cytarabine resistance. In mouse model, SMO inhibition is demonstrated to attenuate leukaemia-initiation potential of AML cells, presumably by targeting leukaemic stem cells.[45] Based on these results, a phase II study was conducted, comparing LDAC to LDAC + glasdegib in AML patients and high-risk myelodysplastic syndrome (MDS) patients. The glasdegib + LDAC combination was found to have an OS benefit in AML patients (median OS 8·8 months, compared to 4·9 months with LDAC alone), which was consistent in all cytogenetic risk groups, albeit less pronounced in high-risk cytogenetics. Despite the survival advantage, only 27% patients achieved CR/CRi. Notably, 17% of patients who received the combination were previously treated with HMAs. Most adverse events more common with glasdegib were gastrointestinal symptoms, mostly grade I/II.[46] Based on these results, glasdegib was approved by the FDA for relapsed/refractory patients over 75 years or those with comorbidities, and a phase III trial for newly-diagnosed patients combining glasdegib with either intensive chemotherapy or HMAs was initiated in 2018.

Our priority for this patient is a combination of venetoclax with azacytidine. While LDAC is a perfectly reasonable option, we prefer the combination with HMA due to the lower dose of venetoclax, used with less risk of drug interactions.

Case 3: Treatment of an unfit AML patient with IDH1/2 mutation

A 77-year-old female presents with normal karyotype, NPM1wt/FLT3-ITD-negative/IDH1-positive *de novo* AML. She is known to have hypertension, treated with valsartan/amlodipine. She had a hip fracture 4 months ago, for which she underwent total hip replacement. She is assisted with a walker, and her ECOG PS is 2. On CBC, she is pancytopenic with WBC of 2500/μl, absolute neutrophil count (ANC) of 1200/μl, 72 000/μl platelets, haemoglobin 7·9 g/dl. The patient is a widow, and her children live abroad. She is afraid that she would not be able to attend frequent visits to the clinic.

Is a total ambulatory care possible in this patient?

IDH1/2 inhibitors

IDH1 and IDH2 mutations are present in about 20% of AML cases, predominantly in normal karyotype AML. The IDH1 inhibitor ivosidenib and the IDH2 inhibitor enasidenib will be discussed together, since their safety profiles and efficacies are very similar. In relapsed/refractory AML, each of these IDH inhibitors is effective as a single agent, with as much as 30% CR + CRi rates and a median survival of over 1 year for CR/CRi responders. Also, many patients who achieved only partial response (PR) had prolonged survival and became transfusion-independent.[47,48] Based on these results, the IDH inhibitors gained FDA approval for relapsed/refractory AML. Interestingly, patients with FLT3-ITD co-mutation and RAS co-mutations respond poorly to IDH inhibition. For newly-diagnosed older patients, both IDH inhibitors were tested in phase I studies as single agents. Ivosidenib treatment achieved 55% ORR and 42% CR/CRh rates, with more than 60% of responses lasting for 12 months. Based on these data, ivosidenib was approved by the FDA for this indication.[49] Enasidenib achieved 31% ORR, with median duration response not reached.[50] Adverse effects with these drugs are minor. Leukocytosis associated with differentiation syndrome is unique but uncommon, and possible QT prolongation, particularly with co-administration of CYP3A4 inhibitors such as azoles, may also occur.

IDH inhibitors were also tested in combination with azacytidine, demonstrating relatively high CR rates of 50–57% and ORR of 68–78%. Grade 3–4 neutropenia occurred in about 30%, whereas grade 3–4 febrile neutropenia occurred in 12% of patients treated with enasidenib and 39% of patients treated with ivosedenib combinations.[13,51]

Given that IDH inhibitors are oral anti-leukaemic agents with a remarkable safety profile, this would easily be our preference for older unfit patients who clearly elect to avoid hospitalisations. The sustained response and easy administration of single agent ivosidenib make this an exciting therapeutic strategy. However, in cases where immobilisation is less of a problem, venetoclax combinations, very effective also in IDH1/2-mutated AML, would be offered to this patient, given the overall greater likelihood of achieving a longer disease-free interval.

Case 4: Treating an older patient with FLT3-ITD-mutated AML

A 75-year-old obese male, known to have diabetes and restrictive lung disease with hypoventilation syndrome, presents to the emergency room with dyspnoea. On examination, his O_2 saturation is 86% in ambient air, and chest radiography demonstrates bilateral pulmonary infiltrates. His CBC shows a WBC count of 140 000/μl with 85% circulating monoblasts, 60 000/μl platelets and haemoglobin 8·4 g/dl. He is treated with supplement oxygen, broad-spectrum antibiotics and hydroxyurea 6 g/day. Two days later, his WBC is 25 000/μl and his lungs are clear. The molecular AML work-up comes back with the diagnosis of normal karyotype, NPM1 wt/FLT3-ITD-mutated (allelic ratio 1·5) AML.

FLT3 is a transmembrane tyrosine kinase receptor, which, upon binding to its ligand, promotes proliferation and survival of normal haematopoietic progenitors through various intracellular pathways. Mutations in FLT3, resulting in constitutive activation of FLT3, are among the most common in AML in younger patients and are less frequent in advanced age. These mutations can be sub-divided into mutations in the juxtamembrane domain (FLT3-ITD mutation) and the tyrosine kinase domain (typically D835 point mutation).[52] FLT3-ITD is a well-known adverse prognostic marker, and is associated with high proliferation index and reduced RFS and OS.[53] The poor prognosis is more pronounced if high allelic ratio (AR) FL3-ITD mutation (defined as >0·5) is noted.[54] Guidelines of the National Comprehensive Cancer Network and the European LeukemiaNet categorise AML with FLT3-ITD mutation as poor-risk AML, based on the high relapse risk after intensive chemotherapy, and recommend allo-SCT as the preferred post-remission treatment. As for FLT3-TKD mutations, their prognostic impact is more uncertain due to conflicting evidence,[55–57] and therefore they are not considered currently as poor prognostic markers.

FLT3-ITD-mutated AML patients treated with low-intensity regimens with no FLT3 inhibitors have poor responses. CR rates of 44% for venetoclax + LDAC and 33% for glasdegib + LDAC were reported, which were lower than results in patients with no FLT3 mutations. The OS was also inferior, with only one-third of patients treated with venetoclax + LDAC being alive after a year. Similar results were recently published, demonstrating 53·3% CR/CRi rates and median OS of 12·4 months for FLT3-ITD-mutated AML patients receiving venetoclax-based combinations.[58] Thus, FLT3-ITD-mutated AML in older patients should be considered separately with novel agents. FLT3 inhibitors have a substantial role in treatment of AML patients presenting with FLT3 mutations. Midosturin, a first-generation FLT3 inhibitor, was the first to be approved as first-line therapy, in combination with 7 + 3 intensive chemotherapy, based on CR and survival benefit demonstrated in a prospective phase III study.[59,60] Sorafenib, another first-generation FLT3 inhibitor, which is biologically active only against FLT3-ITD and not against TKD mutations, was also tested prospectively in combination with either intensive chemotherapy or azacytidine. Addition of sorafenib to chemotherapy during induction and consolidation, with use as a single agent in 1-year maintenance, was found to improve the CR and survival rates in FLT3-ITD-mutated young AML patients.[61] The same survival benefit was demonstrated for FLT3-ITD-mutated AML patients aged 60–69, but not in a more elderly group, presumably because of adverse effects.[62] This is in line with a prior report regarding increased early mortality for patients >60 years treated with chemotherapy combined with sorafenib.[63]

The combination of sorafenib and azacytidine was tested in a phase II trial for newly-diagnosed AML and relapsed/refractory patients and resulted in considerable response rates of 32% for the relapsed patients and 67% for newly-diagnosed ones. Notably, about half of responses to sorafenib combined with azacytidine were CRi and not CR.[64,65]

Next-generation FLT3 inhibitors are more specific and more potent than first-generation inhibitors. Quizartinib was tested against chemotherapy for relapsed/refractory FLT3-ITD + AML patients in a phase III trial, demonstrating improved OS with manageable toxicity. Over 20% of patients receiving quizartinib achieved only PR as best response considered an event, which might have contributed to a less-pronounced EFS advantage.[66] Due to the very short EFS with this drug, the FDA has not approved it for use yet. Gilteritinib is another next-generation FLT3 inhibitor, which was tested as monotherapy against intensive and non-intensive salvage chemotherapy in a phase III trial. Based on improved OS in this setting, it was approved by the FDA for relapsed/refractory AML. Interestingly, only 21% of patients achieved CR/CRh, but nevertheless many others became transfusion-independent and/or could be referred to allo-SCT. It remains to be seen whether adding chemotherapy or a targeted agent to gilteritinib will improve the outcome in advanced FLT3-positive AML. These two next-generation inhibitors are currently being explored in various combinations in other scenarios, including newly-diagnosed AML patients.

This patient has serious comorbidities that preclude him from standard chemotherapy. He also has a highly proliferative AML with high allelic-ratio FLT3-ITD mutation, which

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