Acute myeloid leukaemia in patients we judge as being older and/or unfit

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The definition of older age in AML is arbitrary. In the context of the clinical studies, it starts with age ≥60 or ≥65 years and in recent years ≥70 or 75, depending on the selection of the studied population. In clinical practice, with older age, we often mean that the patient is unfit for intensive chemotherapy. Higher age overlaps with categories such as worse performance status, unfitness, comorbidities, poor-risk cytogenetics, adverse mutation patterns, age-related clonal haematopoiesis and specific disease ontogeny. Intensive induction therapy can result in prolonged overall survival, at least in a subset of elderly patients aged up to 75 years despite the reluctance of some physicians and patients to use treatment regimens perceived as toxic. Venetoclax and azacitidine combination is the new standard of comparison for persons unfit for intensive therapy. New oral hypomethylating agent CC-486 as maintenance therapy led to a prolonged overall survival in a randomized trial of patients ≥55 years of age who were in first complete remission, but not eligible for allogeneic stem cell transplantation. Any therapy is better than no therapy, but a substantial proportion of older patients still receive only palliative care. Making a decision for AML diagnosed in older age should be individualized and shared through the dialog with the patient and relatives or cohabitants, considering medical issues and social factors including personal goals. Although we are witnesses of the advances in basic research and therapy, we are still a very long way from curing older patients with AML.

Keywords: acute myeloid leukaemia, age, azacitidine, survival, therapy, venetoclax.

Introduction

Acute myeloid leukaemia is clinically, cytogenetically and molecularly a heterogeneous disease. Considering that a median age of patients in AML is 71 years, it is a disease of older patients. The aim of this review was to collect the current information on the biology and treatment with old and especially new drugs for this particular group of patients. The analysis is based on the most recent relevant publications in the literature after PubMed search. Data are gathered always not only from the randomized, phase III studies, but also from the population-based studies and retrospective international and national results of the treatment. Conduction of clinical trials and the interpretation of trial results in older persons with AML are impeded by selection biases. There are still too many unanswered questions. Giving the high rate of disease and patient heterogeneity, generalizability of study results to most older persons with AML is difficult. The progress is made in treating younger patients, that is those <60 years of age but much less in the patients >60 years of age. These advances could be applied in the minority of older patients, but with much more care in order to offer the benefit for some specific subgroups. The focus of this review was on the socio-economic factors, and comorbidities and patients’ own perspective. This review focuses on discussing some of the results of the newest studies and some difficult questions and challenges in treating older patients with AML.

What lies behind the age in AML

Age is the dominant risk factor for most chronic diseases, but the mechanisms through which ageing confers this risk are largely unknown [1]. As we age, our tissues accumulate an increasing number
of somatic mutations. Although most of these mutations are of no functional consequence, a mutation may arise that confers a fitness advantage on a single cell. When this process happens in the haematopoietic system, a substantial proportion of circulating blood cells may derive from just one mutated stem cell. This outgrowth, called ‘clonal haematopoiesis’, is highly prevalent in the elderly population [2]. Clonal haematopoiesis of indeterminate potential (CHIP) is linked to leukaemia gene mutations and associates with an increased risk for coronary artery disease and poor prognosis in ischaemic cardiomyopathy, which links deep roots between two major killers: cancer and cardiovascular disease [1, 2]. CHIP itself does not denote a malignancy, nor is it associated with clinically significant alterations in blood counts. But many of the most commonly seen mutations in CHIP are also recurrent drivers of AML, MDS, MPN and certain lymphomas. Presumably, individuals with CHIP would develop haematological malignancies at a rate above background because they have the ‘first hit’ needed for malignant transformation. In population-based cohorts that underwent exome sequencing, the presence of CHIP was associated with an approximately 10-fold increased relative risk of these malignancies followed up over several years. In one particular study, 4% of CHIP carriers developed a haematological malignancy over the subsequent 8 years, corresponding to approximately 0.5% of CHIP cases converting to malignancy per year. By the age of 70, about 10% of individuals with non-haematological malignancies are carrying specific, leukaemia-related, somatic mutations [3]. Of note, the risk of malignancy in the carriers of CHIP was associated with the size of the mutant clone, as those who went on to develop malignancy had substantially larger clone sizes than those who did not. Individuals with previous CH were at about threefold to fivefold increased risk of developing AML in the subsequent years. More than 75% of these CHIP mutations were in one of three genes, DNMT3A, TET2 or ASXL1, whereas mutations in TP53, JAK2, SF3B1, SRSF2 and U2AF1 were linked to especially high risk of developing AML [2–4]. Furthermore, patients with CHIP and concomitant solid tumours or lymphoma have an increased risk of therapy-related myeloid neoplasms after treatment for the primary cancer disease. Most patients with AML are older, where survival decreases rapidly with increased age. The median age at AML diagnosis in Sweden is 71 years (71 years for men; 72 years for women). Based on the Swedish Acute Leukemia Registry data, only 18% of patients are younger than 55 years, 16% are 55–64 years, 42% are 65–79 years old, and 24% are 80 years or older [5]. The achievement of complete remission (CR) is a prerequisite for long-term survival, and most patients require intensive chemotherapy. Performance status decreases with increasing age, and 50% of patients >65 years of age in the Swedish registry have comorbidities. Nevertheless, 85% of patients aged 60–69 years are diagnosed with a PS of 0–1, and 80% of those 70–79 years old have PS 0–II and by that were at least formally eligible for intensive chemotherapy [5]. Many clinical study protocol inclusion criteria state that age over 70 years is sufficient to classify the patient as ineligible for intensive chemotherapy and thus eligible for noncomparative trials with new and possibly less-toxic drugs [6, 7]. The data from SWOG and NCRI/MRC indicate that patients aged >65 years with FLT3-ITDmut/NPM1wt constellation and normal cytogenetics have inferior OS and RFS compared with patients aged 55–65 years and <55 years with the identical findings, presumably favourable according to the current ELN-2017 guidelines [8]. Older patients more frequently present with a secondary AML (sAML) being exposed to a primary leukaemogenic event. One cause of sAML is therapy-related (t-AML) after previous cytotoxic treatment w/o radiation. Another one is following an antecedent haematological disorder (AHD–AML), either MDS or myeloproliferative neoplasms (MPN) [9, 10]. The genetic and biological risk distribution does not sufficiently explain the age factor in AML [10].

Cytogenetics and mutations

The incidence of cytogenetic aberrations in AML is age-dependent. For example, some recurrent low-risk cytogenetic abnormalities such as t(8;21) or inv(16) are more common in younger patients. The same truth is valid for some high-risk abnormalities such as t(11q23)/(KMT2A/MLL) and inv(3) that are present more often in older patients. Deletions of chromosomes 5q, 7q and 17p were also more common in older patients. The presence of complex karyotype (CK) is defined as having 3 or more chromosomal abnormalities in the absence of one of the World Health Organization-designated recurrent genetic abnormalities. Monosomal karyotype is defined as the presence of at least 2 autosomal monosomies or a single autosomal monosomy associated with at least one structural abnormality, as a subgroup of CK with even worse
outcomes. In our registry-based retrospective study, patients with ≥5 chromosome abnormalities have worse OS than those with fewer abnormalities or normal karyotype in all age groups, whereas loss of 5q, 7q and 17p often occurred together within MK [11]. The European LeukemiaNet (ELN)-2017 risk classification incorporates the mutational profile in addition to cytogenetic abnormalities and stratifies AML into three groups: favourable, intermediate and high [10]. The presence of mutations in RUNX1, ASXL1 and TP53 is independently associated with poor outcome identifying a new subgroup of high-risk AML. The current ELN-2017 recommendations result in more patients being classified as favourable risk and significantly more patients classified as adverse risk compared with the previous ELN-2010 classification, which is an improvement in overall risk assessment [10]. A recent study showed that t(8;21) AML and inv(16) AML are characterized by remarkably different molecular patterns and distinct clonal compositions and prognosis despite both being characterized as favourable-risk group. In CBF-AML, t(8;21), trisomy 8, FLT3, and KIT exon 17 mutations confer poor outcome, whereas N Ras and W T1 mutations confer good outcome [12]. Further refinement of the ELN-2017 classification is possible as shown by Eisfeld et al. where application of newly proposed criteria including comutations may refine the ELN-2017 classification for older patients aged >60 years treated with chemotherapy [13]. A recent study demonstrated that the presence of secondary-type mutations identifies a group of de novo AML in older adults that behave like secondary AML (sAML) and confer poor prognosis [14]. Secondary AML is associated with poor outcome and is traditionally based on prior clinical history of AHD. AML ontogeny can be defined using cytogenetic and molecular data and helps in identifying patients with sAML with unknown prior AHD [15]. Patients with secondary AML based on cytogenetics and molecular data have worse outcomes than those with de novo AML. Patients with TP53 mutation particularly have very poor outcome and a high-level overlap with AML associated with complex or monosomal karyotype. The outcome of this very adverse type of AML has not been improved even with allo-SCT, where some groups abandoned the idea of pursuing allo-SCT as the next step of treatment, even in the patients with CR or CRi, because of very short survival and early relapses after allo-SCT [10, 15]. The better classification of sAML may have therapeutic implications. The current risk-group stratification of ELN-2017 is oversimplified, and there are several explanations for this notion. First, only mutations in just a few genes are counted. For example, it has been shown that beyond the interaction between NPM1 mutations and FLT3-ITD variants, the prognostic significance of one mutation can depend on the presence of other mutations [16, 17]. Morphology of typical AML with monoblastic differentiation and Auer rods is depicted in Figure 1. Secondly, the backbone of cytogenetic classification in ELN-2017 is reached on prognostic significance of MRC studies performed many years ago (at best a decade ago), and almost exclusively based on the patients below the age of 60 treated with chemotherapy. Some studies further support the statement that some recurrent cytogenetic abnormalities may have different prognostic significance in different age groups. For example, t(9;11), which has been consistently associated with intermediate-risk group in younger adults, in one patient cohort conferred poor prognosis. A previous study reported that t(9;11) was associated with intermediate outcome only in AML patients younger than 60 years, whereas the outcome of patients with t (9;11) aged ≥60 years was dismal [13, 18]. The reasons for such age differences are not completely understood.

Fitness

Geriatric assessment is a valuable asset in evaluating the fitness of the patient and establishing

Fig. 1  Acute myeloblastic leukaemia with NPM1 mutation, MGG stain ×100. Note the presence of Auer rods in some cells. Obtained with permission and by courtesy of Mats Ehinger, Department of Clinical Science, Division of Pathology, Skåne University Hospital, Lund, Sweden.
prognosis [19]. It is more widely used in US oncology and haematology guidelines than in Europe. Newest AML trials in older patients such as VIALE-A, VIALE-B or BRIGHT AML 1019 have not included formal geriatric assessment, despite the fact that this approach showed a potential to refine the prognostic effect of age [20–22]. The same applies to many other trials in older patients. Patients with higher performance status (PS) are underrepresented in VIALE-A clinical trial, which led to the approval of combination of venetoclax and azacitidine (16% of patients had PS grade 2, and none had PS grade 3 or 4) [20]. Choosing between intensive or nonintensive therapy based on ‘fitness’ or ‘unfitness’ is still subjective. Multidisciplinary decision-making and shared medical decisions are needed but are not always possible in the real life, especially in smaller hospitals. For example, individual physicians facing the same clinical scenarios make decisions according to their personal attitude for risk-taking; those willing to accept higher risks in their own lives were more likely to recommend intensive therapy [23].

Comorbidities

A study based on the data from Danish National Leukaemia Registry (DNLR) revealed that ‘ever-smokers’ (both smokers and those who smoked a shorter period of time and stopped smoking) had a significant shorter median OS than ‘never-smokers’ (17.2 vs 24.5 months). Multivariate analysis revealed smoking status as a significant prognostic factor for inferior OS with a hazard ratio (HR) of 1.22. The authors concluded that the smoking status was associated with inferior OS in intensively treated AML patients [24]. The haematopoietic cell transplantation comorbidity index (HCT-CI) is an independent predictor for early death in elderly patients ≥60 years. A high HCT-CI score predicts shorter survival in adult patients with AML [25, 26]. In another larger cohort study, comorbidities influenced 1-year survival of patients with AML, and comorbidities are best captured by an ‘augmented HCT-CI’ with a predictive estimate of 0.72. Proposed ‘augmented HCT-CI’, age and cytogenetic/molecular risks could be combined into a better AML composite model that could possibly guide treatment decision-making and trial design in AML with a slightly upgraded predictive estimate of 0.76 [27]. Targeting comorbidities with interventions alongside specific AML therapy might further improve survival.

Social factors

Some social factors could have impact on the prognosis of AML. In a Danish Registry Study, older patients who were low-educated received less-intensive therapy compared with high-educated patients (30% vs 48%). However, remission rates and survival were not affected in those intensively treated [28]. Living alone or not and marital status have a substantial effect on treatment decisions and OS in patients with AML aged ≥60 years according to the Danish registry data. Patients living alone were less likely to receive remission induction chemotherapy or undergo postremission SCT, potentially leading to inferior outcomes [29].

Time from diagnosis to initiation of intensive treatment (TDT)

It is a still open question whether we can safely wait until cytogenetics and genomic data become available before we start the treatment. There is a strong belief in the community that AML requires urgent treatment, where 10- to 14-day delay in waiting for results seems unethical, especially in younger patients [30]. However, French study, examining 599 patients with a median time from diagnosis to initiation of intensive chemotherapy (TDT) of 8 days, reported that TDT had no effect on early death (ED) rate or overall survival even in patients with age higher or lower than 60 years or those presenting with WBC > 50 x 10⁹ [31]. These results were confirmed by the SAL group in a larger cohort of 2263 patients with a median TDT of 3 days. It is suggested that a feasible approach is to wait for genetic test results to characterize leukaemias better and stabilize the medical condition of the patient before best available treatment is commenced [32]. Treatment with hydroxyurea was without effect on outcome. Our own population-based study from the Swedish Acute Leukemia Registry using the real-world data in the cohort of the similar size as Röllig et al. (2374 patients) is recently published. It supports the interpretation that in routine clinical practice, patients with typical aggressive AML generally receive a very rapid management and benefit from this management. With increasing age, lower blast counts, and previous medical history, there is commonly a short delay before treatment, which may be due to clinical optimization, waiting for genetic test results and/or discussing alternative options for treatment with patients and relatives [31–33].
Intensive therapy

First-line therapy of eligible older patients is still chemotherapy with combination of anthracycline in a dose no less than 60 mg m⁻² and cytosine-arabinoside as a backbone, where gemtuzumab ozogamicin (GO) or midostaurin should be added in CBFB-AML and FLT3-mutated AML, respectively [6, 7, 10, 34, 35]. In a phase III randomized trial of patients aged 60–75 years with secondary AML CPX-351 demonstrated a significantly higher rate of CR (47.7% vs 33.3%, $P = 0.016$) and superior median OS (9.56 vs 5.95 months; HR 0.69, $P = 0.003$) compared with the current standard of care with conventional 3 + 7 induction [36]. CPX-351 appears to be well tolerated, with lower 30- and 60-day mortality, more patients transitioning to allogeneic SCT and consequentially improved post-transplant survival. Recently updated data with 5 years of follow-up confirmed the improved OS of CPX-351 compared with 3 + 7 in the target population (18 vs 8%) [37]. Results of the study led to the FDA and subsequently EMA approval of CPX-351 as induction therapy in patients with t-AML and AML with myelodysplasia-related changes (MRC) [10]. It needs to be emphasized that CPX-351 is a combination of anthracycline and cytarabine and should be viewed as an intensive induction treatment, and not a lower-intensity alternative to be considered in patients who are deemed unsuitable for intensive chemotherapy. The primary cause of treatment failure especially in older patients has been resistance to therapy rather than treatment-related mortality (TRM) [10]. A significant proportion of patients at high risk of TRM are often excluded from trials because of performance status $>2$ or comorbidities, having demonstrably worse outcomes. A trial whose eligibility criteria were essentially ineligibility for clinical trials has demonstrated the potentially favourable risk/benefit ratio of much broader criteria for trial inclusion [38, 39]. It is of paramount to know before the treatment is started which individual patient is at potential higher risk for death and who has the highest likelihood of achieving remission. Krug et al. proposed a relatively simple score including body temperature, haemoglobin, platelet and fibrinogen levels, as well as age and type of AML (primary or secondary), which can be used to predict the probability of CR and the risk of ED in older patients with AML, otherwise medically healthy, for whom intensive induction chemotherapy is planned [40]. Österoos et al. identified a high-risk group of patients with a CR rate of 20% in AML with mutated TP53, compared with 97% CR in low-risk AML patients defined by high expression of ZBTB7A and EEPD1 without TP53 mutations [41]. New results suggest that the modest improvement in survival in AML is due to the decreasing ED rate of AML, which are at least in Sweden attributable to the improved patient-related factors in general and the performance status at the time of diagnosis in particular [42].

Nonintensive therapy

In the AZA-AML-001 study, patients were randomized to treatment with azacitidine for 7 days in a standard dose 75 mg m⁻² every 4 weeks or conventional care (CCR) including supportive care, LDAC or induction chemotherapy. The response rate (CR and CRi) was similar between the two treatment arms (27.8% for azacitidine vs. 25.1% for CCR, $P = 0.5348$). Median OS was improved in the azacitidine arm vs CCR when censoring for subsequent therapy (12.1 months vs. 6.9 months, $P < 0.019$) [43]. Overall survival was comparable amongst patients preselected to receive induction chemotherapy regardless of subsequent randomization. These results are in accord with a retrospective study that demonstrated similar survival between elderly AML patients treated with intensive induction chemotherapy versus HMA, and Swedish retrospective registry-based study [44,45]. DACO-016 study was implemented in a similar fashion, randomizing patients between 5 days of standard-dose decitabine every 4 weeks and treatment choice (TC), which included LDAC or supportive care (SC). DACO-016 study showed an improvement in the CR rate with decitabine vs TC (17.8% vs. 7.8%, $P < 0.001$) and a small improvement in OS (7.7 vs. 5.0 months, $P < 0.037$) where majority of patients in TC received LDAC (87%) and not just SC [21]. Both HMAs azacitidine and decitabine are approved by EMA and adopted as a standard treatment for elderly AML patients where conventional induction chemotherapy is judged as unsuitable. VIALE-A study compared azacitidine and venetoclax and azacitidine in randomized 2:1 phase III study of 431 patients (286 in the azacitidine–venetoclax group and 145 in the azacitidine–placebo [control] group). The median age was 76 years in both groups (range 49–91). At a median follow-up of 20.5 months, the median overall survival was 14.7 months in the azacitidine–venetoclax group and 9.6 months in the control group (HR for death, 0.66; 95% CI, 0.52–
The incidence of CR was higher with azacitidine–venetoclax compared with the control regimen (36.7% vs. 17.9%, \( P < 0.001 \)), as was the composite CR (CR or CRi) (66.4% vs. 28.3%, \( P < 0.001 \)) with higher haematological toxicity in the experimental arm. The incidence of composite CR was notably improved across all AML genomic risk groups, including patients with poor cytogenetic risk group, sAML and high-risk molecular mutations. These improvements in responses also translated into an increased OS in many of the evaluated subgroups, most notably amongst patients with either de novo or secondary AML, intermediate cytogenetic risk, and \( IDH1 \) or \( IDH2 \) mutations, although the subgroups were small in size [10, 19]. Like single therapy with HMA, venetoclax–azacitidine combination should not be routinely discontinued, as long as it is tolerable and maintained efficacy is observed [46, 47]. Information from real-life studies is expected in order to confirm safety and efficacy of venetoclax–azacitidine combination [48]. Various issues concerning duration of treatment, universally accepted criteria for timing and evaluation of response are still not properly answered. Furthermore, the role of azacitidine–venetoclax combination in poor-risk young adults and older fit patients remains to be definitively clarified (Table 1). The incidence of composite remission in VIALE-A study in those with \( TP53 \) mutation in the azacitidine and venetoclax group was 55.3% (95% CI, 38.3–71.4) vs 0% in the control group (\( P < 0.001 \)). Unfortunately, remission was short-lived, with a median duration of 3.2 months [19]. At the last ASH meetings, there were presented some promising data on effects of combination between magrolimab and azacitidine, especially in those with \( TP53 \) mutation with ORR in 29 of 46 (68%) patients with CRi of 59%, but with a short follow-up [49]. Only three drugs have reached overall survival benefit in older patients with AML. These are combinations of azacitidine and venetoclax, glasdegib and low-dose cytosine–arabinoside and CC-486 as a maintenance therapy for older patients already in complete remission.

### Therapy of FLT3-mutated AML

In a phase III RATIFY trial, combination of midostaurin and ‘3 + 7’ chemotherapy in patients with newly diagnosed FLT3-mutated AML (aged 18–59 years) improved EFS and OS compared with ‘3 + 7’ chemotherapy alone [50]. Another phase II trial in adults up to the age of 70 years has demonstrated the safety of midostaurin in combination with ‘3 + 7’ chemotherapy. In this trial, there was no difference in outcomes between older and younger patients; OS was 34% (age 61–70) vs 39% (age 18–60) at 2 years of follow-up [51]. In a phase III ADMIRAL trial, a second-generation FLT3 inhibitor gilteritinib targeting both FLT3-ITD and FLT3-TKD was associated with significantly longer OS and higher complete remission rates compared to midostaurin alone [52].

### Table 1  Survival in selected studies of older patients with AML

| Study type | Median age (years) | Treatment | CR rate (%) | Number of patients | Median OS (months) | 1 year OS (%) |
|------------|--------------------|-----------|-------------|--------------------|--------------------|--------------|
| Talati [44] Single-centre | 75 | HMA | 22.7 | 231 | 14.4 | 55 |
| Juliussøn [34] Swe-registry | 75 | HMA | 9 | 276 | 8.5 | 36 |
| Juliussøn [86,87] Swe-registry | 75 | IC | 71 | 532 | 11.1 | 46 |
| Dombret [43] RCT | 71 | HMA | 19.5 | 241 | 13.3 | 56 |
| Wei [46] RCT | 76 | VEN + LDAC | 48 | 143 | 8.4 | 33 |
| DiNardo [20] RCT | 76 | VEN + AZA | 36.7 | 286 | 14.7 | NA |
| Wei [59] RCT | 68 | IC + CC-486 | 79 | 238 | 24.7 | 72.8 |
| Cortes [22] RCT | 77 | GDG + LDAC | 19.2 | 88 | 8.8 | 39.4 |

AZA, azacitidine; CC-486, oral azacitidine; GDG, glasdegib; HMA, hypomethylating agents; IC, intensive chemotherapy; LDAC, low-dose ara-C; NA, not assessed; RCT, randomized controlled trial; Swe-registry, Swedish Acute Leukemia Registry; VEN, venetoclax.
with intensive salvage chemotherapy (MEC or Flag-IDA regimens) and nonintensive group (azacitidine or LDAC). Interestingly, median age in this trial was 62 years, and patients >65 years had comparable benefit to patients <65 years [52]. This trial led to the FDA and subsequently EMA approval of gilteritinib for relapsed or refractory FLT3-mutated AML. In a similar study, QUANTUM-R, another FLT3 inhibitor quizartinib showed better results than salvage chemotherapy, but failed in marketing approval by the FDA and EMA, being approved only in Japan. The reasons could be dropouts (23% of the control group did not receive chemotherapy), censoring and concerns about cardiac and infectious adverse events. The search of the www.clinicaltrials.gov shows that FLT3 inhibitors are tested in 19 ongoing trials, but just only one of which specifically targets older patients with AML. It is reasonable to believe that a combination of FLT3 inhibitors with other drugs could do better than single-agent therapy in older patients with AML. The ultimate goal of these combinations should be to prolong overall survival with preserved good quality of life (QoL) and without added toxicity.

Therapy for IDH1- and IDH2-mutated AML

Both isocitrate dehydrogenase (IDH) inhibitors, oral ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor), are approved by FDA for relapsed or refractory AML with IDH1 and IDH2 mutations. Ivosidenib (IDH1 inhibitor) monotherapy led to a CR + CRh rate of 33% with a median duration of response (DOR) of 8.2 months in adults with R/R IDH1-mutated AML. A transfusion independence was also observed in 37% of patients. A minority of patients in CR/CRh also had clearance of IDH1 mutation (21%), which did not correlate with OS [53, 54]. More recently, ivosidenib was approved by FDA for upfront treatment of IDH1-mutated AML in older adults unfit for intensive chemotherapy. Unfortunately, the application for ivosidenib for adult patients with relapsed/refractory (R/R) IDH1-mutated AML was withdrawn in European Union. This decision was based on the EMA assessment that the data from the single-arm, uncontrolled phase I study in the R/R AML setting (NCT02074839) did not sufficiently support a positive benefit–risk balance [55]. In a similar fashion, enasidenib (IDH2 inhibitor) monotherapy achieved 23% of CR or CRh rate with a median DOR of 8.2 months in adults with R/R IDH2mut AML. In late August 2020, the company producing the drug announced that the final results of the IDHENTIFY did not meet the primary end-point of overall survival (OS) in patients with R/R AML with an IDH2 mutation.

In addition to IDH inhibitors, venetoclax in combination with LDAC and azacitidine has also been shown to produce durable responses in IDH-mutated AML (median OS 19.4 and 24.4 months, respectively) [46]. In a cohort of patients older than 75 years who received induction chemotherapy, none of the 13 of 151 (9%) IDH1-mutated patients reached CR, which implicate IDH1 mutations as a novel marker for chemorefractory disease and inferior prognosis [56]. Interestingly, in a recent study mutant IDH1 or IDH2 in patients with AML was associated with increased risk for cardiac dysfunction and a higher prevalence of coronary artery disease (CAD) at the time of AML diagnosis and during treatment with intensive chemotherapy [57]. The authors state that the impact of cardiovascular monitoring and optimal treatment of cardiovascular risk factors in these AML patients on cardiovascular outcomes should be further evaluated.

Maintenance therapy

A phase III study (HOVON97) in older AML patients aged 60 years or greater (median 69 years) with performance status <3 who were in CR (71%) or CRi after two cycles of intensive chemotherapy randomized patients between observation and azacitidine group. Azacitidine dose was 50 mg m~2~ s.c. daily for 5 days every month, up to 12 cycles or until overt relapse. Of 116 patients included in the study, 82% received at least 4 cycles of azacitidine and 62% received 12 cycles with a median follow-up of 41.4 months. After accounting for age, one or two cycles to best response (CR or CRi), adverse risk cytogenetics and platelet count <100 vs >100 (CRi vs CR), azacitidine reduced the risk of relapse or death in remission (HR 0.62, P = 0.03). The 12-month RFS probability was 64% in maintenance vs 42% in the control group. The effect of azacitidine was similar in all age groups, cytogenetic risk group, number of cycles to the best response and performance status, but was higher in patients who had attained platelet count >100 after induction chemotherapy. Unfortunately, there were no differences in OS, because of the more frequent use of salvage therapy in the observation group, likely due to more cases of allo-SCT (11 vs 4). Salvage therapy improved survival in both observation and treatment groups [10, 58]. A phase III, randomized,
double-blind, placebo-controlled trial of the oral formulation of azacitidine (CC-486, not interchangeable with injectable azacitidine), as maintenance therapy in patients with AML who were in CR1 after intensive chemotherapy, was recently published. Patients who were ≥55 years of age, in CR or CRi, and judged not to be candidates for SCT have been randomly assigned to receive either CC-486 or placebo once daily for 14 days per 28-day cycle. The median age in the study was 68 years (range 55–86). Median OS from the time of randomization was shown to be longer with CC-486 than with placebo (24.7 vs. 14.8 months, \(P < 0.001\)). Benefits of CC-486 with respect to OS and RFS were shown in most subgroups. The most common adverse events in both groups were mild gastrointestinal events with grade 3 or 4 haematological toxicity such as neutropenia (41% CC-486 group vs. 24% placebo) and thrombocytopenia (22%, 21%, respectively) [59]. It is encouraging to know that OS and RFS were improved with CC-486 regardless of the number of consolidation cycles received prior to study entry, even though the patients receiving 2 consolidations had longer RFS and OS. Of note, maintenance therapy with CC-486 improves OS independently of MRD status and can induce MRD negativity in MRD-positive patients after intensive chemotherapy is completed. Data from the only randomized trial post-allo-SCT maintenance published in the literature show the overall survival benefit of sorafenib in FLT3-mutated AML. The results from the ongoing studies with other FLT3 inhibitors in the same setting such as midostaurin, quizartinib or gilteritinib are eagerly awaited [60].

**Allogeneic stem cell transplantation**

The majority of data available on performing allo-SCT for older AML patients involves patients aged 65 years or younger than that age group, whilst limited data exist regarding patients transplanted in their seventh or even eighth decade [61]. Their number of allo-SCT has risen steeply since 2000: patients ≥70 years now represent almost 4% of allo-SCT recipients. There are no prospective randomized studies done in this population, and we have to rely on the data from the retrospective cohorts. A retrospective survey from the EBMT compared the outcome of 713 AML patients aged ≥70 years with 16161 patients aged 50 to 69 years who underwent allo-SCT between the years 2004 and 2014. TRM was higher in the older patients (34% vs 24%), and 2-year OS was lower (38% vs 50%). Nevertheless, when selecting only active disease patients, the 2-year OS was comparable, 35% and 33%, respectively [62]. There were no significant differences in the incidence of acute and chronic GvHD in the two age groups. In another large retrospective analysis from the National Clinical Trials Network (NCTN), OS for patients aged 60–77 years was worse in allo-SCT during the first 9 months after CR1 (HR = 1.52, \(P = 0.02\)), but was significantly better thereafter (HR = 0.53, \(P < 0.0001\)) relative to chemotherapy emphasizing the balance between short- and long-term risks in decision-making for older patients. Treatment-related mortality (TRM) following allo-SCT was worse in the first 9 months (HR = 2.8, \(P = 0.0009\)), whilst post-SCT relapse was significantly less frequent beyond 9 months (HR = 0.42, \(P < 0.0001\)). Despite higher early TRM, allo-SCT recipients had superior long-term OS (TRM: 29% (24–34%) versus chemotherapy: 13.8% (9–21%) at 5 years) [63]. These studies on a large number of patients suggest that age limit of 70 years is not an insurmountable barrier, and selection of patients and transplant approaches needs to be taken into account [64].

**Autologous stem cell transplantation**

Prospective studies in older AML patients assessing the benefit of autologous SCT compared with chemotherapy consolidation or allo-SCT are lacking. Retrospective studies in a highly selected group of patients, mostly favourable- and intermediate-risk older AML patients in CR1 in experienced centres, and patients in good performance status, based on single-centre experiences or selective registry data, showed that it could be a feasible alternative for few patients [65]. However, new therapies with maintenance with oral or parenteral hypomethylating agents, in combination with FLT3 inhibitors, IDH inhibitors or venetoclax, could supplement or more likely replace autologous stem cell transplantation.

**MRD negativity in older AML**

Recent meta-analysis of 81 publications reporting on 11 151 patients with AML suggests that achievement of MRD negativity is associated with superior DFS and OS in patients with AML. The estimated 5-year OS was 68% for patients without MRD and 34% for those with MRD. The value of MRD negativity seems to be consistent across all age groups, AML subtypes, time-points of MRD.
assessments, specimen source (PB and BM), and MRD detection methods (MFC, RT-PCR, NGS) [66]. These results support MRD status as an essential end-point for clinical studies that may allow for accelerated evaluation of novel therapies in AML. However, also pointed by Estey, the effect of eliminating MRD on outcome can only be investigated if effective means to eliminate MRD are available [10].

**Precision-based therapy**

In umbrella trials, patients receive therapy based on the specific mutation or biomarker found in their cancer. The drugs being tested may change during the trial, as new targets and new drugs are found. Umbrella trials may allow new drugs to be tested and approved more quickly than traditional clinical trials and in world of AML potentially replace slower ‘Pick-a-Winner’ concept [67]. One example is BEAT AML trial (NCT03013998) where precision medicine therapy strategy in AML is feasible within 7 days from the date of diagnosis allowing patients and physicians to rapidly incorporate genomic data into treatment decisions. It seems that this approach can be used without increasing ED or adversely impacting OS according to this preliminary report [68]. A total of 487 untreated patients with AML ≥60 years were prospectively enrolled. Median age was 72 years (range 60–92; 38% were ≥75 years); 374 patients (94.7%) had genetic and cytogenetic analysis completed within 7 days and were centrally assigned to a BEAT AML substudy; 224 (56.7%) were enrolled on a BEAT AML substudy. The remaining 171 patients were selected for other available therapies. The preliminary report showed that demographic, laboratory and molecular characteristics were not significantly different between patients on the BEAT AML substudies and those receiving standard of care (SOC). Overall survival was significantly longer for patients enrolled, and 30-day mortality was less frequent on the BEAT AML substudies versus those who were selected in the SOC group, although this was not a primary end-point of the study. Another approach for ‘precision-based medicine’ concept is ‘Individualized system medicine’ (ISM) named by the authors from Finland. It is based on molecular profiling and *ex vivo* drug sensitivity with resistance testing (DSRT) [69]. Another method used for the *ex vivo* sensitivity of AML patient samples at a cell population level is 96-well format flow cytometry (FC)-based drug sensitivity assay, which showed a potential to reveal the association between venetoclax response and differentiation stage in AML [70].

**Patients’ perspective**

Decision between intensive and nonintensive, and no treatment is a complex process that is usually made when patients are acutely ill, likely shocked by the suddenness of the diagnosis, especially amongst those with *de novo* AML. Interestingly, at least in one study, most patients felt that they had not been offered a treatment choice at all [71]. Studies have shown that patients with newly diagnosed cancer retain less than half of information presented, and older patients retain less information than the younger patients [72]. Moreover, patients with lower health literacy and worse prognoses have poorer recall [73]. Shared decision-making (SDM) is an approach to medical decision-making for those situations in which most clinicians would agree that there is more than one correct choice for a patient.

**Doublets, triplets and new drugs**

If we want to summarize most recent results from single-centre studies, registry-based studies and randomized controlled trials in older AML patients, the median overall survival for patients over the age of 75 is between 8.4 and 14.7 months, which is unsatisfactory. Longer overall survival is achieved only in the group with maintenance therapy and CC-486 with median of 24.7 months. We have to bear in mind that these patients are younger (median age 68 years), were previously fit for intensive therapy and likely have more favourable cytogenetic and molecular profile where 85% of the patients were with intermediate-risk AML (Table 1). New combinations of drugs are planned to be tested as doublets, triplets or quadruplets in clinical trials. The list of possible combinations is almost inexhaustible, although there is often a backbone with old (proven) drug combined with the new (unproven) drug. A search of a ‘perfect couple’ or ‘three musketeers’ is ongoing. There are some preclinical data suggesting a synergistic effect between combination of venetoclax and FLT3- and IDH-targeted therapies. Triplet regimens involving azacitidine and venetoclax with FLT3 or IDH1/2 inhibitor, APR-246, anti-CD47 antibody magroli-mab, myeloid cell leukaemia-1 (MCL1) inhibitors, or immune therapies such as different CD123 antibody-directed drugs and programmed cell
death protein 1 (PD-1) inhibitors are currently being evaluated [74]. There is a hope that new combinations, when applied in appropriate patient subsets, will further significantly improve remission rates, and more importantly remission durations and overall survival. A strategy for treatment of patients without specific targetable mutations is needed, because of the fact that 50% of the patients do not have FLT3 and IDH mutations at the presentation [22, 75–81]. In order to optimize the effects of drugs for the older AML patients, it is essential that the backbone of treatment has a proven efficacy and a toxicity profile with potential for synergy. Some doublets and triplets are summarized in Table 2. Another approach is combination of anthracycline and cytosine-α-carboxilic induction chemotherapy (‘2 + 5’) and new drugs (venetoclax) as in recently published phase Ib CAVEAT dose-escalation study for the newly diagnosed AML patients where the median age of patients was 71 years. This study clearly shows that myelosuppression caused by venetoclax may dictate tolerability, and the ideal dose and schedule in induction and consolidation will need careful planning for the future studies. Notably, these early results suggest that venetoclax combined with intensive chemotherapy may be best suitable for NPM1, IDH2 and SRSF2 AML, as is the case when venetoclax is combined with azacitidine or LDAC [46, 81]. Thus, for these groups, it would be worth testing the possibility of consolidation with less aggressive and outpatient-based cycles of venetoclax–azacitidine or venetoclax–LDAC, rather than venetoclax combined with intensive chemotherapy [81, 82]. We should be aware that prolonged myelosuppression can jeopardize the introduction of new drugs in this fragile population. On 21 December 2020, it was announced that the phase III LACEWING trial (NCT02752035) failed to meet its primary end-point of a statistically significant improvement in overall survival with gilteritinib plus azacitidine, versus azacitidine alone, in patients with newly diagnosed, FLT3-mutated AML, who were ineligible for intensive induction chemotherapy [83]. The trial is one of the many cautionary tales about that giving ‘more’ therapy in AML is not always translated to the ‘better’ outcome. Trial enrolment and design, and the dose of drug(s) should be consistent with the goals of care of older patients with AML. Hope for

| HMA backbone doublet | Venetoclax backbone doublet | FLT3 inhibitor doublet | Venetoclax + HMA backbone triplet |
|----------------------|-----------------------------|------------------------|--------------------------------|
| AZA + IDH inhibitor (ivosidenib, enasidenib) | VEN + AZA (DEC) | Gilteritinib + AZA | VEN + AZA + FLT3 inhibitor (gilteritinib, quizartinib, midostaurin) |
| AZA + APR-246 | VEN + CPX-351 | Gilteritinib + VEN | VEN + AZA + IDH inhibitor (ivosidenib, enasidenib) |
| AZA + magrolimab | VEN + FLAG-lda | Gilteritinib + induction | VEN + AZA + APR-246 |
| AZA + FLT3 inhibitor (quizartinib, gilteritinib) | VEN + idasanutlin (MDMA inhibitor) | Gilteritinib + CC-90009 (CELMoD) | VEN + AZA + MCL1 inhibitor (e.g. CYC065, AMG 176) |
| AZA + PD-1 inhibitor (e.g. nivoluzumab) | VEN + CDK9 inhibitor (alvocidib, voruciclib) | Quizartinib + CPX-351 | VEN + AZA + PD-1 inhibitor (e.g. nivoluzumab) |
| AZA + anti CD 123 Ab (e.g. IMGN632) | VEN + MCL1 inhibitor (e.g. S64315, AZD5991) | Quizartinib + VEN | VEN + AZA + anti CD 123 Ab (e.g. IMGN632) |
| AZA + RARα agonist (SY-1425) | VEN + induction | Quizartinib + induction | VEN + AZA + magrolimab |
| AZA + Pevonedistat (NEDD8 inhibitor) | VEN + Pevonedistat (NEDD8 inhibitor) | Crenolanib + salvage chemotherapy | VEN + AZA + anti CD 70 Ab (cusatuzumab) |

Ab, antibody; AZA, azacitidine; CDK, cyclin-dependent kinase; CELMoD, cereblon E3 ligase modulator; DEC, decitabine; IDH, isocitrate dehydrogenase; MCL1, myeloid cell leukaemia-1; MDMA, mouse double minute 2; NEDD8, neuronal precursor cell-expressed developmentally down-regulated protein 8; PD-1, programmed cell death protein 1; RARα, retinoic acid receptor alpha; VEN, venetoclax.
the future is the pursuit of the new drugs or drug combinations, where search of the website www.clinicaltrials.gov indicates there are currently 44 phase III trials for adults aged ≥65 years with AML activated for inclusion.

Conclusions

Older adults with AML often have high-risk cytogenetic and molecular features conferring chemoresistance, and poor functional status leading to increased treatment intolerance; hence, survival of older adults has largely remained unchanged in the last few decades [84]. Data from the recent ‘real-life’ population-based study from Sweden show that HMA treatment results were similar to intensive chemotherapy in patients aged ≥60 years in terms of OS using multivariate analysis, as well as in a propensity score matching analysis, whilst there was a clear benefit of HMA compared with palliative treatment (Figure 2a-d) [44]. After a long time of having a relatively simple ‘one-size-fits-all’ 3 + 7 approach followed by consolidation (with or without allo-SCT), we are now sailing into the age of more genetically directed therapy, where understanding genetic landscape at diagnosis may dictate quite differing treatment options. More-intensive therapy is recommended over less-intensive therapy when deemed tolerable [85–88]. If we assume that intensive chemotherapy is feasible up to the higher age, there are many reasons to believe that even stem cell transplantation strategy should be applied in selected patients up to the age of 75, with potential to have adjusted conditioning regimens and even post-transplantation maintenance therapy as concepts of modern treatment. Venetoclax and

Fig. 2  Real-world data on treatment patterns and outcomes of hypomethylating therapy in patients with newly diagnosed acute myeloid leukaemia aged ≥60 years in Sweden. (a) Overall survival (OS) of all patients divided by the three types of treatment: intensive chemotherapy (IC), hypomethylating agents (HMA) and palliative care (PC). (b) Survival of patients included in the propensity score matching (PSM) analysis divided by the three types of treatment. (c) Comparison of OS between HMAs and IC in PSM groups within cytogenetic risk groups (high risk and low/intermediate risk, respectively). Variables used for PSM were age, gender, WHO performance status, cytogenetic risk, previous myelodysplastic syndrome and previous myeloproliferative disorder. (d) Comparison of OS between HMA and PC in PSM groups within the cytogenetic risk groups. For all survival analyses, patients who underwent allogeneic transplantation were censored at the date of transplantation [44].
azacitidine combination (or venetoclax and LD Ara-C in few other countries such as Australia and New Zealand) is the new standard of comparison for persons unfit for intensive therapy [10, 20]. Identification of such persons is often subjective, and we are witnesses of efforts to be more objective in this assessment. Any therapy is better than no therapy, and presumably, with new therapies coming along, fewer patients should be offered purely palliative care [84, 85]. However, all recommendations are guided by the principle that throughout a patient’s disease course, optimal care involves ongoing discussions between clinicians and patients, addressing goals of care and the risk–benefit balance of treatment [88]. It should be again emphasized that there are many biases in choosing the ‘perfect’ treatment of AML in older patients and that ‘meaningful clinical benefit’ lies in the eye of the beholder [10]. We should remind ourselves that as attending physicians, we are in the middle of the ring balancing between different perspectives on treatment, prognosis and quality of life of pharmaceutical companies, patients and their families, healthcare payers and our own personal preferences and attitudes [10, 23]. Although the advances in the knowledge are most welcomed by AML community, we are still a very long way from curing older patients with AML.

Conflicts of interest

The author declares no conflicts of interest.

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