Chapter

Treatment of AML in Older Patients

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Abstract

Acute myeloid leukaemia (AML) is a disease mostly diagnosed in older adults. Treatment of older patients with AML remains challenging with higher rates of intrinsic chemotherapeutic resistance and decreased treatment tolerance. Indeed AML in older patients has different clinical and biologic characteristics compared to younger patients. Several treatment options are available for treatment of AML in older patients, namely conventional intensive chemotherapy ('3 + 7'), low-dose cytarabine, and hypomethylating agents. Combinations with new drugs have been recently approved or are in advanced stages of clinical testing, namely venetoclax, midostaurin, glasdegib. Clinical decision making should take into account disease characteristics (e.g. cytogenetic and molecular abnormalities, white blood cell count), patient characteristics (e.g. performance, comorbidities, geriatric assessment) and patients' preference when considering which treatment option is most suitable for the older patient. Allogeneic haematopoietic cell transplantation (HCT) as post-remission strategy should also be considered for older patients with AML. Allogeneic HCT following reduced-intensity conditioning or non-myeloablative conditioning has made this treatment option more suitable for older patients with a reduction in treatment-related mortality.

Keywords: AML, older patients, hypomethylating agents, venetoclax, transplantation

1. Acute myeloid leukaemia: a disease of older individuals

Acute myeloid leukaemia (AML) is a heterogeneous group of malignant haematological diseases. It is predominantly a disease of older adults, with a median age at diagnosis of 68 years [1]. Indeed, 75% of the AML patients are older than 60 years (**Figure 1**). Besides a higher incidence of AML at older age, AML in older adults differs biologically and clinically from AML in younger adults [2]. AML in older adults is characterised by a markedly reduced long-term survival resulting from the combination of poor chemotherapeutic tolerance and inherent chemotherapy resistance compared with younger AML patients [3]. AML in older adults has a lower frequency of favourable core-binding chromosomal abnormalities and a higher incidence of complex aberrant karyotypes [4, 5]. These differences in clinical and cellular behaviour of AML in older adults suggest activation of different target genes by oncogenic events in aged stem or progenitor cells compared with younger stem or progenitor cells. Indeed a distinct gene-expression profile noted for older compared to younger adults with AML supports a molecular basis for disparities in outcome related to age [2, 5, 6]. In addition, more frequent comorbid conditions,

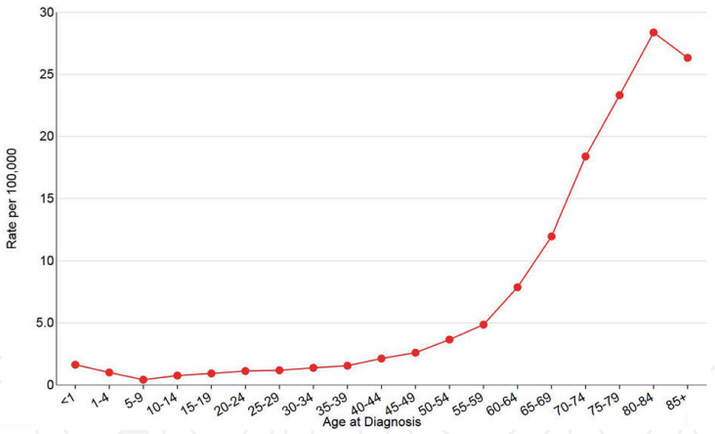

Figure 1.
AML incidence rates by age at diagnosis (2013–2017). Reproduced from: SEER Cancer Stat Facts: Acute Myeloid Leukaemia. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/amyl.html

the decreased immune competence of older patients and psychosocial factors influence treatment outcome of AML in older adults. The effects of age on both disease- and patient-related factors result in a lower rate of disease remission, a higher incidence of early death during chemotherapy, and a reduced probability of long-term survival [2, 3]. In light of this, population based studies report a treatment percentage of only 30% in AML patients aged 65 and older [7, 8]. Indeed, regardless of treatment, outcomes for older AML patients are unsatisfactory, with median overall survival (OS) of 5–10 months and 5-year survival of about 10% [9–11]. In contrast with the progress made for younger adults with AML, the treatment in older adults has not improved significantly in recent decades, despite numerous efforts to find effective and tolerable treatments [12].

2. Treatment options in older adults with AML

The optimal treatment of older adults with AML in daily clinical practice remains challenging, and is dependent on patient characteristics (age, performance, comorbidities), disease characteristics (cytogenetic and molecular abnormalities, white blood cell count) and the preference of the patient [3]. Regular treatment options include: best supportive care (BSC), low-dose chemotherapy (e.g. low dose cytarabine (LDAC)), hypomethylating agents (HMA), and intensive chemotherapy (IC) (**Table 1**).

Population data from the Swedish Acute Leukaemia Registry suggest the majority of older patients should be considered candidate for antileukemic therapy [13]. However, only few prospective randomised studies in older AML patients are available to guide treatment decisions. A pivotal clinical trial, although with a limited number of patients (n = 60), showed that standard IC decreases early death rates and improves long-term survival compared with BSC [14]. Also LDAC and gemtuzumab ozogamicin (GO) have been reported to result in superior survival compared with BSC; although neither had an effect in patients with adverse cytogenetics [15, 16].

In addition to IC and LDAC, the armamentarium for the treatment of AML has been expanded in recent years with two cytosine analogues with DNA hypomethylating properties: azacitidine and decitabine. The hypomethylating agents (HMAs) azacitidine and decitabine have relatively mild side effects and are particularly feasible for the treatment of AML in older patients and patients with comorbidities.

	Response: CR/CRi (%)	Median OS (months)	2-year OS (%)	5-year OS (%)
Intensive chemotherapy [9, 14, 30]	41–70	10–20	12–42	10–30
+ Gemtuzumab ozogamicin [31, 32, 35, 36]	36–78	7–34	53	36
Low dose chemotherapy [15]	18	4	—	—
Hypomethylating agents [17, 18, 40, 41, 44]	15–47	8–13 (25)	20–50	Not curative, unless consolidated with HCT
New agents	—	—	—	—
A. Venetoclax	—	—	—	
+ HMA [19]	66	14.7	—	
+ LDAC [60]	48	8.4	—	
B. IDH inhibitors [61, 62]	30–40	11–13	—	
C. FLT3-inhibitors + IC [33]	— 78	—	45.6	
D. Glasdegib				
+ IC [65]	40	14.7		
+ LDAC [66]	17	8.8		
D. CPX-513 (68,67)	53–67	15		

Table 1.
Treatment options and outcomes for older AML patients.

Importantly, both azacitidine and decitabine have proven efficacy in patients with adverse cytogenetic abnormalities. Although not in their primary analyses, recent phase III trials have shown the superiority of azacitidine and decitabine treatment compared with conventional care for older AML patients [17, 18].

New combinations of HMAs with targeted drugs are being explored. Recently, the results of a phase 3 study of azacitidine in combination with venetoclax versus azacitidine alone in treatment-naïve adults with AML, who were ineligible for standard induction therapy, have been reported (VIALE-A trial; NCT02993523). This study confirmed the additive value of venetoclax to azacitidine treatment by an increase in remission rate from 28–66% and an increase in median OS from 9.6 months to 14.7 months [19]. The high remission rate which was achieved by adding venetoclax to azacitidine treatment is striking. Studies are ongoing to explore the added value of IDH1 or IDH2 inhibitors (ivosidenib or enasidenib) in combination with azacitidine and azacitidine plus venetoclax, for those older AML patients with mutated *IDH1* or *IDH2*.

2.1 Treatment selection: who is fit and who is not fit?

Optimal treatment selection for older patients also requires consideration of treatment tolerance and life expectancy, derived from the evaluation of comorbidities, physical function and cognition [2]. Charlson comorbidity index >1 and haematopoietic cell transplantation comorbidity index (HCT-CI) >2 have been reported to be associated with lower remission rates, increased early mortality and decreased survival in patients treated with IC [20–22]. In a study on 177 patients aged ≥65 years who received IC the early death rates were 3% if the HCT-CI score was 0, 11% if the HCT-CI score was 1 to 2, and 29% if the HCT-CI score was ≥3 [20].

In addition, performance status, scored according to ECOG or WHO guidelines, has shown to be associated with survival in several studies [10, 23, 24].

To adequately assess fitness in older patients, beyond performance status and comorbidities, geriatric assessment (GA) is attracting more attention. GA is an approach to the evaluation of multiple patient characteristics (i.e. physical function, comorbid disease(s), cognitive function, psychological state, social support, polypharmacy, nutritional status) to help characterise individual patient complexity and discriminate among fit, vulnerable and frail patients. GA in older AML patients has been associated with treatment outcomes. In a single-institution prospective study conducted with AML patients ≥60 years of age treated with IC, geriatric assessment performed at diagnosis was associated with survival. In this study (n = 74, median age 68 years), impaired physical performance (measured as short physical performance battery (SPPB) score < 9) and impaired cognition (measured as modified mini-mental state (3MS) exam score < 77) were independently associated with OS, after accounting for other disease and patient characteristics [25]. In a study of 107 non-intensively treated AML patients, the scores for independence in activities of daily living and the Karnofsky score for performance status were associated with survival in multivariate analysis [21]. Although randomised data of comprehensive assessment of older AML patients are lacking, the above mentioned studies support the use of pre-treatment performance and comorbidity assessment in the setting of AML therapy.

2.2 Treatment selection: predicting outcome with algorithms.

Various studies have been undertaken with the aim to create prediction models for treatment effectiveness and to provide support for an educated treatment choice in the setting of AML. These algorithms include patient-specific factors (e.g. performance, comorbidity, body temperature, age) and disease-specific factors (e.g. cytogenetics, white blood cell counts, blast counts, primary or secondary leukaemia, haemoglobin level, platelet count, fibrinogen level, serum concentration of lactate dehydrogenase (LDH)) [23, 24, 26, 27]. However, most prediction models have not been successfully validated in independent cohorts of older patients. In addition, the data used to create most of these algorithms come from a patient population selected to receive intensive chemotherapy and therefore likely do not reflect the real world of older patients with AML. Although prediction models might be useful in identifying patients who are 'fit' for intensive chemotherapy, this does not automatically imply for AML patients with specific disease characteristics (or combinations) associated with poor outcome. This includes the high-risk AML subtypes with mutant *TP53*, complex cytogenetic abnormalities (in particular monosomal karyotype), mutations in *ASXL1* or *RUNX1* and high allelic burden *FLT3*-ITDs. An inclusive and validated prediction model for older AML patients has yet to be published.

3. Treatment of patients considered to be fit

The combination of anthracycline and cytarabine ('3 + 7') has been the standard of care for patients with AML for the last four decades [28]. However, the use of this regimen in older patients with AML does not yield similar results to those reported for younger patients, even in carefully selected patients. Although 50–60% of patients will attain a complete remission (CR), this does not translate into a similar survival benefit as for younger patients, with a 2-year survival of only 15–20% [3, 29]. To improve the outcome for older AML patients receiving intensive chemotherapy (IC)

many studies have evaluated modifications of the traditional '3 + 7' combination. Strategies have included dose attenuation [9, 30], addition of gemtuzumab ozogamicin (GO) [31, 32], addition of midostaurin [33], addition of lenalidomide [34], and other attempts (e.g. growth factors, modulation of multidrug resistance).

The HOVON43 study assessed the effect of an escalated daunorubicin dose (90 mg/m^2 vs. 45 mg/m^2) in older AML patients (> 60 years) receiving conventional '3 + 7' chemotherapy [9]. Median age was 67 years and 24% of patients had an unfavourable or very unfavourable cytogenetic risk. Although the CR rate was higher in the escalated-treatment group (64% vs. 54% [P = 0.002]), this did not translate into a survival benefit (2-year OS 31% vs. 26% [P = 0.16]). However, an unplanned post-hoc analysis showed that patients in the escalated-treatment group who were 60 to 65 years of age had higher CR rates and increased survival compared to patients aged 60 to 65 years in the conventional dose group (CR rates 73% vs. 51% and 2-year OS 38% vs. 23%, respectively). These data suggest the survival benefit of an escalated dose of daunorubicin was limited to the younger part of older patients. The MRC-AML-14 study randomised patients four times to a higher (50 mg/m2) or lower (35 mg/m^2) dose of daunorubin, a higher (400 mg/m^2) or lower (200 mg/m^2) dose of cytarabine, allocation to receive the multidrug resistance modulator PSC-833 or not, and to receive three or four courses of treatment [30]. The CR rate was 54% and 5-year OS 12% for all patients, and no benefits were observed in either dose escalation groups, or from a fourth course of treatment.

Several studies investigated the addition of GO to standard chemotherapy to improve outcome in older AML patients. The MRC-AML-16-I study (addition of 3 mg/m^2 GO on day 1 of course 1) found 3-year relapse incidence and survival was significantly better in the GO arm (relapse 68% vs. 76%; survival 25% vs. 20%), although there was no difference in CR rate between both arms [31]. There was no difference in 30- or 60-day mortality and no major increase in toxicity with GO. The French ALFA-0701 trial investigated addition of fractionated doses of GO (3 mg/m^2 on day 1, 4, and 7) to standard chemotherapy and found similar results in patients aged 50–70 years. The CR rate did not differ between both arms (81% in GO-arm vs. 75% in no GO-arm), but survival was increased in the GO-arm (median 34 vs. 19 months; 2-year OS 53.2% vs. 41.9%) [35]. However, in the EORTC-GIMEMA-AML17 trial, randomising patients to a course of GO (6 mg/m^2 on day 1 and 15) followed by IC or IC alone, a trend for inferior survival in the GO-arm was observed (median OS 7.1 vs. 10 months) [32]. Patients aged ≥70 years did significantly worse with GO due to the combined effect of increased induction mortality and poorer OS among those not achieving CR. This study incorporated a higher dose of GO (6 mg/m^2 vs. 3 mg/m^2). GO, especially in higher doses, has been associated with increased toxicity and after initial FDA approval in 2000 was voluntarily withdrawn in 2010 after safety concerns. Since then fractionated doses have been proved safe and efficacious in a large meta-analysis of five randomised controlled trials, leading to re-approval in 2017 [36].

There is ongoing discussion whether older AML patients benefit from treatment with intensive chemotherapy. Retrospective analysis of the outcomes 446 older AML patients (≥70 years) treated with intensive chemotherapy between 1990 and 2008 showed that despite a reasonable CR rate of 45%, the median OS was only 4.6 months and 1-year survival 28% [37]. The surprisingly low median OS was due to high 4-week and 8-week mortality rates of 26% and 36%, and the authors concluded that intensive chemotherapy may not be beneficial to most older patients with AML, although some subgroups (e.g. CBF AML and good risk status) might benefit. In response to this, a Swedish group published updated outcomes of 998 unselected older AML patients, of who 55% received intensive chemotherapy

between 1997 and 2006 and concluded that older patients do benefit from intensive treatment with a median OS in *de novo* AML of over 1 year [13]. This highlights that choosing the optimal treatment for older patients with AML remains challenging.

4. Treatment of patients considered unfit for intensive chemotherapy: hypomethylating agents

For patients not eligible for intensive chemotherapy treatment a choice can be made between best supportive care (BSC), low dose chemotherapy (LDAC) or hypomethylating agents (HMAs). Several studies have shown the efficacy of the HMAs azacitidine and decitabine. In addition, HMAs are well-tolerated and have low extra-medullary toxicity. Therefore HMAs are very suitable for the treatment of older patients with AML.

Azacitidine was first studied in the context of high-risk myelodysplastic syndromes (MDS). A phase III trial conducted in intermediate-2 and high-risk MDS patients included a subset of patients with 20–30% blasts, who were reclassified to AML according to redefined WHO criteria [38, 39]. The relative efficacy and safety of azacitidine versus conventional care regimens (CCR; comprising prespecified allocation to BSC, LDAC, or IC) was thus compared in this subgroup of patients (n = 113) and showed an increased median OS (24.5 vs. 16.0 months, P = 0.005) and increased 2-year survival (50% vs. 16%, P = 0.001) for azacitidine-treated patients compared with CCR patients [40]. In addition, a phase III study on the efficacy of azacitidine versus CCR (standard IC, LDAC or BSC) in newly diagnosed AML patients with >30% blasts was conducted [17]. The median OS was longer in the azacitidine group compared to the CCR group (10.4 vs. 6.5 months), although in multivariate analysis significance was lost (HR 0.85 [95% CI 0.69–1.03], P = 0.101). However, in a pre-planned sensitivity analysis censoring for subsequent AML therapy, the median OS was 12.1 months versus 6.9 months in the azacitidine-arm and CCR-arm respectively, with a stratified HR 0.76 (95% CI 0.60–0.96, P = 0.019). Azacitidine was well tolerated as more than half of the patients received six or more treatment cycles. The difference in median OS between the two reported studies (24.5 months vs. 12.1 months) could be explained by the lower blast count in the first study and thereby selection of more indolent disease. Unfortunately both studies were not powered to detect direct differences between azacitidine treatment and intensive chemotherapy.

Decitabine is another hypomethylating agent registered for treatment of AML. Two decitabine schedules are currently in use in clinical practice: the 5-day schedule and the 10-day schedule. A randomised phase III trial compared the efficacy and safety of 5-day decitabine (20 mg/m^2) (n = 242) with treatment choice of BSC (n = 28) or LDAC (n = 215) in older patients(≥ 65 years) with newly diagnosed AML and poor- or intermediate-risk cytogenetics [18]. The CR rate in the decitabine group was 15.7%. Although the planned primary analysis after 396 deaths did not show a significant improvement of OS with decitabine versus treatment choice (median OS 7.7 months vs. 5.0 months), an unplanned analysis after 446 deaths showed a significant benefit for decitabine (HR 0.82 [95% CI 0.68–0.99], P = 0.037). A small but pivotal phase II trial in 53 patients evaluated the effect of a longer 10-day decitabine schedule and found an increased CR rate of 47% and overall response of 64% with a median OS of 13 months [41]. The beneficial effects of the 10-day decitabine schedule were confirmed in two large single-centre retrospective studies that found response rates and median OS of 40% and 11 months, and 35% and 11 months, respectively [42, 43]. Recently, the result

of a phase II trial directly comparing 5-day versus 10-day decitabine treatment was reported. The researchers concluded both schedules have similar efficacy (CR rates 29% vs. 30% [P = 0.88], median OS 5.5 vs. 6.0 months [P = 0.47]), although there was an uncorrected imbalance in disease characteristics favouring the 5-day schedule and the randomisation allocation was skewed towards the 10-day schedule [44]. Therefore caution has to be taken when interpreting the results. However, these data show that decitabine, both in 5-day and 10-day schedules, is efficient and suggest that decitabine as a single agent might provide a framework upon which to build future combination studies to improve outcomes for older AML patients.

Guadecitabine is a next generation HMA given subcutaneously which provides prolonged in vivo exposure to its active metabolite decitabine, thus offering potential clinical advantages over current HMAs. In a large randomised trial 815 untreated AML patients not eligible for IC were randomised to either guadecitabine (5 days 60 mg/m^2 every 4 weeks) or a preselected treatment of azacitidine, decitabine, or LDAC (ASTRAL-1 trial, NCT02920008). Although this trial showed that guadecitabine is an effective drug, the trial did not achieve its primary endpoints of statistically significant superiority of guadecitabine vs. preselected treatment for CR or OS [45].

ASTX727 is a next generation HMA with a unique fixed-dose combination of the hypomethylating agent decitabine and the novel cytidine deaminase inhibitor, E7727 (cedazuridine). ASTX727 was designed to deliver decitabine by oral administration. By inhibiting cytidine deaminase, cedazuridine inhibits the major mechanism by which decitabine is degraded in the gastrointestinal tract and liver, and the combination therefore permits the efficient delivery of decitabine orally. It has shown promising effects in a phase II trial conducted in intermediate- and high-risk myelodysplastic syndromes and chronic myelomonocytic leukaemia patients [46]. This trial is now expanding to include AML patients (NCT04093570).

An important question is whether intensive chemotherapy is superior to hypomethylating agents in older AML patients. The results of the above reported clinical trials cannot be directly compared due to differences in patient population studied. The MD Anderson Cancer Center reported the results of a retrospective cohort study of 671 patients, including 114 patients treated with HMAs (either azacitidine or decitabine) and 557 patients treated with IC [47]. Both groups were balanced according to cytogenetics and performance status and were older than 65 years. Patients who had received IC had a higher CR rate compared to patients who had received HMAs (42% vs. 28% [P = 0.001], respectively). However, the median OS was comparable in the 2 groups (6.7 vs. 6.5 months, P = 0.41). Multivariate analysis confirmed that type of AML therapy (IC or HMAs) was not an independent prognostic factor for survival. Interestingly, this study revealed that decitabine was associated with improved median OS compared with azacitidine (8.8 vs. 5.5 months, respectively, P = .03), also in multivariate analysis. No published prospective randomised trials have compared the efficacy of azacitidine with decitabine nor the efficacy of intensive chemotherapy ('3 + 7') with hypomethylating agents. The results of the EORTC-1301 phase III trial, comparing upfront treatment with intensive chemotherapy or decitabine, are eagerly awaited (NCT02172872).

5. Treatment of patients considered not to be fit: LDAC

Low-dose cytarabine (LDAC) (20 mg twice daily for 10 days) has been used in the treatment of AML for several years. Treatment with LDAC has low toxicity and a higher CR rate than best supportive care (18% vs. 1%) [15]. Although the OS for the LDAC-treated group has been demonstrated to be statistically

significantly better, it is worth noting that in absolute terms, the therapeutic advantage is marginal, with a prolongation of OS of only a few months. Additionally, the benefit is restricted to the small fraction of patients who achieve a response (median survival 19 months vs. 2 months in responders vs. non-responders respectively) [15]. Patients with adverse cytogenetics do not seem to benefit from LDAC. Combinations of LDAC with other agents have been tested in clinical trials and although some additions resulted in higher CR rates survival was not improved [48–53]. Thus, the OS in patients receiving LDAC is still highly unsatisfactory (median 5 months) [3]. Recently, the results of the VIALE-C trial have been reported, demonstrating an increased efficacy by adding venetoclax to LDAC (see 7.1).

6. New developments

Since 2017 the FDA has approved 8 new drugs for the treatment of AML [54]. New developments to treat AML, especially in older patients, include 1) drugs targeting specific signalling pathways (like the hedgehog pathway or apoptosis); 2) drugs specifically targeting mutations in AML (e.g. targeting the epigenetic modifiers IDH1/IDH2 and mutated cytokine receptor FLT3) and 3) an alternative formulation of classic chemotherapeutic drugs (CPX-315).

6.1 Venetoclax

Venetoclax (ABT-199/GDC-0199), an orally available inhibitor of the anti-apoptotic molecule Bcl-2, has shown great efficacy in chronic lymphocytic leukaemia [55–57]. After observing single-agent activity in AML cell lines [58], venetoclax has been tested as monotherapy in relapsed and refractory AML patients showing activity with a CR/CRi rate of 19% [59]. Promising results have been reported for combinatorial studies with venetoclax in AML. In the randomised phase 3 trial VIALE-C (LDAC +/− venetoclax) 211 patients were randomised 2:1 to venetoclax (n = 143) or placebo (n = 68) in 28-day cycles, plus LDAC on days 1 to 10 [60]. The primary analysis showed a 25% reduction in risk of death with venetoclax plus LDAC vs. LDAC alone, although not statistically significant (hazard ratio [HR], 0.75; P = .11), and a median OS of 7.2 vs. 4.1 months, respectively. An unplanned analysis with additional 6-month follow-up did demonstrate a significant benefit with a median OS of 8.4 months for venetoclax added to LDAC (HR, 0.70; P = .04).

In addition, the results of a phase 3 study of venetoclax in combination with azacitidine versus azacitidine alone in treatment-naïve older AML patients, who were ineligible for standard induction therapy, have recently been reported (VIALE-A trial; NCT02993523). This study confirms the additive value of venetoclax to azacitidine by a significant increase in CR/CRi rate from 28–66% and an increase in median OS from 9.6 months to 14.7 months [19]. The high remission rate which can be achieved by adding venetoclax to azacitidine treatment is striking. The impressive results of this study will likely make the combination of an hypomethylating agent with venetoclax the new standard for the treatment of older unfit AML patients.

6.2 IDH inhibitors

IDH mutations are present in approximately 20% of AML patients and are more frequent in older patients. Mutations in *IDH* lead to the production of the oncometabolite 2-hydroxyglutarate and result in DNA hypermethylation and arrest

of myeloid differentiation [54]. Inhibition of these mutant metabolic enzymes by ivosidenib (IDH1) and enasidenib (IDH2) induces myeloid differentiation of leukaemic blasts. In a subgroup analysis of 34 newly diagnosed AML patients unfit for standard chemotherapy harbouring IDH1 mutations, monotherapy with ivosidenib resulted in a remission rate of 42.4% and median OS of 12.6 months [61]. In a phase I/II trial of older untreated AML patients, enasidenib induced a response in 30.8% of patients of whom 18% had a complete remission and a median OS of 11.3 months [62]. In addition to the proven efficacy and tolerability, ivosidenib and enasidenib are orally available, making them attractive for treatment of older AML patients. Both inhibitors are under investigation in combination with other AML treatments, including intensive chemotherapy ("3 + 7") and hypomethylating agents.

6.3 FLT3 inhibitors: midostaurin and gilteritinib

The *FLT3* mutations (mainly *FLT3* internal tandem duplications (*FLT3*-ITD), but also tyrosine kinase mutations (*FLT3*-TKD)) occur in about 20–30% of adult AML patients, although its prevalence decreases in older patients. The RATIFY study proved the favourable impact of adding midostaurin to intensive chemotherapy for AML patients with mutated *FLT3* under 60 years of age [63]. In older patients with *FLT3*-ITD the CR rate and 2-year OS was 77.9% and 45.6% respectively with the addition of midostaurin to conventional chemotherapy [33]. In comparison to historical controls, addition of midostaurin resulted in significant risk reduction for an event (refractory disease, relapse, death) with an HR of 0.42. Based on the results of this study the treatment label of midostaurin was expanded to include older patients with mutated *FLT3*. New FLT3 inhibitors, like gilteritinib, have shown to be potent inhibitors of mutated *FLT3* in relapsed/refractory AML patients, though limited data is available on the safety and efficacy of gilteritinib when combined with intensive chemotherapy or hypomethylating agents.

6.4 Glasdegib

Glasdegib is small molecule inhibitor of the hedgehog receptor smoothened. The hedgehog pathway is important during embryogenesis but repressed after birth. However, aberrant hedgehog signalling has been identified in AML, particularly in leukaemic stem cells, and has been associated with chemoresistance [64]. Inhibition of hedgehog signalling with glasdegib has shown promising results. A phase II study evaluating the combination of glasdegib and intensive chemotherapy in patients over 55 years of age with newly diagnosed AML reported a CR rate of 40% and median OS of 14.7 months [65]. Glasdegib was also evaluated in combination with LDAC in older patients unfit for intensive chemotherapy. Patients receiving glasdegib + LDAC had increased CR rates, 17.0% vs. 2.3%, and improved median OS 8.8 vs. 4.9 months, compared to patients receiving LDAC alone [66]. Based on these results, the FDA has approved glasdegib in combination with LDAC for AML patients ≥75 years or patients ineligible for intensive chemotherapy. In addition, glasdegib is being evaluated in combination with hypomethylating agents and a phase III trial of glasdegib in combination with intensive chemotherapy is ongoing (BRIGHT AML1019, NCT03416179).

6.5 CPX-315

CPX-315 is a liposomal formulation that delivers a 5:1 fixed-molar ratio of cytarabine and daunorubicine. With the liposomal encapsulation both drugs can be delivered in a fixed ratio with the highest proportion of synergy to enhance

treatment efficacy [67]. CPX-351 preferentially targets leukaemic cells to a greater degree than non-leukaemic cells in the bone marrow, leading to decreased cytotoxicity against normal haematopoietic cells [68]. A small study of CPX-351 as first-line therapy in 30 newly-diagnosed AML patients ≥65 years showed a promising remission rate of 53.2% with a median OS 14.5 months [68]. In a randomised phase II trial in older adults with untreated AML comparing CPX-351 and conventional '3 + 7' treatment a trend towards increased response rates was observed in the CPX-351 group, 66.7% vs. 51.2%. Survival was comparable between both treatment groups (14.7 vs. 12.9 for the CPX-351 and '3 + 7' group respectively). However, CPX-351 treatment was superior in the subset of secondary AML patients with a median OS of 12.1 months vs. 6.1 months in the '3 + 7' group [67]. Superiority of CPX-351 to conventional '3 + 7' chemotherapy in secondary AML, also including AML with MDS related changes, was confirmed in a phase III trial including 309 older AML patients. The observed remission rates were 47.7% vs. 33.3% and median OS was 9.6 vs. 6.0 months in favour of CPX-351 [69]. The safety profile of CPX-351 was similar to that of conventional chemotherapy.

7. Allogeneic haematopoietic cell transplantation in older patients

Allogeneic haematopoietic cell transplantation (HCT), as post-remission treatment, offers the highest potential for long-term survival and cure for patients with AML. For younger patients, the choice for consolidation with an allogeneic transplant is nuanced, as particular younger patients with high-risk disease, entailing high-risk mutations and presence of measurable residual disease after treatment, benefit post-remission treatment with an allogeneic HCT. As older patients generally have low chance for long-term survival, also if they have "good-risk" cytogenetic abnormalities, allogeneic HCT should be considered in older (fit) AML patients [10, 70, 71]. Nevertheless, only a minority of older patients actually receives an allogeneic HCT [72, 73]. Allogeneic HCT in older patients is limited by concerns related to treatment-related mortality (TRM) (e.g. TRM is >40% in patients with a HCT-comorbidity score ≥ 3) [74]. However, the development of less toxic conditioning regimens (reduced intensity conditioning (RIC) and non-myeloablative (NMA)), has been an important conceptual change that has created the opportunity for older patients with AML to receive an allogeneic HCT. These conditioning regimen are less dependent on cytotoxic effects of the conditioning regimen and more dependent on the graft-versus-leukaemia effect.

Several studies evaluating allogeneic HCT after RIC in older AML patients have shown promising results. A phase II study of 114 older patients receiving an allogeneic HCT after RIC with fludarabine and busalfan reported a 2-year OS of 48% with a non-relapse mortality (NRM) of 15%. However, cumulative incidence of relapse was 44% at 2 years [75]. A large retrospective study analysing the outcomes of 1080 AML patients who underwent allogeneic HCT after RIC found a 2-year OS of 36% in patients age ≥ 65 years, a NRM of 34%, and 2-year relapse probability of 33% [76]. This analysis included several age groups ranging from 40 to above 65 years and found no significant impact of age on NRM, relapse, disease-free survival, or OS. In addition, studies comparing allogeneic HCT after RIC to conventional post-remission treatments have reported favourable outcomes with allogeneic HCT after RIC. A study comparing allogeneic HCT after RIC (n = 97), chemotherapy (n = 44), autologous transplantation (n = 23), and no further treatment (n = 336) as post-remission therapy reported a 5-year OS of 35% for patients receiving allogeneic HCT after RIC compared to 26% and 21% for chemotherapy/autologous transplantation and no treatment, respectively [77]. Multivariate analysis

confirmed the beneficial effect allogeneic HCT after RIC on 5-year survival. A comparison between allogeneic HCT after RIC and chemotherapy in patients age 60–70 years showed that allogeneic HCT after RIC was associated with a lower risk of relapse at 3 years (32 vs. 81%) although NRM was increased (36% vs. 4%), leading to an OS of 37% vs. 25% at 3 years [78]. These studies underscore the delicate balance between sufficient antileukemic effect and treatment toxicity, which is challenging in post-remission treatment of older AML patients.

The efficacy and safety of NMA conditioning consisting of low-dose total body irradiation alone or combine with fludarabine (90 mg/m^2) in older patients was evaluated in a prospective cohort of 372 patients aged 60 to 75 years. The OS at 5 years post-transplantation was 35% with an NRM of 27%. Relapse rate was 41% at 5 years indicating the need for further improvement [73]. Nevertheless, these data compare very favourably with historical data on long-term survival of about 10% after treatment of older AML patients with intensive chemotherapy without post-remission treatment with allogeneic HCT.

8. Refractory/relapsed AML

Treatment of relapsed or refractory (R/R) AML, in general, has presented challenges for haematologists for decades. Despite numerous clinical studies, outcomes are consistently disappointing with 5-year OS rates of ~10%. Allogeneic HCT at the time of second complete remission remains the only reliable option with curative potential. For older patients, treatment of R/R AML is even more difficult and outcomes poorer. However, the availability of new drugs, like venetoclax, gilteritinib, ivosidenib and enasidenib offer reasonable chances of temporally disease control with acceptable side effects. This implies the importance of detailed molecular analysis, also in the R/R setting, as the R/R disease might contain different (targetable) mutations. Phase 1 studies are generally an option for those patients with a strong wish to receive treatment. Finally, only best supportive care with antibiotics and transfusions can be a preferable option.

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