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ACUTE MYELOID LEUKEMIA IN THE ELDERLY: DO WE KNOW WHO SHOULD BE TREATED AND HOW?

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Abstract

Acute myeloid leukemia (AML) in the elderly is associated with several distinctive biological and clinical features compared to younger patients. Despite the advances in supportive care and the introduction of less intensive chemotherapy regimens, the overall outcome for this population remains poor. More importantly, the decision making process for choosing the appropriate treatment for individual patient, based on their comorbidities and the biological features of their disease, continues to be challenging for the treating physicians. Currently, a significant number of elderly patients with AML do not receive treatment above and beyond supportive care; several studies have suggested that patients who receive any therapy have a better outcome than patients who receive palliation alone. Furthermore, the development of novel, targeted, and less intensive therapies is providing new options suitable for older patients with multiple comorbidities and with high risk disease features. In this review, we will highlight the challenges that face the treating physicians when encountering elderly patients with AML and will describe some of the potential strategies under development for treating older AML patients and the available data from recent clinical trials.

INTRODUCTION

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults in the US, with approximately 12,000 new cases per year [1]. Although AML can present at any age, it is mainly a disease of elderly with median age at diagnosis of 65-70 [1,2]. An increased incidence of AML in the older population has been observed in United States and worldwide; this is likely due to an increase in the overall life-expectancy of general population along with an overall increase in exposure to environmental toxins, as well as increased and more successful use of chemotherapy and radiation in patients with other cancers. In a recent analysis from the Swedish Acute Leukemia Registry, more than 3300 patients diagnosed with AML between 1997 and 2006 were analyzed [3]. Among them, 66% were aged 65 years or more and 24% were 80 year old and older [3].

Despite the recent advances in the management of patients with hematologic malignancies, the development of novel targeted therapies, and improvement of supportive care measures, the overall outcome for elderly patients with AML remains poor with a 5-years overall

survival (OS) of less than 5% in patients 70 years and older and less than 1% in patients older than 80 years [3]. Poor outcome in this population has been related to several factors including: concomitant comorbidities, lower responses to chemotherapy, and the differences in the biology of the disease that is related to the presence of high risk features such as complex karyotype and secondary AML [3,4].

In this review, we will discuss the prognostic markers that predict the outcome in elderly patients with AML and explore the existing challenges in choosing the optimal treatment strategy for these patients, which include a significant proportion deemed to be unfit for intensive chemotherapy.

OUTCOME PREDICTION IN ELDERLY AML

Age has always been identified as a strong independent prognostic marker for overall survival (OS) in patients with AML; with a worse outcome as the age advances [4,5]. In a retrospective analysis from the German AML co-operative group, the 4-year OS for patients 60 years old was significantly lower than patients younger than 60 years (16% vs. 37% ($p<0.001$)) [5]. Although age is considered to be a continuous variable and identifying a cutoff to classify patients as young or old is completely arbitrary, age 60 years has been commonly used as the criterion for defining elderly patients in the majority of AML trials. In a retrospective analysis of 968 patients with AML included in 5 Southwest Oncology Group (SWOG) clinical trials [4], Appelbaum et al, have shown that increasing age was associated with less favorable cytogenetics, poorer performance status at presentation, lower white blood cell counts, and lower percentage of marrow blasts [4]. In addition, increasing age was also associated with a lower response rate (only 33% responded to induction chemotherapy among patients older than 75), a higher rate of early death during induction therapy, and shorter survival (median OS was 3.5 months among patients older than 75) [4]. More importantly, poorer performance status at diagnosis was associated with higher induction mortality rates particular in elderly patients suggesting that the presence of other comorbidities has a significant impact on the overall outcome of these patients [4].

There are several other factors that play a major role in the outcome of patients with AML in general and more specifically in elderly patients. These include medical comorbidities and end organs dysfunction, uncontrolled infections, and inherent resistance of leukemia cells to chemotherapy. Cytogenetic analysis at diagnosis remains one of the most important prognostic indicators in AML [6-8]. Several studies have shown the importance of pre-treatment karyotype in elderly patients with AML [9-12]. In a large analysis of 2483 newly diagnosed patients with AML 60 years old, who were treated on the MRC AML11 and AML14 trials, cytogenetic risk group, age, white blood count, performance status and type of AML (de novo versus secondary) were all related to the outcome in multivariate analysis [10]. Although the OS in all cytogenetic groups was poor, patients with favorable and intermediate risk groups survived longer than patients with adverse group (defined as per MRC criteria [13]) [10]. In another analysis from the German-Austrian AML study group high risk cytogenetics and age above 70 years were also identified as independent predictors for a worse OS [11]. A very important question remains as to whether cytogenetic analysis should be taken into consideration for choosing therapy in older patients with AML

especially when the result of this analysis may take up to a week and whether delaying the treatment until the result is available may change the overall outcome. Several studies have shown that the time from diagnosis to therapy may not in general affect the outcome [14,15]. Sekeres et al have demonstrated that in patients older than 60 years with white blood cell (WBC) lower than $50 \times 10^9/L$ and after taking into consideration all the parameters available at diagnosis, the period from diagnosis to starting therapy did not impact the response rate or OS. This suggests that delaying the treatment until more information is available regarding all the prognostic markers is feasible and should be exercised routinely to better identify the best treatment options for this patients population [14]. Clearly, this strategy is highly dependent on the availability of treatment modalities that target specific characteristics of the disease in patients who are unlikely to benefit from standard induction regimens [15].

More recently, molecular studies that evaluate multiple molecular aberrations have been used to define subgroup of patients with AML who may have a better or worse outcome [16]. Several studies have evaluated the role of these molecular abnormalities and their influence on the outcome of elderly patients with AML [17,18]. More importantly, some of these mutations have been identified as therapeutic targets and several drugs targeting them are in clinical development. For example, Internal Tandem Duplication mutations of the juxtamembrane domain of the FMS-like Tyrosine Kinase 3 (*FLT3-ITD*) gene have been associated with an inferior relapse-free and overall survival [19,20]. Several agents that target the FLT3 kinase are currently under development with promising efficacy as single agent or in combination with cytotoxic chemotherapy agents [21]. A higher incidence of resistant leukemic blasts, mediated by expression of multidrug resistance gene *MDR1* and its protein pump product (and other efflux pumps that actively extrude chemotherapeutic agents from leukemic cells), has been shown in older patients and is associated with inferior outcome and higher likelihood of relapse [22].

TREATMENT OF ELDERLY PATIENTS WITH AML

What is the best choice?

Treatment of elderly patients with AML is challenging and the choice of the best treatment strategy for most patients remains debatable. These challenges are related to several factors including: 1) historically, most of the trials conducted in AML had focused mainly on younger patients making it difficult to apply their results to the elderly population, 2) there is some reluctance by physicians and patients alike to use intensive chemotherapy regimens in elderly patients. This is because of the fact that chemotherapeutic regimens used for AML are more intensive than those used for other tumors [23], and 3) up to recently, the majority of trials conducted in elderly AML have excluded patients with poor performance status and co-morbid medical conditions, making it difficult to apply the results of these trials to routine clinical practice.

In a retrospective analysis, Menzin et al evaluated 2657 elderly patients with AML who were identified in the Medicare database between January 1991 and December 1996 and matched them to the SEER database [24]. Only 30% of the patients received treatment with chemotherapy, ranging from 49% of patients between 65-75 years old to only 7% in patients

older than 85 [24]. The median OS was 2.5 months and was 6 months longer for patients who received treatment. The study demonstrated clearly that the outcome of these patients is generally poor and that a very low percentage of the elderly patients received treatment in the community practice.

Another aspect of the treatment decision in elderly patients with AML is the subjectivity of treating physicians and the factors that determine their decision relating to whether the patient is “unfit for intensive chemotherapy” as well as the patient’s expectations for treatment. In a retrospective analysis of 1672 elderly patients with AML from 6 separate health regions included in the Swedish Leukemia Registry database [25], the percentage of patients who were judged to be fit to receive intensive chemotherapy varied significantly between the different geographic regions. Interestingly, the OS was better in regions where patients were more likely to receive treatment with standard chemotherapy compared to palliation only [25]. Furthermore, early mortality was lower in patients who received intensive therapy compared to palliation alone, even among those with poor performance status [25]. Similar conclusions have also been reported by several other studies that have compared intensive or non-intensive chemotherapy to palliative care [26,27].

In an attempt to better identify older patients with AML who may benefit the most from intensive chemotherapeutic regimens, several risk scoring systems have been established [9,10,15]. In a retrospective analysis of 998 patients with AML or high-risk MDS ≥ 65 years who received intensive chemotherapy at the University of Texas - MD Anderson Cancer Center, Kantarjian et al identified several prognostic factors for predicting a worse outcome including: age ≥ 75 years, performance status > 2, unfavorable cytogenetics, ≥ 12-months history of antecedent hematologic disorders, lactate dehydrogenase (LDH) > 600, elevated serum creatinine, and treatment outside a laminar flow room, (Table 1) [9]. Based on the number of these factors, patients were divided into three groups: favorable (1-year OS > 50%, CR rate > 60% and induction mortality of 10%), intermediate (1-year OS of 30%, CR rate > 50%, and induction mortality of 30%) and unfavorable (1-year OS <10%, CR rate < 20%, and induction mortality of > 50%) [9]. In another retrospective analysis of AML patients ≥ 60 years old who participated in MRC AML 11 and AML14 trials, Wheatley et al identified 5 risk factors for poor outcome: advanced age, adverse cytogenetic group, higher white blood cell count, poorer performance status, and type of AML[10]. Based on these factors a prognostic model was developed which divided patients into three groups: good, standard, and poor risk groups, with 1-year OS of 53%, 43%, and 16%, respectively [10] (Table 2).

The hematopoietic cell transplantation comorbidity index (HCTCI) has also been used to predict early death and OS in elderly AML patients. Giles et al, analyzed the outcome of 177 patients over 60 years old with newly diagnosed AML. In patients with HCTCI score of 0,1-2, ≥ 3, early death rates were 3%, 11%, and 29%, respectively and median OS of 45, 31, and 19 weeks, respectively [28]. These scoring systems represent an important tool to identify patients who are fit to receive intensive chemotherapy as opposed to those who are unsuitable for this approach.

Standard AML therapy in Elderly

The combination of cytarabine and anthracycline (3+7) has been the standard of care for patients with AML for the last 4 decades [29]; however, the application of this regimen in the elderly population does not yield a similar result to that reported for younger patients [30,31]. As a result, many studies have evaluated modifications of this combination in order to improve the outcome. However, most of these studies did not include patients with poor performance status or poor organ function.

Lowenberg et al evaluated the use of a higher dose of daunorubicin at induction (90 mg/m²) compared to traditional dose (45 mg/m²) in newly diagnosed patients with AML, > 60 years old [31]. Although CR rate was better in patients who received the higher dose of daunorubicin (64% vs 54%, $P = 0.002$), OS and EFS were similar in the two induction groups. However, a subgroup analysis of patients aged 60-65 years showed higher CR rate (73% vs. 51%), 2-year EFS (29% vs. 14%, $P = 0.002$), and OS (38% vs. 23%, $P < 0.001$) in those who received the high dose daunorubicin compared to the traditional dose [31]. In another study by the French Cooperative Group ALFA (Acute Leukemia French Association), Pautas et al compared the high dose of daunorubicin (80 mg/m² daily $\times$ 3) to idarubicin (12 mg/m² daily for 3 or 4 days) in addition to standard dose cytarabine in patients aged 50 to 70 years [32]. Although there were no statistically significant differences in OS, and EFS between the treatment groups, use of idarubicin was associated with a higher CR rate [32]. In yet another trial, Lowenberg et al randomized 60 patients with AML aged >65 years to receive either immediate intensive induction chemotherapy or palliative treatment with only mild cytoreductive chemotherapy intended only to stabilize their disease [26]. CR rate and OS were higher among patients who were treated with intensive chemotherapy compared to palliation (58% and 21 weeks versus 0% and 11 weeks, respectively) [26]. In another study, Tilly et al randomized 87 patients 65 years and older to receive low dose cytarabine (20 mg/m² daily for 21 days) versus intensive chemotherapy with cytarabine and an anthracycline [33]. Although the CR rate was higher among patients who received intensive chemotherapy, the OS was similar between the two groups [33]. Furthermore, results from the non-intensive chemotherapy arm of the AML14 trial showed that treatment with low-dose cytarabine (20 mg twice daily for 10 days, every 4 to 6 weeks) compared to hydroxyurea was associated with an higher CR rate (18% versus 1%, $P = 0.00006$) and longer OS (odd ratio, 0.60; 95% confidence interval 0.44-0.81; $P = 0.0009$) [27]. These results demonstrate that this patient population benefits at least modestly from receiving chemotherapy as opposed to palliation alone.

Clearly the decision regarding the intensity of chemotherapy to be administered to elderly patients with AML remains difficult. The heterogeneity of this population complicates the identification of patients who are fit or unfit for intensive chemotherapy. Furthermore, the prediction of response to intensive therapy may be highly divergent between physicians and patients; this in turn further complicates the process of decision-making [14]. However, elderly patients with good performance status (< 2) and no comorbidities (fit for intensive chemotherapy) could receive induction therapy consisting of 3 days of anthracycline and 7 days of cytarabine. The choice of anthracycline (idarubicin vs. daunorubicin) and the dose schedule (daunorubicin 60 mg/m² vs. 90 mg/m²) remain debatable.

The appropriate postremission therapy and the duration of treatment (whether more is better than less) also remain controversial. In the MRC AML 11 study, patients who stopped treatment after the third course had a similar outcome to patients who received a total of 6 courses [34]. The Cancer and Leukemia Group B (CALGB) compared 2 intensive cycles of cytarabine 100 mg/m² q12h × 6 doses; mitoxantrone 5 mg/m² q12h × 6 doses) to 4 less intensive (cytarabine 100 mg/m² continuous infusion on days 1-5) and found no differences in the outcome [35]. In the AMLCG92 trial, older patients achieved longer remission duration from monthly myelosuppressive maintenance (cytarabine 100 mg/m² per q12h × 10 with an anthracycline or thioguanine) compared with a single course of cytarabine (500 mg/m² per q12h on days 1, 2, 8, and 9). Several other studies have found different results using different therapies with different dose schedules [36,37]. Based on these data no clear recommendation for postremission therapy can be given. However, for patients with good performance status and no comorbidities, standard induction therapy followed by repetitive cycles of modest dose of consolidation is widely acceptable strategy.

Investigational agents in elderly patients with AML

The long-term survival data clearly reveal a very poor outcome for elderly patients with AML highlighting the importance of identifying less toxic and more effective therapies for this population. Several investigational agents have been explored (Table 3). However, more effective strategies are still desperately needed to improve the outcome of these patients. Therefore, elderly patients with AML should always be encouraged to participate in clinical trials with new investigational agents specially patients who are deemed unfit to receive intensive chemotherapy.

Gemtuzumab ozogamycin (GO) is an antibody-linked immunotoxin that targets cells expressing the antigen CD33 (commonly expressed in AML cells and not on other tissues). GO was initially approved for treating older patients ≥ 60 years with AML in first relapse but was recently withdrawn from the market. In three open-label, multicenter trials of GO in elderly AML patients at first relapse, GO was given as a 2-hour intravenous infusion at a dose of 9 mg/m² on days 1 and 14 [38]. Among the 142 patients treated, 30% achieved a response; however, a number of adverse events including myelosuppression, hyperbilirubinemia, infections, mucositis, and elevated liver enzymes were encountered [38]. In the final report of efficacy and safety of GO, an overall response rate of 26% (13% CR and 13% CR without full platelet recovery (CRp) was reported [39]. The median relapse-free survival was 6.4 months for patients with CR and 4.5 months for patients with CRp. Several side effects were documented including: grade 3 or 4 hyperbilirubinemia in 29% of patients, grade 3 or 4 neutropenia and thrombocytopenia in 98% and 99% respectively, and hepatic enzyme elevations in 15% [39]. GO has also been explored in the frontline therapy of patients with AML ≥ 65 years [40]. CR rate was 8%. When compared with a historical group of patients who received idarubicin and cytarabine (IA), the CR rate and OS were significantly higher in patients who received IA [40]. In a report from the LRF AML14 and NCRI AML16 pick-a-winner trials, 495 elderly AML patients were randomized to receive low dose cytarabine with or without GO at a dose of 5 mg/m² on day 1 of each course of low dose cytarabine [41]. Although GO improved the remission rate (30% versus 17%, $P = 0.006$), the OS at 12 months was similar with or without GO (25% versus 27%,

respectively) [41]. In a phase III randomized trial conducted in France (ALFA-0701), 280 patients with de novo AML aged 50-70 years were randomized to receive standard induction chemotherapy (3+7) with or without GO (3 mg/m² on days 1, 4, and 7 during induction and day 1 of each of the two consolidation chemotherapy courses) [42]. Although the CR/CRp rates were similar in patients who received or not received GO (75% versus 81%, $P = 0.25$), the 2 year EFS (40.8% versus 17.1%, $P = 0.0003$), RFS (50.3% versus 22.7%, $P = 0.0003$) and OS (53.2% versus 41.9%, $P = 0.0368$) were significantly higher in patients who received GO compared to the no GO group [42]. However, hematologic toxicities particularly persistent thrombocytopenia were more common among patients who received GO without an increased risk of death from toxicity [42].

Tipifarnib, a farnesyltransferase inhibitor was also investigated in elderly patients with AML and myelodysplastic syndrome (MDS). In a phase II trial of 158 elderly patients (median age, 74 years) with poor-risk AML treated with Tipifarnib, 22 (14%) patients achieved CR [43]. The median CR duration was 7.3 months and the median OS among the responders was 18 months. As expected, adverse karyotype, age ≥ 75 years, and poor performance status correlated negatively with survival. Early death in the absence of progressive disease was rare; however, non-hematological toxicities were documented in 47% of the patients [43]. In a phase III, randomized, multicenter trial of tipifarnib versus best supportive care (BSC), 457 elderly patients with AML (median age 74 years) were enrolled [44]. CR rate for tipifarnib was 8%, which is lower than previously reported [44]. Furthermore, there was no difference in OS between the patients who received tipifarnib compared to BSC. Tipifarnib was also investigated in combination with other agents. A higher CR rate of 30% reported when tipifarnib was combined with oral etoposide in patients older than 70 years [45]. In another report, tipifarnib was used in combination with low dose cytarabine in 64 AML patients with median age of 74 years [46]. The addition of tipifarnib to low dose cytarabine had no effect on response rate, toxicity, or OS [46]. Tipifarnib was also investigated as maintenance therapy in AML patients in remission after receiving salvage therapy or over age of 60 in first remission [47]. Although patients who received tipifarnib had better OS at 10 months compared to observation only ($P = 0.05$), this benefit was subsequently lost. Furthermore, there was no difference in disease free survival or long term overall survival between the two groups [47].

Clofarabine is a second generation nucleoside analogue that has shown significant activity as monotherapy or in combination for the treatment of young and elderly patients with AML. In a phase II study of clofarabine monotherapy in newly diagnosed older adults with AML (median age 71 years, range, 60-88), clofarabine was given at 30 mg/m² intravenously for 5 days and 20 mg/m² during reinduction/consolidation, for up to 6 cycles [48]. The ORR was 46% (38% CR, 8% CRp). Responses were durable with median remission duration of 56 weeks. The median OS was 41 weeks for all patients and 59 weeks for responders. Induction mortality was 9.8% [48]. More recently, in a randomized, multicenter trial in United Kingdom, Denmark, and Australia, 406 patients were randomized to receive clofarabine 20 mg/m² IV days 1-5 versus low dose cytarabine 20 mg subcutaneous twice daily [49]. Although treatment with clofarabine resulted in higher CR/CRi (38%) compared to low dose cytarabine (20%, $P < 0.0001$), the OS and relapse free survival (RFS) were

similar between the two treatment arms [49]. The authors concluded that the lack of OS benefit in the clofarabine arm could be partially explained by the ability to salvage patients who receive low dose cytarabine and did not achieve an initial CR as opposed to clofarabine treated patients who had worse salvage options [49].

Clofarabine was also investigated in combination with several other agents in older patients with AML. In a phase II trial of clofarabine in combination with intermediate-dose cytarabine (1 g/m²/day for 5 days) in patients with newly diagnosed AML, 50 years and older, the ORR was 60% (52% CR and 8% CRp) [50]. Induction mortality was 7%; however the survival was similar to other regimes [50]. In a subsequent trial, patients were randomized to receive clofarabine alone or in combination with low dose cytarabine (20 mg/m² cytarabine subcutaneously daily for 14 days during induction and 7 days during consolidation)[51]. The median age was 71 years. The CR rate (63% vs 31%; $P = 0.025$), event-free survival (7.1 months vs. 1.7 months; $P = 0.04$), but not OS (11.4 months vs. 5.8 months; $P = 0.1$) were higher with the combination, compared to clofarabine single agent, respectively [51]. Furthermore, in a randomized, multicenter trial of clofarabine (40 mg/m² for 5 days) plus cytarabine (1 g/m²/day for 5 days) compared to cytarabine alone in relapsed or primary refractory patients with AML 55 years and older, the overall all response rate (ORR) was higher in the combination arm compared to cytarabine alone (46.9% vs. 22.9%, respectively, $P < 0.01$) [52]. Although EFS was higher for patients who received the combination, the OS was similar between the two arms [52]. Clofarabine was also combined with low dose cytarabine followed by a prolonged consolidation alternating with decitabine [53]. Although this treatment schedule was well tolerated and produced an ORR of 66%, the relapse-free survival was similar to an historical cohort of patients who received clofarabine in combination with low dose cytarabine alone with a shorter consolidation [53]. In the UK NCRI AML 16 trial, elderly patients with AML were randomized to receive two courses of daunorubicin+cytarabine (DA) versus daunorubicin + clofarabine (DClo) [54]. The ORR was (71% [CR 63%, CRi 8%] vs 66% [CR 57%, CRi 9%], $P = 0.12$, respectively), 60 days mortality (15% vs 14%, respectively), RFS (18% vs 21%, $P = 1.0$, respectively), and OS (23% vs 22%, $P = 0.3$) were all similar between the two treatment groups [54].

Hypomethylating agents (HMA), 5-azacytidine and decitabine, have also both been investigated either alone or in combination in elderly patients with AML. In a subgroup analysis of AZA-001 trial in elderly patients with bone marrow blasts percentage between 20% and 30%, treatment with 5-azacytidine prolonged OS compared to conventional care regimens including intensive chemotherapy [55]. It should be noted however that a small percentage of patients in the conventional care arm received intensive chemotherapy (19%) and the median OS for this patient population (16 months) was longer than expected for AML patients receiving supportive care or low dose cytarabine only. In a phase III, randomized, multicenter trial of single agent decitabine for 5 days every 4 weeks compared to supportive care or low-dose cytarabine, treatment with decitabine was associated with higher CR rate and better OS leading to its approval for this indication in Europe [56]. Furthermore,

Quintas-Cardama et al have reviewed the outcome of 671 patients with newly diagnosed AML 65 years and older, treated with intensive chemotherapy versus HMA (5- azacytidine

and decitabine) [57]. Although the response rate was higher for patients receiving intensive chemotherapy compared to HMA (42% vs. 28%, respectively, $P = 0.001$), the relapse-free survival and OS were similar in the two groups. Additionally, decitabine was associated with better OS when compared with 5-azacitidine (8.8 vs. 5.5 months, respectively, $P = 0.03$) [57]. This observation was also confirmed by other retrospective analysis from different groups [8,9,58].

Sapacitabine, is a novel oral cytosine nucleoside analogue, that causes breaks in the DNA strands leading to apoptosis [59]. In a phase II, multicenter study in newly diagnosed or first relapse AML patients 70 years or older, sapacitabine was given in 3 doses schedule: 200 mg twice a day for 7 days, 300 mg twice a day for 7 days, and 400 mg twice a day for 3 days each week for 2 weeks [60]. Among 105 patients included (86 with newly diagnosed AML and 19 at first relapse), 36 patients achieved CR, CRp, CR with incomplete hematologic recovery, and partial response. Median OS was 197 days for patients treated with 200 mg dose schedule, 102 days in 300 mg group, and 213 days in 400 mg dose. Sapacitabine was well tolerated with 13% induction mortality; however, frequent dose reduction was required due to myelosuppression [60]. The authors concluded that 400 mg dose schedule had the best efficacy profile. Trials comparing sapacitabine with low dose cytarabine in patients who are unfit for chemotherapy, or in combination with other low intensity strategies such as HMA are currently underway.

Cloretazine (laromustine), a sulfonylhydrazine alkylating agent, has been explored in a phase II trial in elderly patients with newly diagnosed AML [61]. The ORR was 32% (CR in 23% and CRp in 8%). Median OS was 3.2 months and 1-year survival was 21%. Cloretazine was well tolerated with 30-days mortality of 14% [61].

Many other agents including vosaroxin, lintuzumab, CPX-351 and the aminopeptidase inhibitor, tosedostat are being evaluated in this setting. Many of these trials were designed to include only patients with either very advanced age (typically > 70 years) or with at least one additional adverse feature such as poor or intermediate-risk cytogenetics, performance status of 2, or history of antecedent hematological disorder. In a phase IIb study that randomized newly diagnosed elderly (aged 60-75 years) patients with AML to receive CPX-351 versus 3+7 [62], CPX-351 was associated with better outcomes in patients with adverse cytogenetics and/or secondary AML [62]. Tosedostat was investigated in elderly patients with relapsed or refractory AML [63]. Seventy six patients, 60 year or older, were randomly assigned to receive tosedostat 120 mg once daily for 6 months or 240 mg once daily for 2 months followed by 120 mg for 4 months. Seven patients (10%) had complete remission or complete remission with incomplete platelet recovery. The treatment was well tolerated [63]. Interesting responses were more common in patients who had received prior therapy with hypomethylating agents. Studies combining tosedostat with hypomethylating agents or low dose cytarabine in patients with high-risk myelodysplastic syndromes and AML are ongoing or planned [64].

The role of allogeneic stem cell transplant (SCT) in elderly patients with AML is beyond the scope of this review. The introduction of reduced intensity conditioning (RIC) regimens has allowed the exploration of this modality in older patients; however, recent studies have

demonstrated its limited feasibility in first CR in this population [65,66]. Therefore, RIC allogeneic SCT is only recommended in the setting of clinical trials [67].

In conclusion, the outcome of elderly patients with AML remains very poor. Patients with good performance status and no comorbidities could receive intensive chemotherapy; however, patients should always be encouraged to participate in clinical trials whenever possible. For patients who are unfit to receive intensive chemotherapy, treatment with novel investigation agents is highly recommended. Table 4 summarizes the ongoing and recently completed trials in elderly AML that are conducted by the major cooperative groups in the United States and Europe.

In general, the authors believe that patients who have a high likelihood of induction mortality ($> 30\%$), low likelihood of achieving CR ($< 30\%$) and low likelihood of long term remission ($< 10\%$) based on their clinical features and disease biology (as described earlier) should be offered investigational agents on clinical trials. Those with a high likelihood of achieving CR ($>40\%$) and a low likelihood of induction mortality ($< 15\%$) should be treated on standard regimens. The population in between these, would benefit most from trials that compare standard chemotherapy to investigational approaches (Table 5).

Existing challenges include: more precise identification of patients unsuitable to receive cytotoxic chemotherapy, better utilization of currently available treatment options including the less toxic agents such as HMA alone or in combination with other non-toxic therapies, and most importantly, development of novel targeted agents directed at dysfunctional pathogenic pathways responsible for leukemogenesis which are most likely to improve the overall outcome of these patients.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin.* 2006; 56:106–130. [PubMed: 16514137]
2. Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. *N Engl J Med.* 1999; 341:1051–1062. [PubMed: 10502596]
3. Juliusson G, Lazarevic V, Horstedt AS, Hagberg O, Hoglund M. Acute myeloid leukemia in the real world: why population-based registries are needed. *Blood.* 2012; 119:3890–3899. [PubMed: 22383796]
4. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood.* 2006; 107:3481–3485. [PubMed: 16455952]
5. Buchner T, Berdel WE, Haferlach C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol.* 2009; 27:61–69. [PubMed: 19047294]
6. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood.* 1998; 92:2322–2333. [PubMed: 9746770]
7. Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood.* 2001; 98:1312–1320. [PubMed: 11520776]
8. Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de

- novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood*. 2002; 100:4325–4336. [PubMed: 12393746]
9. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006; 106:1090–1098. [PubMed: 16435386]
 10. Wheatley K, Brookes CL, Howman AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. *Br J Haematol*. 2009; 145:598–605. [PubMed: 19344426]
 11. Frohling S, Schlenk RF, Kayser S, et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. *Blood*. 2006; 108:3280–3288. [PubMed: 16840728]
 12. van der Holt B, Breems DA, Berna Beverloo H, et al. Various distinctive cytogenetic abnormalities in patients with acute myeloid leukaemia aged 60 years and older express adverse prognostic value: results from a prospective clinical trial. *Br J Haematol*. 2007; 136:96–105. [PubMed: 17129222]
 13. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010; 116:354–365. [PubMed: 20385793]
 14. Sekeres MA, Stone RM, Zahrieh D, et al. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. *Leukemia*. 2004; 18:809–816. [PubMed: 14762444]
 15. Malfuson JV, Etienne A, Turlure P, et al. Risk factors and decision criteria for intensive chemotherapy in older patients with acute myeloid leukemia. *Haematologica*. 2008; 93:1806–1813. [PubMed: 18838471]
 16. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008; 358:1909–1918. [PubMed: 18450602]
 17. Becker H, Marcucci G, Maharry K, et al. Favorable prognostic impact of NPM1 mutations in older patients with cytogenetically normal de novo acute myeloid leukemia and associated gene- and microRNA-expression signatures: a Cancer and Leukemia Group B study. *J Clin Oncol*. 2010; 28:596–604. [PubMed: 20026798]
 18. Marcucci G, Haferlach T, Dohner H. Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications. *J Clin Oncol*. 2011; 29:475–486. [PubMed: 21220609]
 19. Santos FP, Jones D, Qiao W, et al. Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. *Cancer*. 2011; 117:2145–2155. [PubMed: 21523727]
 20. Schnittger S, Schoch C, Dugas M, et al. Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study and usefulness as a marker for the detection of minimal residual disease. *Blood*. 2002; 100:59–66. [PubMed: 12070009]
 21. Pemmaraju N, Kantarjian H, Ravandi F, Cortes J. FLT3 inhibitors in the treatment of acute myeloid leukemia: the start of an era? *Cancer*. 2011; 117:3293–3304. [PubMed: 21319142]
 22. Leith CP, Kopecky KJ, Godwin J, et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. *Blood*. 1997; 89:3323–3329. [PubMed: 9129038]
 23. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999; 341:2061–2067. [PubMed: 10615079]
 24. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. *Arch Intern Med*. 2002; 162:1597–1603. [PubMed: 12123403]
 25. Juliusson G, Billstrom R, Gruber A, et al. Attitude towards remission induction for elderly patients with acute myeloid leukemia influences survival. *Leukemia*. 2006; 20:42–47. [PubMed: 16327841]

26. Lowenberg B, Zittoun R, Kerkhofs H, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. *J Clin Oncol*. 1989; 7:1268–1274. [PubMed: 2475589]
27. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer*. 2007; 109:1114–1124. [PubMed: 17315155]
28. Giles FJ, Borthakur G, Ravandi F, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol*. 2007; 136:624–627. [PubMed: 17223919]
29. Yates J, Glidewell O, Wiernik P, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. *Blood*. 1982; 60:454–462. [PubMed: 6953986]
30. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009; 361:1249–1259. [PubMed: 19776406]
31. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009; 361:1235–1248. [PubMed: 19776405]
32. Pautas C, Merabet F, Thomas X, et al. Randomized Study of Intensified Anthracycline Doses for Induction and Recombinant Interleukin-2 for Maintenance in Patients With Acute Myeloid Leukemia Age 50 to 70 Years: Results of the ALFA-9801 Study. *J Clin Oncol*.
33. Tilly H, Castaigne S, Bordessoule D, et al. Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. *J Clin Oncol*. 1990; 8:272–279. [PubMed: 2299370]
34. Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001; 98:1302–1311. [PubMed: 11520775]
35. Stone RM, Berg DT, George SL, et al. Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with standard-dose cytarabine. *Blood*. 2001; 98:548–553. [PubMed: 11468148]
36. Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood*. 2007; 109:5129–5135. [PubMed: 17341661]
37. Schlenk RF, Frohling S, Hartmann F, et al. Intensive consolidation versus oral maintenance therapy in patients 61 years or older with acute myeloid leukemia in first remission: results of second randomization of the AML HD98-B treatment Trial. *Leukemia*. 2006; 20:748–750. [PubMed: 16437135]
38. Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol*. 2001; 19:3244–3254. [PubMed: 11432892]
39. Larson RA, Sievers EL, Stadtmauer EA, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. *Cancer*. 2005; 104:1442–1452. [PubMed: 16116598]
40. Estey EH, Thall PF, Giles FJ, et al. Gemtuzumab ozogamicin with or without interleukin 11 in patients 65 years of age or older with untreated acute myeloid leukemia and high-risk myelodysplastic syndrome: comparison with idarubicin plus continuous-infusion, high-dose cytosine arabinoside. *Blood*. 2002; 99:4343–4349. [PubMed: 12036860]
41. Burnett AK, Hills RK, Hunter AE, et al. The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. *Leukemia*. 2013; 27:75–81. [PubMed: 22964882]

42. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012; 379:1508–1516. [PubMed: 22482940]
43. Lancet JE, Gojo I, Gotlib J, et al. A phase 2 study of the farnesyltransferase inhibitor tipifarnib in poor-risk and elderly patients with previously untreated acute myelogenous leukemia. *Blood*. 2007; 109:1387–1394. [PubMed: 17082323]
44. Harousseau JL, Martinelli G, Jedrzejczak WW, et al. A randomized phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older. *Blood*. 2009; 114:1166–1173. [PubMed: 19470696]
45. Karp JE, Flatten K, Feldman EJ, et al. Active oral regimen for elderly adults with newly diagnosed acute myelogenous leukemia: a preclinical and phase 1 trial of the farnesyltransferase inhibitor tipifarnib (R115777, Zarnestra) combined with etoposide. *Blood*. 2009; 113:4841–4852. [PubMed: 19109557]
46. Burnett AK, Russell NH, Culligan D, et al. The addition of the farnesyl transferase inhibitor, tipifarnib, to low dose cytarabine does not improve outcome for older patients with AML. *Br J Haematol*. 2012; 158:519–522. [PubMed: 22639959]
47. Luger SZL, Paietta E, et al. R115777 (tipifarnib) Improves Early Survival when Used As Maintenance Therapy for Elderly or Relapsed/Refractory Patients with Acute Myelogenous Leukemia in Remission. *Blood (ASH Annual Meeting Abstracts)*. Nov.2012 120:676.
48. Kantarjian HM, Erba HP, Claxton D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. *J Clin Oncol*. 2010; 28:549–555. [PubMed: 20026805]
49. Burnett ARN, McMullin M, et al. A Randomised Comparison of Clofarabine Versus Low Dose Ara-C As First Line Treatment for Older Patients with AML. *Blood (ASH Annual Meeting Abstracts)*. Nov.2012 120:889.
50. Faderl S, Verstovsek S, Cortes J, et al. Clofarabine and cytarabine combination as induction therapy for acute myeloid leukemia (AML) in patients 50 years of age or older. *Blood*. 2006; 108:45–51. [PubMed: 16403905]
51. Faderl S, Ravandi F, Huang X, et al. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood*. 2008; 112:1638–1645. [PubMed: 18565853]
52. Faderl S, Wetzler M, Rizzieri D, et al. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I Trial. *J Clin Oncol*. 2012; 30:2492–2499. [PubMed: 22585697]
53. Faderl S, Ravandi F, Huang X, et al. Clofarabine plus low-dose cytarabine followed by clofarabine plus low-dose cytarabine alternating with decitabine in acute myeloid leukemia frontline therapy for older patients. *Cancer*. 2012; 118:4471–4477. [PubMed: 22282348]
54. Burnett ARN, Kell J, et al. A Comparison of Daunorubicin/Ara-C (DA) Versus Daunorubicin/Clofarabine (DClo) and Two Versus Three Courses of Total Treatment for Older Patients with AML and High Risk MDS: Results of the UK NCRI AML16 Trial. *Blood (ASH Annual Meeting Abstracts)*. Nov.2012 120:892.
55. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol*. 2010; 28:562–569. [PubMed: 20026804]
56. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012; 30:2670–2677. [PubMed: 22689805]
57. Quintas-Cardama A, Ravandi F, Liu-Dumlao T, et al. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. *Blood*. 2012; 120:4840–4845. [PubMed: 23071272]

58. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood*. 2000; 96:4075–4083. [PubMed: 11110676]
59. Azuma A, Huang P, Matsuda A, Plunkett W. 2'-C-cyano-2'-deoxy-1-beta-D-arabino-pentofuranosylcytosine: a novel anticancer nucleoside analog that causes both DNA strand breaks and G(2) arrest. *Mol Pharmacol*. 2001; 59:725–731. [PubMed: 11259616]
60. Kantarjian H, Faderl S, Garcia-Manero G, et al. Oral sapacitabine for the treatment of acute myeloid leukaemia in elderly patients: a randomised phase 2 study. *Lancet Oncol*. 2012; 13:1096–1104. [PubMed: 23075701]
61. Schiller GJ, O'Brien SM, Pigneux A, et al. Single-agent laromustine, a novel alkylating agent, has significant activity in older patients with previously untreated poor-risk acute myeloid leukemia. *J Clin Oncol*. 2010; 28:815–821. [PubMed: 20026800]
62. Lancet JCJ, Kovacsovic T, et al. A comparison of CR versus CRi response following CPX-351 treatment of newly diagnosed AML in elderly patients (pts). *J Clin Oncol*. 2012; 30 suppl; abstr 6601.
63. Cortes J, Feldman E, Yee K, et al. Two dosing regimens of tosedostat in elderly patients with relapsed or refractory acute myeloid leukaemia (OPAL): a randomised open-label phase 2 study. *Lancet Oncol*. 2013; 14:354–362. [PubMed: 23453583]
64. Mathisen MS, Ravandi F. Efficacy of tosedostat, a novel, oral agent for elderly patients with relapsed or refractory acute myeloid leukemia: a review of the Phase II OPAL trial. *Future Oncol*. 2012; 8:351–357. [PubMed: 22515438]
65. Giralt S. Allografting older patients--myths and realities. *Biol Blood Marrow Transplant*. 2009; 15:146–148. [PubMed: 19147096]
66. Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood*. 2007; 109:1395–1400. [PubMed: 17038533]
67. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 115:453–474. [PubMed: 19880497]

Table 1

Prognostic models for elderly patients with AML – MD Anderson model [9]

Parameter		Hazard risk
Age	75	1.3
Performance status	2, ECOG	1.5
Complex karyotype		1.4
Treatment outside laminar airflow room		3.1
ADH duration	12 months	1.4
Creatinine	> 1.3 mg/dl	1.4

Risk group	No. Adverse factors	8 weeks mortality %	CR %	Median OS (months)	1-year survival %
Low	0	10	59	16	58
Intermediate	1-2	19-36	57-40	9-4	35-22
High	3	65	19	1	8

Table 2

Wheatley scoring model [10]

Parameter	Score
Cytogenetic group	1 = favourable/intermediate, 5 = adverse, 2 = unknown
WBC group	1 = <10·0, 2 = 10·0–49·9, 3 = 50–99·9, 4 = 100+ ($\times 10^9/l$)
Performance status	Performance status score: 0, 1, 2, 3, 4
Age group	1 = 60–64, 2 = 65–69, 3 = 70–74, 4 = 75+ (years)
AML type	1 = <i>de novo</i> , 3 = secondary
Total Score (Cytogenetic group) + Score (WBC group) + Score (Performance status) + Score (Age group) + Score (AML type)	
Risk Group, Good = 4-6, Standard = 7-8, Poor = 9	

Table 3

Investigational agents under development and its mechanism of action

Investigational agent	Brand name	Class	Mechanism of action
Gemtuzumab Ozogamycin	Mylotarg	Monoclonal antibody	Recombinant humanized monoclonal antibody conjugated with calicheamicin directed against the surface glycoprotein CD33
Tipifarnib	Zarnestra	Farnesyl transferase inhibitor	Competitively and irreversibly inhibit Farnesyl transferase enzyme, a key enzyme that regulates cancer cell signaling, proliferation, and differentiation
Clofarabine	Clolar	Second generation purine analog	Inhibit DNA synthesis and repair via inhibition of ribonucleotide reductase (RnR) and DNA polymerases
5-azacytidine	Vidaza	DNA Methylation Inhibitor	Cause hypomethylation of DNA that leads to direct cytotoxicity on abnormal hematopoietic cells in the bone marrow
Decitabine	Dacogen	DNA Methylation Inhibitor	Cause hypomethylation of DNA that leads to direct cytotoxicity on abnormal hematopoietic cells in the bone marrow
Sapacitabine	Cyclacel	Nucleoside analogue	Interferes with DNA synthesis by causing single strand breaks which are subsequently converted to double strand breaks resulting in cell death. It also induce cell cycle arrest in G2/M-Phase and delays progression to S-Phase resulting in apoptosis
Cloretazine	Laromustine	sulfonylhydrazine alkylator	Inhibit the nucleotidyl transferase activity of purified human DNA polymerase β (Pol β), a principal enzyme of DNA base excision repair (BER)
Tosedostat		Aminopeptidase inhibitor	Inhibit aminopeptidase activity, which results in the depletion of cellular amino acid pools selectively in tumour cells that disrupts the turnover of cell cycle
CPX-351		liposomal formulation of a fixed combination of cytarabine and daunorubicin in 5:1 molar ratio	It combined the antitumor activity of cytarabine (DNA polymerase inhibitor) and anthracycline (Topoisomerase II inhibitor)
Vosaroxin		Topoisomerase II inhibitor	Inhibit topoisomerase II activity that results in replication-dependent, site-selective double-strand breaks in DNA
Quizartinib Sorafenib Midostaurin	Nexavar	FLT3 inhibitor	Inhibit class III receptor tyrosine kinase (FLT3) leading to inhibition of ligand-independent leukemic cell proliferation and apoptosis

FLT3 = *FMS*-related tyrosine kinase 3

Table 4

Ongoing and recently completed cooperative group clinical trials in elderly AML

Cooperative group	Study ID	Phase	Purpose	Status
ECOG	E2906	III	Evaluate Clofarabine as Induction and Post-Remission Therapy vs. Standard Daunorubicin & Cytarabine Induction and Intermediate Dose Cytarabine Post-Remission Therapy, Followed by Decitabine Maintenance vs. Observation in Newly-Diagnosed Acute Myeloid Leukemia in Older Adults (Age $\geq$ 60 Years)	Ongoing
ECOG	E3999	II	Evaluate Daunorubicin & Cytarabine +/- Zosuquidar in Treating Older Patients with Newly Diagnosed Acute Myeloid Leukemia or Refractory Anemia	Completed
SWOG	S0605	II	Evaluate Lenalidomide for Previously Untreated Non-M3, Deletion 5Q AML in Patients Age 60 or Older Who Decline Remission Induction Chemotherapy	Ongoing, not recruiting
SWOG	S0703	II	Evaluate Azacitidine Plus Gemtuzumab Ozogamicin as Induction and Post-Remission Therapy in Patients of Age 60 and Older With Previously Untreated Non-M3	Ongoing, not recruiting
SWOG	S0301	II	Evaluate Induction With Daunorubicin, Cytarabine, And Cyclosporine All By Continuous IV Infusion For Previously Untreated Non-M3 AML In Patients Of Age 56 Or Older	Completed
Leukaemia Lymphoma Research and NCRI Working Group	Pick a Winner Program (LI-1)	II/III	Evaluate low dose cytarabine vs. sapacitabine vs. vosaroxin vs low dose cytarabine + vosaroxin vs. low dose cytarabine + AC220	Ongoing
	MRC AML 18 pilot	I/II	To Establish the Feasibility of Combining Either the Tyrosine Kinase Inhibitor AC220 or the CXCR4 Inhibitor Plerixafor or the HSP90 Inhibitor, Ganetespib, with Chemotherapy in Older Patients with Acute Myeloid Leukemia and High Risk Myelodysplastic Syndrome in Patients Over 60 Years	Ongoing

ECOG = Eastern Cooperative Oncology Group, SWOG = Southwest Oncology Group, NCRI = U.K. National Cancer Research Institute, MRC = Medical Research Council.

Table 5

Decision making in elderly AML based on expected outcomes

Induction Mortality	CR Rate	3-year Survival	Conventional Chemotherapy
< 15%	> 40%	> 15%	YES
> 30%	< 20%	< 10%	NO *
15-30%	20-40%	> 10%	? **

* Clinical trials of novel, investigational agents recommended

** Clinical trials comparing standard regimens to new strategies recommended CR = complete remission