Acute myeloid leukemia in older patients: conventional and new therapies

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A B S T R A C T

Acute myeloid leukemia (AML) in older patients continues to pose significant treatment challenges. In this age group, the benefit associated with intensive chemotherapy remains marginal and the chance for cure continues to be below 10% overall. While treatment outcome is compromised by a higher prevalence of comorbidities, it is now clear that AML in older patients is a biologically distinct disease that is intrinsically less responsive to chemotherapy. Improving risk-assessment tools is critical to identify those patients who are most likely to benefit from intensive chemotherapy, but optimal induction and post-remission therapies have yet to be determined in this population. New strategies and treatments are emerging and under current assessment. In particular, investigations of monoclonal antibodies, hypomethylating agents, signal transduction inhibitors, and novel cytotoxics hold promise for improving the outcome for older patients with AML, including those for whom traditional chemotherapy is not considered appropriate, either because of anticipated lack of efficacy or unacceptable mortality. Further progress in the care of elderly AML is largely dependent upon building a critical mass of patients and physicians willing to participate in clinical trials.

Learning goals

At the conclusion of this activity, participants should be able to:
- describe current and emerging therapies for older patients with newly diagnosed AML;
- select appropriate up-front therapy based upon patient and disease characteristics;
- discuss treatment options for older patients who may or may not be candidates for intensive chemotherapy;
- understand the importance of encouraging older patients to participate in clinical trials for AML.

Introduction

Acute myeloid leukemia (AML), a disease affecting primarily older adults with a median age at presentation of approximately 68 years, continues to pose significant treatment challenges.[1] Although there have been improvements in treatment outcomes for AML in recent years, these have mostly benefited younger patients under the age of 60 years.[2] Advanced age is considered an adverse prognostic indicator resulting from both a more aggressive underlying disease biology and a decreased capacity of patients to tolerate chemotherapy due to the frequent presence of significant co-morbidities and poor organ reserve. In clinical trials, which typically exclude patients with severe co-morbidities, complete remissions are observed in 40-65% of patients treated intensively, of whom almost 90% relapse within three years.[3,4] Age continuously affects treatment results, as do other independent prognostic factors including performance status, organ dysfunction, white blood cell count, cytogenetics, molecular abnormalities, overexpression of multidrug resistance proteins, and secondary leukemia. Because of this, it is difficult to recommend precise age cut offs for clinical decision-making.[5-7] Much interest is currently being directed at the development of multifactorial risk scores to more accurately predict the outcome for patients who may then be given the choice of intensive or alternative treatment approaches, including less intensive therapy, investigational therapy or palliative care.[8-11] The importance of patient selection is apparent in a review of 2657 elderly patients with AML collected by Medicare and the Surveillance, Epidemiology, and End Results (SEER).[12] Only approximately 30% of patients underwent induction chemotherapy and the median survival across all study population was 2.4 months with a 2-year survival of 6%. However, the analysis also showed that patients who did receive chemotherapy had a survival benefit, even though this was modest. As the general population lives longer, the number of patients in this age group will increase. Therefore, there is an urgent need to find new treatments that are more effective and less toxic for these patients who are traditionally not catered for in most trials. In this review, we provide an outline of the current and developing treatments for older patients with newly diagnosed AML.

Choice of treatment

Despite the reluctance to treat older patients with intensive chemotherapy because of toxicity concerns, induction of a complete remission (CR), even if short-lived, is an appropriate goal for most AML patients over 60 years of age. This concept was established in the late 1980s based on the results of the EORTC AML-7 trial which prospectively compared induction therapy with daunorubicin, vincristine and cytarabine *versus* supportive care with palliative chemotherapy (hydroxyurea or low-dose cytarabine) in patients over 65 years of age.[13] The patients who received induction chemotherapy had a higher CR rate (58% *vs.* 0%), lower incidence of early mortality (3 of 31 *vs.* 18 of 29), longer median survival (21 *vs.* 11 weeks) and greater chance of survival at 2.5 years (13% *vs.* 0%). Importantly, there was no difference in the number of days that patients were hospitalized. Furthermore, registry data from nearly 3000 unselected older patients in Sweden showed reduced rates of early mortality for those who received intensive chemotherapy *versus* palliative care, as well as improved long-term survival in geographical regions where the use of intensive treatment approaches was more common.[14] Thus, achieving CR is a requisite end point for better survival and improved quality of life in elderly AML, and data from large population-based studies have validated the use of intensive chemotherapy over less intensive treatment approaches in patients up to the age of 80 years.

Although it is clear that intensive chemotherapy produces the highest response and survival rates in selected elderly patients with AML, it is ineffective and highly toxic in many others. The challenge is to appropriately identify which patients, based on their disease biology and clinical characteristics, are likely to benefit more from intensive chemotherapy and which require alternative treatment approaches. Several risk scores are available that account for age, performance status, cytogenetics, secondary AML and other covariates to arrive at a prognosis for patients over 60 years of age treated with intensive chemotherapy (Table 1). Despite the differences in variables and end points and methods used, these tools can be used to more accurately individualize the treatment prospects. Patients with the expectation of a low early mortality, high CR rate, and a reasonable long-term survival should be treated with intensive chemotherapy, while those with the expectation of a high risk of early mortality or a poor chance of long-term survival should be offered low-intensity investigational therapy.

Conventional remission induction therapy

For over 30 years, the "3+7" regimen combining daunorubicin (45-50 mg/m^2 for 3 days) and cytarabine (100-200 mg/m^2 by continuous infusion for 7 days) has been the mainstay of induction therapy for older patients with AML.[1] On average, this regimen offers older patients a CR rate of 40-65% with an attendant treatment-related mortality of 15-20%, a median survival of 8-12 months, and a less than 15% probability of sustained remission for three years. Multiple attempts have been made to improve outcome by substituting newer anthracyclines (idarubicin or mitoxantrone) for daunorubicin, escalating the dose of cytarabine, adding other cytotoxic drugs, and priming with growth factors, but none of these strategies has emerged as convincingly superior to "3+7".[4] However, a recent com-

Table 1. Selected prognostic risk scores in elderly AML.

	Prognostic factors	CR rate (%)	Early death rate (%)	Overall survival (%)
ALFA-9803[8]	Poor cytogenetics			(1-year)
(n=416)	Age ≥75			P-CG or 2/3 factors: 19
	PS ≥2			Others: 58
	WBC ≥50x10^9/L			
MRC AML11/14[9]	Cytogenetics			(1-year)
(n=1071)	Age			
	WBC			Good: 53
	PS			Standard: 43
	De novo vs. sAML			Poor: 16
				(2-year)
MDACC[10]	Age ≥80	# 0: 57	# 0: 16	# 0: 30
(n=446)	Complex karyotype	# 1: 52	# 1: 31	# 1: 15
	PS ≥2	# 2: 29	# 2: 55	# 2: 7
	Creatinine >1.3	# ≥ 3: 16	# ≥ 3: 71	# ≥ 3: 0
SAL AML-96[11]	Cytogenetics			(3-years)
(n=909)	Age >65			
	WBC > 20x10^9/L			F-CG: 39.5
	LDH >700			I-CG (good): 30
	CD34 >10%			I-CG-(adverse): 10.6
	NPM1 mutation			P-CG: 3.3

P-CG: poor-risk cytogenetics; F-CG: favorable-risk cytogenetics; I-CG: intermediate-risk cytogenetics.

bined analysis of two randomized ALFA trials (9801 and 9803), enrolling a total of 727 AML patients age 50 years and over (median 67 years) showed a somewhat superior long-term outcome with idarubicin compared to daunorubicin (cure rate 16.6% *vs.* 9.8%; *P*=0.018). Interestingly, the long-term impact of idarubicin was also evident in the cohort of patients under 65 years of age, although all of the younger patients in the control arm received daunorubicin at higher doses (80 mg/m^2 × 3).[15]

Options for improvement

Most recently, efforts to improve the complete remission rate and long-term outcome beyond that which is achieved with the traditional "3+7" regimen, have concentrated on anthracycline dose escalation, the addition of novel agents, and alternatives to cytarabine. Lowenberg *et al.* showed a higher CR rate when 813 patients over 60 years of age with newly diagnosed AML were randomized to receive three days of daunorubicin 90 mg/m^2 *versus* 45 mg/m^2 in combination with cytarabine 200 mg/m^2 daily for seven days (64% *vs.* 54%; *P*=0.002).[16] The early death rate was similar between the two groups. Although, overall, there was no difference in survival between patients treated with the standard-dose *versus* the escalated-dose regimen, patients aged 60-65 years gained advantage from daunorubicin intensification with regards to all the major clinical end points. In this subgroup, substantial improvements in CR rate, event-free and overall survival were observed, while patients with core binding factor abnormalities appeared to benefit from high-dose daunorubicin irrespective of age. On the other hand, a randomized trial by the French ALFA group failed to show any clinically relevant superiority of high-dose daunorubicin (80 mg/m^2 x 3 days) over three or four days of idarubicin (12 mg/m^2) when combined with cytarabine for remission induction in 468 patients aged 50-70 years, suggesting therapeutic equivalence between these two drugs at these doses.[17] Whether these studies justify a higher anthracycline dose as the standard of care for older patients with AML is not clear, but they do convincingly demonstrate that there is no increase in toxicity with these regimens.

Other agents with novel mechanisms of action and with non-overlapping toxicity can potentially improve the outcome when added to standard chemotherapy. One option to improve the remission rate and overall outcome could be to incorporate gemtuzumab ozogamicin (GO), an immunoconjugate consisting of a humanized anti-CD33 monoclonal antibody linked to the toxin calicheamicin, into treatment. This strategy has been investigated in three large European studies, two of which show a significant improvement in survival (Table 2). The French ALFA group randomized 280 patients aged 50-70 years (median 62 years) with newly diagnosed AML to standard induction therapy ("3+7") with or without GO given in a fractionated schedule of 3 mg/m^2 on Days 1, 4 and 7.[18] Although remission rates were much the same in the two groups, patients given GO had lower relapse rates and significantly longer event-free (40.8% *vs.* 17.1%; *P*=0.0003) and overall survival (53.2% *vs.* 41.9%; *P*=0.03) at two years than did controls. This benefit was mainly seen in patients with better-risk disease, but not in those with poor-risk cytogenetics. A more recent study reported by Burnett and colleagues came to the same conclusion as the previous trial.[19] The United Kingdom NCRI AML16 trial randomly assigned 1115 patients (median age 67 years) with newly diagnosed AML to receive induction therapy with daunorubicin and either cytarabine or clofarabine, with or without a single dose of GO 3 mg/m^2. While there was no difference in the rate of response between the two arms, the cumulative incidence of relapse at three years was significantly reduced with GO (68% *vs.* 76%; *P*=0.007) and overall survival was improved (25% *vs.* 20%; *P*=0.05). Again, the benefit was more evident in those subsets with favorable and intermediate-risk cytogenetics. Importantly, in none of these two trials was the addition of GO associated with excess toxicity. Contrary to the design of these two trials, a sequential rather than concomitant administration of GO and chemotherapy was investigated in a study reported by the EORTC/GIMEMA consortium.[20] This randomized trial compared pre-treatment with GO (6 mg/m^2 on Days 1 and 15) before initiating induction chemotherapy with the MICE regimen (mitoxantrone, etoposide and cytarabine) in 472 patients aged 61-75 years with previously untreated AML. However, when used in this way, there was no overall benefit, but induction response and survival rates were significantly compromised with GO in patients aged 70 years or older due to excess early mortality. A randomized study from the Ulm group evaluated the effect of all-trans retinoic acid (ATRA) administered in combination with standard induction and consolidation therapy to 242 elderly patients with AML. They showed that addition of ATRA significantly improved CR rate, and event-free and overall survival in these patients.[21] A retrospective analysis of three trials by the French GOELAMS group suggested better response and survival outcomes when lomustine, an alkylating agent, was added to conventional chemotherapy for first-line treatment in older patients with *de novo* AML.[22] A confirmatory randomized study of lomustine in elderly AML is currently ongoing. The already mentioned

Table 2. Randomized trials of gemtuzumab ozogamicin (GO) in combination with conventional chemotherapy in older patients with previously untreated AML.

Trial	N. of patients (age range in years)	GO dose/ schedule	Results
ALFA-0701[18]	278 (50-70)	3 mg/m^2 Day 1/4/7 with D + A	Similar response rate Longer EFS, RFS, OS No benefit in pts with P-CG
NCRI AML16[19]	1.115 (51-84)	3 mg/m^2 Day 1 with D + A or Clo + A	Similar response rate Longer RFS, OS Less benefit in pts with P-CG
EORTC/GIMEMA AML-17[20]	472 (61-75)	6 mg/m^2 Day 1/15 with sequential MICE	Similar response rate Higher induction mortality No benefit in OS, EFS, DFS Too toxic for pts aged > 70 years

D: daunorubicin; A: cytarabine; Clo: clofarabine; MICE: mitoxantrone+cytarabine+etoposide; OS: overall survival; EFS: event-free survival; DFS: disease-free survival; P-CG: poor-risk cytogenetics; pts: patients.

NCRI AML16 trial also compared the purine nucleoside analog clofarabine (20 mg/m^2 x 5 days) against cytarabine, both in combination with standard-dose daunorubicin, in 806 patients age 56-84 years (median 67 years), but there was no evidence of clinical benefit in any risk subgroup.[23]

Postremission therapy

It is generally accepted that the ability to prolong remission and cure patients with AML depends heavily on the administration of some form of postremission therapy.[2] Standard approaches in older patients typically involve cytarabine, either alone or in combination with anthracyclines, for 1-2 cycles. However, there are no randomized trials confirming the benefit of postremission therapy in older patients. Studies of dose-escalated cytarabine in the postremission setting did not produce therapeutic benefits in these patients, and toxicity was prominent.[24,25] Some trials have also failed to show a clinical benefit with increased numbers of consolidation cycles.[26,27] Indeed, there is evidence from the French ALFA-9803 study that multiple less intensive cycles delivered on an outpatient basis may improve survival as compared to a single intensive consolidation course.[28] Randomized trials of postremission maintenance therapy with low-dose cytarabine or attenuated multi-agent chemotherapy have produced improvement of disease-free survival but not overall survival.[29,30] Recent studies of gemtuzumab ozogamicin or interleukin-2 failed to show a benefit in favor of postremission therapy.[31,32]

Allogeneic stem cell transplantation is a curative treatment option for patients with AML, but its application to the elderly population had previously been limited by high rates of transplant-related mortality caused by toxicities from traditional myeloablative conditioning regimens. However, with the use of reduced-intensity conditioning (RIC-SCT) regimens, allogeneic transplantation has become a plausible option to consider for older patients in first complete remission. As suggested by recent reports, these transplants are feasible in selected patients up to 75 years of age and may yield better outcomes than consolidative chemotherapy, but prospective trials are necessary.[33-35]

Alternative treatment approaches

Given the limited success of intensive chemotherapy in providing short- and long-term disease control, and in consideration of the fact that a substantial proportion of patients are deemed unlikely to benefit from traditional regimens based on their disease and clinical characteristics, more contemporary trials have focused on less intensive treatment approaches that may have the potential of preserving efficacy while reducing toxicity in older patients with AML. Low-intensity chemotherapy, investigational new agents, and palliative care represent the spectrum of current alternatives for these patients.

Low-intensity chemotherapy

Subcutaneous administration of low-dose cytarabine (LDAC) is a practical treatment for older patients with AML, and many uncontrolled trials have shown that useful responses, including complete remissions, are achievable with various dose schedules in approximately 15-30% of patients.[36] As part of the United Kingdom NCRI AML14 trial, 217 patients (median age 74 years) who were felt to be unfit for intensive chemotherapy were randomized to either 20 mg cytarabine twice daily subcutaneously for ten days every 4-6 weeks or hydroxyurea.[37] Treatment with LDAC did not increase toxicity and produced a higher CR rate (18% *vs.* 1%; P=0.00006) and better overall survival (P=0.0009). This was accounted for by the achievement of CR (median survival 19 months compared with 2 months in non-responders). However, patients with adverse cytogenetics did not benefit from LDAC. While the overall survival in patients receiving LDAC was still poor (median 5 months), this trial does provide a simple and tolerable low-intensity regimen that could be used as the standard comparator for randomized trials of novel agents in this group of patients. Combining LDAC with either arsenic trioxide, gemtuzumab ozogamicin, or the farnesyl transferase inhibitor tipifarnib produced no survival benefit in older patients unfit for intensive chemotherapy entered into the randomized NCRI AML16 trial ("Pick a Winner" design), although the remission rate was almost doubled with the addition of GO to LDAC (30% *vs.* 17%; P=0.006).[38-40]

Clofarabine, a 2nd generation purine nucleoside analog, has been shown to have activity in elderly AML as a single agent or in combination with cytarabine. A multicenter phase II study of clofarabine monotherapy (30 mg/m^2 daily for 5 days) in 112 previously untreated AML patients aged 60 years and over with at least one adverse prognostic feature (aged 70 years or over, performance status 2, antecedent hematologic disorder, or non-favorable cytogenetics) showed an overall response rate (ORR) of 46%, with a CR rate of 38% and a 30-day all cause mortality of 10%.[41] Interestingly, the ORR was 42% among patients with poor-risk cytogenetics and 38% for patients presenting with multiple risk factors. Median disease-free survival was 37 weeks, and median survival was 41 weeks for all patients. In two consecutive European studies of 106 untreated older patients considered unfit for intensive chemotherapy, patients were given four to six 5-day courses of single agent clofarabine (30 mg/m^2 per day).[42] Median age was 71 years (range 60-84 years), 30% had adverse-risk cytogenetics, 36% had a WHO performance score of 2 or higher, and 46% had Wheatley poor-risk disease. The ORR was 48% (32% CR, 16% CRi) and 18% died within 30 days. The median survival was 19 weeks for all and 45 weeks for those who achieved a CR or a CRi. Importantly, the ORR was consistently high in patients with adverse cytogenetics (44%), patients with secondary AML (31%), and in patients over 70 years of age (49%). While these results suggest encouraging activity in older patients with poor-risk AML, in a recently reported randomized trial of 406 newly diagnosed older patients considered unsuitable for intensive treatment, clofarabine (20 mg/m^2 daily for 5 days) has been shown to significantly improve the response rate compared to LDAC (CR+CRi 38% *vs.* 20%; P<0.0001). However, disappointingly, it did not result in a survival benefit overall, or identify any demographic or risk subgroup.[43] Since clofarabine can potentiate the intracellular metabolism of cytarabine, a study of low-intensity therapy compared treatment with clofarabine (30 mg/m^2 daily for 5 days) with or without LDAC in 70 patients aged over 60 years with untreated AML.[44] The

CR rate was significantly higher in the combination therapy group (63% *vs*. 31%; *P*=0.025), with a non-significant difference in induction mortality (19% *vs*. 31%). However, there was no difference in overall survival. An alternative approach is to take advantage of inhibiting the hypermethylation of tumor suppressor genes thought to play a critical role in the pathobiology of AML. Two hypomethylating agents, azacitidine and decitabine, have been investigated in older patients with AML who are considered not to be candidates for intensive chemotherapy. In a phase III international trial (AZA-001) comparing azacitidine (75 mg/m^2 subcutaneously for 7 days of each 28-day cycle) to conventional care regimens (CCR: doctor's choice of LDAC, intensive chemotherapy or supportive care alone) in patients with intermediate-2 and high-risk myelodysplasia, 113 patients (median age 70 years) had bone marrow blast percentages of 20-29%, which reclassified them as having AML according to the WHO criteria.[45] Although CR rates were similar for azacitidine compared to CCR (18% *vs.* 16%), azacitidine was better tolerated and resulted in a significant survival benefit (median 24.5 *vs.* 16.0 months; *P*=0.005), including higher 2-year survival (38% *vs.* 0%) in patients with adverse cytogenetics. In a phase II study of 55 older patients with untreated AML, intravenous decitabine (20 mg/m^2 daily) was administered for five days monthly until disease progression.[46] An overall response rate of 24% was reported with a 30-day mortality of 7% and a median survival duration of 7.7 months. Notably, responses were seen in all cytogenetic risk groups as well as in patients with prior myelodysplasia. In another study, decitabine was administered at a more myelosuppressive dose schedule (20 mg/m^2 daily for 10 days) to 53 patients (median age 74 years) who were unsuitable for standard chemotherapy.[47] The overall response rate was 64% (CR 47%, CRi 17%), with a 30- and 60-day mortality of 2% and 15%, respectively. Median overall and disease-free survival were 55 and 46 weeks, respectively. Responses occurred in all subgroups, regardless of age, cytogenetics, leukocyte count, and prior myelodysplasia. Recently, decitabine 20 mg/m^2 daily for five days per cycle was compared with conventional care (doctor's choice of supportive care or LDAC) in a large phase III trial of 485 AML patients aged 65 years or older who were unfit for intensive chemotherapy.[48] Treatment with decitabine resulted in a higher response rate (CR+CRp 17.8% *vs.* 7.8%; *P*=0.001) and a non-significant improvement in overall survival (7.7 months *vs.* 5 months) which, however, became significant (*P*=0.03) when more mature survival data were analyzed. Combining decitabine and azacitidine with other epigenetic modulators has been evaluated in several trials.[49-51] Generally, combined epigenetic therapy appears safe and promising, but randomized trials will be required to establish the incremental benefit of this approach on response rates and duration of survival in older patients with AML. Another strategy that is being explored is the integration of epigenetic therapy with low-intensity chemotherapy. Recently, a trial evaluating the combination of clofarabine plus LDAC followed by a prolonged consolidation alternating with decitabine reported an overall response rate of 66% including a CR rate of 58% with few early relapses (median relapse-free survival 14.1 months, median overall survival 12.7 months) in 59 older patients (median age 70 years) with newly diagnosed AML.[52] Based on these promising results, strategies of improving survival with epigenetic therapies without necessarily improving remission rates may be particularly suitable for older patients, but larger studies and long-term follow up are needed to better define the role of this treatment modality in this challenging patient population.

Novel agents

A number of investigational agents that represent alternatives to conventional chemotherapy have shown promise as first-line treatment in older patients with AML. The novel alkylating agent laromustine was reported to have significant single agent activity in 85 previously untreated older patients (median age 72 years) with poor-risk AML, showing an ORR of 32% (CR 23%, CRp 9%) and a 30-day mortality rate of 14%, following a single intravenous infusion at 600 mg/m^2. Response rates were consistent across a spectrum of poor-risk features. The median overall survival was 3.2 months (12.4 months in responders), with a 1-year survival of 21% (52% in responders).[53] CPX-351 is a liposomal formulation of a 5:1 fixed molar ratio of daunorubicin and cytarabine. Among 125 previously untreated patients aged 60-75 years who were randomized between CPX-351 (100 units/m^2 on Days 1, 3 and 5) and standard daurorubicin plus cytarabine induction chemotherapy, the rate of response was increased with CPX-351 (CR+CRp 66.7% *vs*. 51.2%), largely due to a higher CRp rate. The 60-day mortality rate was reduced compared to "3+7" regimen (4.7% *vs*. 14.6%). Interestingly, the trend towards higher response rates was observed particularly for patients with adverse cytogenetics, aged over 70 years, and secondary AML.[54] High-dose lenalidomide (50 mg/day for 28 days for two cycles) for remission induction followed by a lower dose (10 mg/day for 28 days for 12 months) as maintenance was administered to 33 untreated AML patients (median age 71 years) with intermediate- or poor-risk cytogenetics. Responses (CR/CRi) occurred rapidly in 30% of patients, and in 53% of those completing the two induction courses. Importantly, a cytogenetic remission was achieved in 4 of the 5 patients with clonal cytogenetic abnormalities at diagnosis and, similar to the experience with hypomethylating agents, no responses were noted in patients with rapidly progressing, hyperproliferative AML.[55] Sapacitabine, a novel oral cytosine nucleoside analog, has been investigated in a randomized phase II study of three different dose schedules in 105 patients over 70 years of age with AML (86 were previously untreated).[56] The dose schedule with the best efficacy profile was 400 mg twice daily for three days each week for two weeks (cycles repeated every 28 days). Among the 20 patients allocated to receive this schedule, responses were observed in 45% (6 patients had CR or CRi and 3 hematologic improvement), the 30-day mortality was 10%, and the 1-year overall survival was 30%. Randomized trials assessing sapacitabine against LDAC or decitabine are ongoing in elderly AML.

New evidence of the pathobiology and molecular background of the disease has led to the development of a number of targeted agents, and their use, either as single agents or in combination with cytotoxics, may provide us with more effective, less toxic strategies for treating older patients with AML. Tipifarnib, an orally active farnesyl transferase inhibitor, has been assessed in elderly AML, with one phase II study showing good tolerance and an overall response rate of 23% (CR rate 14%) in 158 older

Table 3. Selected targeted agents under investigation in elderly AML.

Class	Agent	Trial status
Farnesyl transferase inhibitors	Tipifarnib	Phase II/III
FLT3 inhibitors	Lestaurtinib, midostaurin, sorafenib, AC220	Phase II/III
Polo-like kinase inhibitors	Volasertib	Phase II/III
Aminopeptidase inhibitors	Tosedostat	Phase I/II
Topoisomerase II inhibitors	Voreloxin	Phase II/III
NF-kB inhibitors	Bortezomib	Phase I/II
PI3K/AKT/mTOR inhibitors	Rapalogs, BKM120	Phase I/II
Hsp90 inhibitors	Ganetespib	Phase I/II
Hedgehog inhibitors	PF-04449913	Phase I/II

patients (median age 74 years) with newly diagnosed, poor-risk AML.[57] However, in a randomized study that compared tipifarnib (600 mg twice a day for the first 21 days, in 28-day cycles) with best supportive care (BSC) for 457 older patients, there was no difference in overall survival (median of 107 days for tipifarnib and 103 days for BSC). In addition, the CR rate for tipifarnib was lower than that previously reported at 8%.[58] Activating mutations of the receptor tyrosine kinase FLT3, in particular internal tandem duplication, are identified in 20-30% of all AML patients and are associated with poor outcome.[59] Despite a strong biological rationale, studies targeting the FLT3 mutations with a number of small-molecule inhibitors (lestaurtinib, midostaurin, sorafenib) have shown modest clinical activity as monotherapy, but trials in combination with chemotherapy are underway.[60,61] Whether more selective and potent 2nd generation inhibitors will have better efficacy in FLT3 mutated AML remains to be seen, but a recently reported phase II trial of quizartinib (AC220) monotherapy in 132 patients aged 60 years or older with first relapse or primary refractory AML showed a high degree of activity in FLT3 mutated patients (n=90: CR+CRp+CRi 53%), suggesting activity also in non-mutated patients (n=42: CR+CRp+CRi 36%).[62] Further studies of quizartinib as monotherapy and in combination with other agents are ongoing or being planned in elderly AML. Volasertib is an inhibitor of Polo-like kinase 1 (Plk1) which is involved in spindle assembly during mitosis. Preliminary results from a phase II study in which 87 newly diagnosed AML patients (median age 75 years) ineligible for intensive chemotherapy were randomized to treatment with LDAC alone or LDAC plus volasertib, showed an improved complete remission rate with the combination regimen compared to controls (CR+CRi 31% *vs.* 11%; *P*=0.02). Responses with LDAC plus volasertib were observed across genetic subgroups, including patients with adverse cytogenetics.[63] A randomized phase III trial is about to start. A number of other agents that target various aspects of the leukemia cell machinery are currently under investigation, including tosedostat (an aminopeptidase inhibitor), vosaroxin (a novel topoisomerase II inhibitor), bortezomib (a NF-kB inhibitor), ganetespib (a Hsp90 inhibitor), PI3K/AKT/mTOR inhibitors, and hedgehog inhibitors (Table 3).

Conclusion

Treatment of AML in the elderly remains a challenge. A higher frequency of unfavorable biological and clinical prognostic factors, rather than age *per se*, is the major determinant for the poor outcome in this patient population. Conventional intensive chemotherapy is frequently inappropriate and unsuccessful for older patients with this disease. Therefore, treatment approaches should be personalized to the individual patient. It is becoming critically important to appropriately define and select patients who will benefit from intensive chemotherapy, and recently developed prognostic risk models can be used by physicians to guide treatment decisions. Intensive chemotherapy with curative intent should be offered to older patients who are otherwise healthy and without adverse prognostic factors, but current induction and postremission strategies need to be optimized. Patients who are unlikely to benefit from intensive chemotherapy should enter investigational trials of lower intensity or targeted therapies. After so many years of therapeutic nihilism, the development of risk-adapted and more targeted treatment approaches has introduced an era of personalized antileukemia therapy that may bring new hope to older patients with AML. In order to ensure progress continues, it is imperative that all patients be offered the opportunity to participate in clinical trials.

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