REVIEW

Induction therapy for elderly patients with acute myeloid leukemia

Mike G. Martin*, Camille N. Abboud

Section of Bone Marrow Transplantation and Leukemia, Division of Medical Oncology, Siteman Cancer Center, Washington University in Saint Louis, MO 63110, United States

Summary   Acute myeloid leukemia (AML) is a disease of older adults. Efforts to intensify therapy along traditional avenues have failed to yield improved results. There remains significant clinical equipoise as to how to ''induce'' patients and whether or not 7 + 3-style regimens improve outcomes over low-dose cytarabine. What is certain is that even in those not receiving active therapy, AML is an exceptionally morbid disease. Diverse interventions are being explored in the management of older patients with AML and the currently available data will be reviewed.
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Background

It is a misnomer to label elderly patients with acute myeloid leukemia (AML) as a subgroup. With a median age at diagnosis between 65 and 70, AML is a disease of older adults.[1] Unfortunately most of the therapeutic progress made in the past decade through intensification of therapy for AML has only been in those under 60.[2] Current management of AML in older adults is both unsatisfactory and the focus of intense research efforts. A standard of care is yet to emerge and the National Comprehensive Cancer Network (NCCN) guidelines recommend clinical trials as the first option for nearly all patients with AML over the age of 60.[3]

After age 5—10, every year of age worsens the prognosis for patients with AML.[2] In this continuum the literature has set an arbitrary cut-point of 60 years old to define ''elderly'' in respect to AML. Changes in both the host and the disease occur as patients age. They accumulate more co-morbidities and hence may have greater susceptibility to the complications of AML or its therapy. This is reflected in a ''performance status migration'', with higher proportions of older patients presenting with ECOG performance status scores greater than 2.[4]

There are also differences in the disease, not just the host, which when compounded with a diminished physiologic reserve leads to deteriorations in nearly all clinical outcomes and increases in treatment related mortality (TRM) as patients age.[4] Even when performance status, co-morbidities and disease specific variables are controlled

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* Corresponding author. Tel.: +1 314 362 9405; fax: +1 314 362 9333.
  E-mail address: mmartin@im.wustl.edu (M.G. Martin).

for, AML in older individuals is a more recalcitrant disease. The disease tends to be less proliferative with average bone marrow blast counts of 20% in those older than 60% and 40% in those younger than 60. When compared with those younger than 56, those older than 56 are less likely to have favorable cytogenetics (16% vs. 5%) and more likely to have unfavorable cytogenetics (33% vs. 50%). Furthermore the protective effect of the core binding factor leukemias on disease-free and overall survival seems to disappear in older cohorts.[4,5] MDR acts as an efflux pump for anthracyclines and its presence decreases the rate of complete responses (CR) obtained with anthracycline based regimens.[6] The rates of MDR positive blasts doubles when patients younger than 56 and older than 56 are compared (33% vs. 62%).[4] Taken together these biologic differences contribute to older patients having lower rates of CR (60% vs. 33%) with conventional 7 + 3-style induction therapy.[2] But even when a CR is obtained, DFS and OS are shorter in older than younger cohorts. In this context we will review the evidence for induction therapy in older individuals and for emerging initial AML therapies.

Should any patients over 60 receive conventional induction therapy?

The goal of induction therapy is to produce a CR, with the intention of completing the cure with some form of consolidative therapy. CR rates are significantly lower in older patients and they are significantly less durable. Median DFS sinks from ~22 months for those younger than 56 to ~7−8 months in those older than 56.[4] Median OS statistics are more dismal, with median OS for patients older than 75 years being just 3.5 months despite intensive induction therapy. Furthermore the TRM with conventional induction therapy is significant. Depending on age and performance status TRM with 7 + 3-style induction may reach 50−80%. Those who survive the induction are destined to relapse and 6-month mortality rates remain embarrassingly high and related to both disease and host factors[2,4,7] (Table 1). These results have lead to a degree of nihilism and only about 30% elderly patients with AML receive treatment.[8] Given these results, what is the evidence for induction therapy instead of low-dose therapy or best supportive care (BSC) for elderly AML?

First to try and answer this question, Lowenberg et al. randomized 60 patients 65 and older to either immediate chemotherapy with a 7 + 3-like regimen or low-dose chemotherapy and hydroxyurea for

symptom control.[9] As evidence of a selection bias they were able to achieve a CR rate of 58% with a TRM of only 10% in the intensive therapy arm. They showed an approximately 10 week advantage in median overall survival (11 weeks vs. 21 weeks) in the intensive therapy arm. Notably, patients in both arms of the study spent a similar amount of time hospitalized (~50 days). This study demonstrated two things: there is a large amount of morbidity associated with both treated and untreated AML and that a well selected group of older patients may benefit from 7 + 3-like regimens, though cures remain elusive.

A second trial reported 1 year later compared intensive induction therapy with immediate, low-dose cytarabine.[10] Of the 87 patients aged 65 and older 52% in the intensive arm achieved CR compared to 32% in the low-dose arm. There were significant differences in TRM with 31% dying in the intensive arm vs. 10% in the low-dose arm. Patients receiving intensive therapy spent more days in the hospital and had an improved median OS, 8.8 months vs. 12.8 months. The survival curves demonstrated an abrupt drop representing TRM in the intensive therapy arm but then crossed the low-dose arm from around 10 months. If TRM could be minimized and an effective consolidative regimen employed then these curves suggest a benefit for intensive therapy.

As a part of the complex UK NCRI AML-14 trial 217 patients deemed unfit for intensive induction therapy were randomized to receive either low-dose cytarabine or hydroxyurea.[11] The low-dose cytarabine (20 mg twice daily for 10 days) group produced more CRs (18% vs. 1%) and a better OS in patients that achieved a CR (80 weeks vs. 10 weeks). The median CR duration was 8 months. There was no substantial difference in toxicity and supportive care needs between the two groups. Early mortality was not trivial with 1/4 of patients in both arms dying in the first 30 days and 40% dead by 8 weeks. Notably patients with adverse cytogenetics did not benefit for treatment with cytarabine. The authors concluded that low-dose cytarabine should be the standard of care for elderly patients with AML not fit for intensive induction.

The results of the registry trial AML-97 were reported at the annual meeting of the American Society of Hematology (ASH) in 2007.[12] This trial followed 644 older patients with AML and also documented a TRM of 17% despite modern supportive care with intensive induction therapy. Patients receiving low-dose chemotherapy and BSC had median OS of 54 and 11 days respectively. The M.D. Anderson experience 998 older adults receiv-

Table 1 Median OS and 6 month mortality figures associated with various host and disease specific variables (ASH 2007; 2861)

Characteristic	Prevalence (%)	Median OS	Six-month mortality (%)
High-risk cytogenetics	12	4.8	64
Documented infection	8	4.7	63
PS >2 and age >75	7	2.9	54
PS >2	27	7.0	47
Age >75	20	7.9	42
CAD	10	6.8	43
DM	7	14.2	41
Arrhythmia	8	14.6	31
Post-MDS AML	15	10.6	29

Abbreviations: OS, overall survival; m, month; PS, performance status; CAD, coronary artery disease; DM, diabetes mellitus; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

ing intensive induction therapy for AML confirmed many of the above observations and attempted to define different prognostic groups using commonly tested variables.[13]

Taken in summary these trials all suffer from various methodological flaws but illustrate the toxicity of induction therapy in elderly patients with AML and suggest that OS can be improved over BSC and low-dose options by intensifying therapy in appropriate patients.

The more the better?

There have been many attempts to improve outcomes by intensifying 7 + 3 through adding additional agents, substituting alternative anthracyclines or dose-escalation. Despite a host of efforts, there have been no consistent, reproducible improvements on 7 + 3 in the last 25 years. Anthracycline based induction therapy offers older patients a CR rate of ~45% with an attendant TRM of 15—20%, a median OS of 8—12 months and probability of 2-year OS of 20%.[2] We will briefly review two notable, recently reported randomized trials.

The ALFA 9803 trial randomized four-hundred and sixteen patients between the ages of 65 and 85 to induction with either idarubicin (9 mg/m^2 D1—4) or daunorubicin (45 mg/m^2 D1—4) combined with a 7-day continuous infusion of cytarabine.[14] The CR rate was equivalent between the arms, though fewer patients required a second induction to achieve CR in the idarubicin arm. TRM was 10% in both arms. This trial is consistent with previously reported comparisons of idarubicin and daunorubicin in AML where idarubicin may have a small initial efficacy advantage of questionable long-term significance.

The second trial is the AML-13 trial.[15] These investigators randomized 346 patients with AML be-

tween the ages of 61 and 80 to MICE induction therapy augmented with either G-CSF priming, G-CSF rescue, both or neither. They found no convincing evidence for the utility of adding G-CSF in any fashion to standard induction therapy for older patients with AML.

Novel induction strategies

There have been various attempts to improve induction therapy either by adding novel agents to 7 + 3 style regimens or abandoning anthracycline based therapy all together. For example, the FLT3 and multi-tyrosine kinase inhibitor (TKI) lestaurtinib (CEP701) was studied as a single agent for initial therapy but produced zero CRs and the addition of the Bcl-2 antagonist oblimersen sodium to 7 + 3 failed to improve rates of CR or 1-year survival[2,16]. Likewise the addition of the MDR1 antagonists PSC-833 and zosuqidar to 7 + 3 failed to demonstrate any benefits and in both cases seemed to worsen outcomes.[17,18] In the following sections we will review therapies whose evaluation is still ongoing and that may help to redefine standard therapy for older patients with AML.

Monoclonal antibodies

Gemtuzumab ozogamicin (GO) is a monoclonal IgG4 kappa antibody which targets the CD33 antigen that is conjugated with the cytotoxic antitumor antibiotic, calicheamicin. CD33 is present on approximately 80% of leukemic blasts and both normal and leukemic myeloid CFU's.[19] Estey et al. conducted a randomized phase II trial looking at the activity of GO with or without IL-11 compared with a historic group also treated at MD Anderson

with 7 + 3 Ida.[20] Fifty-one patients were enrolled with a median age of 71 and over 50% with antecedent hematologic disorders and 30% with karotypic abnormalities of either chromosome 5 or 7. All of the patients in the historic cohort met the inclusion criteria for the GO trial. The results were disappointing with single agent GO achieving CR in just 22% of patients and providing a median OS of 8—12 weeks compared with 7 + 3 producing a 48% CR rate with a median OS of 47 weeks.

Others have attempted to incorporate GO into conventional induction strategies for elderly patients with AML. The EORTC and GIMEMA groups conducted the phase II trial AML-15. In this trial elderly patients with AML received two doses of GO at 9 mg/m^2 on days 1 and 15 to be followed in about 28 days with standard MICE induction.[21] Fifty-seven patients were enrolled with a median age of 68. With GO alone 22.8% of patients went into CR and after standard induction an additional 35.1% achieved CR. Despite the combined CR rate of nearly 58%, TRM was significant with almost 20% of patients dying from treatment related toxicities. Median DFS was 27.1 weeks and 34% of patients were alive at 1-year. AML-17 is an ongoing phase III trial looking at a lower dose of GO followed by MICE in a similar older patient population.

Finally GO has been combined with 7 + 3 Ida.[22] Investigators combined idarubicin 8 mg/m^2 IV days 1—5 and cytarabine 100 mg/m^2 CIVI days 1—7 with GO 6 mg/m^2 on day 3 in 44 patients aged 60—75 with AML with poor risk cytogenetics who were felt to be fit for traditional induction chemotherapy. The CR rate was 38% and 14% of patients had toxic deaths. Both DFS and OS data are immature. In summary, the role of the addition of GO to traditional induction therapy remains to be defined but GO alone is inferior to standard induction.

Epigenetic modifiers

Hypomethylating agents

There has been a considerable amount of recent interest in agents that modify the epigenetics changes felt to be important in the pathophysiology of AML.[23] Silencing of tumor suppression genes and loss of gene function can be the result of epigenetic changes rather than the loss of genetic material as in deletions. Such changes may be reversible using agents such as DNA methylation inhibitors and histone deacetylation inhibitors. DNA methylation occurs when a methyl group is attached to a cytosine by one of the three known active cytosine methyltransferases. Most methylation occurs in CpG islands that are associated with genes, usually in the promoters and first exons. This methylation alters the interactions between DNA and proteins, the structure of the chromatin and the transcription rate of genes. Consequently genes may be either the over-expressed or silenced depending on whether a positive or negative regulatory element is involved.

Two hypomethylating agents have been studied in AML. The first, decitabine, is an analogue of the nucleoside 2′-deoxycytidine. It is incorporated into DNA after phosphorylation and inhibits DNA methyltransferase. In addition to inducing hypomethylation it also has some cytotoxicity in rapidly dividing cells. Lubbert et al. gave decitabine at 135 mg/m^2 over 72 h to 29 elderly patients with AML.[24] This was a high-risk group with a median age of 72-years and 65% with complex cytogenetics and 51% with an antecedent hematologic illness. Fourteen percent of patients achieved a CR and the median OS was 7.5 months with 24% of patients surviving 1-year.

Cashen et al. modified the dosing schema of decitabine based on efficacy data from myelodysplastic syndrome (MDS) and delivered 20 mg/m^2 IV daily for 5 days every month to 27 patients 60 and older with de novo AML.[25] Twenty-six percent of patients had an objective response, including 46% in patients with a history of MDS. DFS and OS statistics are immature.

Azacitidine likewise has been used in AML.[26] Twenty patients were treated with 75 mg/m^2 IV daily for 7 days on a 28-day cycle. Four patients (20%) achieved a CR and an additional 40% had an objective response with 7/20 becoming completely transfusion independent. Median time to response was 3-months, consistent with the proposed mechanism of action, and the median duration of response was 8 months. Furthermore the median OS for responders was an encouraging 15 plus months compared with only 2.5 months in non-responders. TRM was reminiscent of that seen with 7 + 3 with 20% of patients dying from infections.

Histone deacetylase inhibitors

Histone deacetylase inhibitors compose the second group of epigenetic modifiers that have been tried alone and in combination in older patients with AML. Histones are proteins that interact with DNA and non-histone-proteins to form chromatin. Histone acetylation modulates chromatin topology and hence physical accessibility of genes to transcription factors and polymerases. Acetylation is controlled by the balance of histone deacetylases (HDACs) and histone acetyltransferases (HATs). Per-

turbations of the balance between HDACs and HATs leading to abnormal acetylation has been described in a variety of malignancies and associated with the abnormal expression of numerous genes including RAR-alpha, CBP, AML1, BCL6 and STAT5.[27,28] The histone deacetylase inhibitors block the removal of the acetyl groups by specific members of the histone deacetylase family leading to the opening of chromatin, allowing genes to be transcribed. In vitro these agents lead to cell cycle arrest and apoptosis.

Vorinostat (SAHA), an inhibitor class I and II HDAC enzymes, was evaluated in a Phase I trial of patients with mixed malignancies, of which 31 had relapsed/refractory AML. Though this was not a trial of elderly patients, the median age was 54, there were 2 CR, 2 CRp and 6 others with some hematologic improvement. Median time to response was 2 cycles (~6 weeks) and the median duration of response was 6 weeks.[29] As is typical with this class of agents, the predominate toxicity was gastrointestinal but ~50% of patients also experienced grade 3/4 thrombocytopenia and ~33% experienced grade 3/4 febrile neutropenia.

Another compound, panobinostat (LBH589), is being evaluated in a phase IA/II trial of patients with advanced hematologic malignancies. The median age of patients is 66 and 42 of the 77 enrolled patients have AML. The first report regarding panobinostat's activity in AML that came out of this trial w as a case report of a 60-year patient with relapsed AML who had tumor lysis.[30] Further reports from this trial have shown two CRs out of seven patients with AML and ''anti-leukemic'' activity in 4 others. On an alternative dosing schedule also being evaluated on this trial 2/2 patients with AML have experienced tumor lysis syndrome.[31] Unfortunately one of these patients has already relapsed and the other died of sepsis.

Combination therapy

Several trials have been reported and are being conducted with various combinations of these agents. Blum et al. have reported a phase I trial combining decitabine with valproic acid (VPA) in AML.[32] Twenty-five patients with a median age of 70 were enrolled. Twelve patients were treatment na and 15 had adverse cytogenetics. Four patients (16%) achieved a CR, including two on decitabine alone, and the overall response rate was 44%. Durations of responses were relatively brief, lasting 3, 3, 8, and 10 months. Toxicity was significant with 64% of patients experiencing neutropenic fevers, 48% with fatigue and 48% with infections.

MD Anderson also conducted a trial with azacitidine, all trans retinoic acid (ATRA), and dose-escalation of VPA.[33] The rational was that APL and AML cells that are resistant to the differentiation effects of ATRA regain sensitivity to it when pre-treated with hypomethylating agents and HDACs. This phase I trial enrolled 33 elderly patients with AML who were treatment na. Eleven patients (33%) experienced a CR and 3 a CRp (9%). Median duration of remission was 26 weeks and median OS was not reached. The TRM was low at 5% and grade 3/4 non-hematologic toxicity was predominantly confusion and somnolence due to the escalating doses of VPA.

Vorinostat has also been combined with decitabine in a phase I trial of patients with relapsed and refractory leukemias.[34] The median age of enrollment was 62 and there was a single CR lasting 5.5 weeks. A second, phase II trial was conducted with this combination and produced a disappointing CR rate of 4% in 27 patients with a median age of 67.

Various other trials are ongoing combining HDAC and hypomethylating agents in different regimens and with different dosing schedules in an effort to maximize clinical activity.

Novel chemotherapy agents

Two new cytotoxic agents have entered clinical trials in elderly AML. Clofarabine is a novel adenosine analogue that works through depleting the dNTP pool as well as direct inhibition of DNA polymerases and toxicity to mitochondria. As a single agent in patients older than 65, Burnett et al. showed encouraging results; 66 patients with a median age of 71% and 31% with unfavorable cytogenetics were given clofarabine 30 mg/m^2 intravenous on days 1—5 and 44% had a CR or Cri.[35] The TRM at 30 days was 21%. Median duration of remission was 6 months and median OS was 5 months. Twenty-six percent of patients were alive at 1 year. Based on these results the CLASSIC II trial is ongoing with single agent clofarabine in older patients with AML.

Others have reported trials combining clofarabine with low-dose, CIVI or intermediate dose cytarabine in older patients with AML.[36-38] DFS and OS results are maturing but the combination with low-dose cytarabine and intermediate dose cytarabine appear promising with CR rates of ~50%. The combination of CIVI cytarabine with clofarabine was poorly tolerated.

VNP40101M (Cloretazine) is a novel sulfonylhydrazine alkylating agent that is administered as a single intravenous infusion. In a phase II trial 22/44 older patients with de novo AML achieved a

CR.[39] Based on this a follow-up study enrolling patients with AML older than 60 with one of the following high-risk characteristics: age greater than 70, ECOG performance status of 2, unfavorable cytogenetics, or cardiac, pulmonary or hepatic dysfunction. Patients with prior MDS are excluded.[40] To date 80 patients have been enrolled and are evaluable. The median age is 73 and 49% of patients have unfavorable cytogenetics and 43% have ECOG performance status of 2. Twenty-five percent of patients have achieved a CR with an additional 10% with CRp. Ninety-three percent of patients that have achieved a CR did so with a single dose. ANC nadir occurs at a median of 15 days and count recovery occurs at a median of 35 days. DFS and OS data are immature. Morbidity and mortality, as one would predict based on the population being studied, has been significant. The TRM within 30 days is 15% (6 deaths from infection and 4 from progressive disease) and 24% within 42 days (7 from infection and 9 from progressive disease).

Other novel agents

Farnesyl transferase inhibitor

Farnesyl transferase moves farnesyl moieties on to cysteine residues of substrate proteins. Inhibition of this blocks post-translational prenylation and theoretically decreases production of mature proteins. Prenylation is essential to the generation of mature members of various pathways including Ras, Rho-B, Rac and Rheb as well as the centromeric proteins that interact with the mitotic spindle.[41] Tipifarnib is an orally bioavailable inhibitor of farnesyl transferase.

After encouraging results from a phase I trial where 29% of patients with AML had objective responses to single agent tipifarnib, a multi-center, phase II trial was done in elderly patients with poor risk AML.[42,43] The phase II trial enrolled 158 treatment na patients with high-risk AML characterized by a median age of 74, 47% with unfavorable cytogenetics and 75% with prior MDS. Fourteen percent of patients achieved a CR with a median duration of 7.3 months. Median OS for responders was 18 months. There were no drug-related deaths within the first 30 days though 47% of patients had serious adverse events. These grade 3/4 events were characterized by febrile neutropenia in 22% and gastrointestinal toxicity in 11%. Disappointingly, a randomized phase 3 trial comparing tipifarnib to best supportive care (including hydroxyurea) failed to show a benefit in treatment na patients 70 and over.[44]

Following these single agent studies, a trial of tipifarnib added to daunorubicin and cytarabine in patients with de novo AML older than 60 was reported.[45] Many of the results are still immature but 41% of patients achieved a CR. They reported no TRM. Other ongoing studies with tipifarnib in elderly AML include combinations with bortezomib or etoposide.

Immunomodulatory agent

The mechanism of action of lenalidomide is incompletely understood, though it is postulated to work through both antiangiogenic effects and through immunomodulation by inhibiting the secretion of pro-inflammatory cytokines and increasing anti-inflammatory cytokine secretion.[46] About 25% of patients with non-5q minus MDS will respond to lenalidomide and the majority with del(5q) will respond, including cytogenetic responses.[47,48] In the MDS trials it was noted that even patients with excess blasts could achieve a durable remission with single agent lenalidomide. Based on this investigators at Washington University are enrolling patients older than 60 with AML without changes in 5q or favorable cytogenetics. Patients are treated with single agent high-dose of lenalidomide. Fifteen patients have been enrolled to date with a median age of 71 and 1/3 with prior MDS. Nine of twelve patients have had significant reductions in day 15 bone marrow blast counts and a patient has achieved a CR.[49,50] Other centers are conducting similar, parallel trials.[51]

Small molecule inhibitors

There are several TKI's, including lestaurtinib, sorafenib and sunitinib, in various states of clinical development in elderly AML.[16,52] It is difficult to reach conclusions for many of these due to the immature of currently available results. Interestingly Boehrer et al. have recently published a manuscript on erlotinib's, a small molecule TKI of the epidermal growth factor receptor (EGFR), off-target activity in MDS and AML.[53] Interest in erlotinib in myeloid disorders arose from a case-report of a patient who presented with synchronous non-small cell lung cancer (NSCLC) and AML and was prescribed erlotinib.[54] Though the patient died from his NSCLC his AML went into CR. In vitro studies as reported by Boehrer et al. show that erlotinib induces differentiation, cell cycle arrest and apoptosis in EGFR-negative myeloblasts from patient samples and cell lines. They went on to explain a potential mechanism of action through the inhibition of JAK2 and nucleocytoplasmic translocation of nucleophosmin-1 (NPM-1) and p14ARF. Gefitinib, also an EGFR TKI, has been

shown to induce differentiation in three AML cell lines.[55] The applications of these and other like agents to therapy for elderly patients with AML presents an exciting opportunity for an advancement in the management of this terrible illness.

Conclusions and future directions

The commonly recognized poor prognosis of elderly AML has lead to years of therapeutic nihilism. Several new agents and combinations of agents are potentially promising (Table 2). We believe that the successful management of elderly patients with AML will require the use of multiple agents targeting multiple pathways. It is unlikely that a single agent or the disruption of a single pathway will yield a panacea. A successful induction strategy must first be tolerable. Unique problems with AML include that unlike other malignancies, the life expectancy of older patients with AML who opt for palliative care alone may be measured in days, not weeks or months and since it is a bone marrow intrinsic process both the disease and treatment

Table 2 Summary of currently reported activity of novel induction strategies

Agent or combination	N	Median age	AHD/ unfavourable cytogenetics	CR/CRp	Median DFS (months)	Median OS (months)	1-year OS	TRM (30 days)
Low-dose cytarabine (Burnett cancer 2007, AML-14)	217	74	40%/20%	18%/NR	8[a]	19.2[a]	NR	26%
Intensive induction (Kantajrain)	998	71	44%/54%	45%/NR	NR	5.4	30%	29%
GO +/− IL-11	51	71	69%/30%	22%/NR	NR	2	NR	37%
Sequential GO and MICE	57	68	NR/16%	35%/11%	6.3	NR	34%	14%
Concurrent GO and 7 + 3 Ida	44	NR	NR/NR	38%/NR	NR	NR	NR	14%
Decitabine 135 mg/m^2 over 72 h	29	72	51%/65%	14%/NR	NR	7.5	24%	NR
Decitabine 20 mg/m^2 D1−5	27	NR	NR/NR	26%/NR	NR	NR	NR	NR
Azacitidine 75 mg/m^2 D1−7	20	NR	NR/NR	20%/NR	8[a]	15+[a]	NR	20%
Vorinostat (SAHA)	31	54	NR/NR	6%/6%	1.5	NR	NR	0%
Panobinostat (LBH589)	9	NR	NR/NR	44%/NR	NR	NR	NR	NR
Decitabine and VPA	25	70	28%/36%	16%/NR	3[a]	NR	NR	
Azacytidine, VPA and ATRA	33	74	NR/NR	33%/9%	6.5[a]	NR	NR	5%
Decitabine and voinostat	31/27	62/67	NR for any	3% and 4% CR	NR/NR	NR/NR	NR/NR	0%/NR
Tipifarnib	158	74	75%/75%	14%/NR	7.3[a]	18[a]	NR	0%
7 + 3 and Tipifarnib	22	NR	NR/32%	41%/NR	NR	NR	NR	NR
Cloretazine (VNP40101M)	80	73	NR/NR	25%/10%	NR	NR	NR	15%
Clofarabine	66	71	NR/31%	44% (Both)	6[a]	5	26%	21%
Clofarabine and low-dose cytarabine	44	71	53%/NR	55%/NR	NR	NR	NR	17%
Clofarabine and intermediate dose cytarabine	23	68	NR/NR	50%/NR	NR	NR	NR	4%

Abbreviations: GO, gemtuzumab ozogamicin; MICE, mitoxantrone, intermediate-dose cytarabine and etoposide; Ida, idarubicin; NR, not reported; VPA, valproic acid; ATRA, all-*trans*-retinoic acid; CIVI, continuous venous infusion.
[a] Reported for responders only.

Table 3 Selected ongoing clinical trials in elderly AML

Agent or combination	Class	Phase	Population	Institution(s)
Sirolimus and low-dose aracytin	mTOR inhibitor	II	60 and older, untreated, ineligible for induction	University Hospital, Toulouse
Arsenic trioxide and low-dose cytarabine vs. cytarabine alone	HDAC inhibitor and cytotoxic	III	60 and older, untreated, ineligible for induction	Multi-center
Bortezomib and idarubicin	Proteosome inhibitor	I	60 and older, untreated, ineligible for induction	University of Kentucky
Standard induction +/− sorafenib	FLT-3 and VEGFR TKI	Randomized II	61 and older	German multi-center
MGCD0103	HDAC inhibitor	II	70 and older, treatment na, ineligible for induction	Multi-center
Imatinib and low-dose cytarabine	c-KIT TKI	II	60 and older, ineligible for induction	MD Anderson Cancer Center
Clofarabine dose-escalation with cytarabine CIVI	Cytotoxic	I/II	60 and older with treatment na disease	Multi-center
Clofarabine	Cytotoxic	II	60 and older with one adverse prognostic factor and treatment naive	Multi-center
VNP40101M	Cytotoxic	II	60 and older with one adverse prognostic actor and treatment naive	Multi-center
Tipifarnib and etoposide	Farnesyl transferase inhibitor	I	70 and older, treatment na and no WBC >30,000	Sidney Kimmel Comprehensive Cancer Center
Cytarabine and sorafenib	FLT-3 and VEGFR TKI	I/II	60 and older, treatment na, no CNS involvement	Multi-center
Temozolamide	Cytotoxic	II	60 and older, unfit for conventional therapy and either poor cytogenetics or AHD	Stanford University
Lintuzumab and low-dose cytarabine	CD33 mab	Randomized II	60 and older, treatment na, 50% blasts with CD33 and WBC less than 30,000	The Center for Hematology-Oncology

Abbreviations: AHD, antecedent hematologic disorder; mab, monoclonal antibody; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor; CIVI, continuous venous infusion; HDAC, histone deacetylase inhibitor; VEGR, vascular endothelial growth factor receptor; WBC, white blood cell count.

lead to significant amounts of toxicity through neutropenia, anemia and thrombocytopenia. In conclusion, there is much work left to be done (Table 3).

Conflict of interest

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