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The artful management of older patients with acute myeloid leukemia

Jay Yang, **Charles A. Schiffer**

Division of Hematology/Oncology, Department of Oncology, Barbara Ann Karmanos Cancer Center and Wayne State University School of Medicine, Detroit, MI 48201, USA

Abstract

Acute myeloid leukemia in older patients has historically had a dismal 10–15% long-term survival rate. Although patient frailty plays a role in this disappointing outcome, the primary driver of poor results remains the resistance of disease to current therapies. The optimal management of this difficult-to-treat disease should include a careful consideration of disease, patient and treatment factors. Disease factors include cytogenetic and molecular features and the history of an antecedent hematological disorder. Patient factors include age, performance status, comorbid conditions and individual patient preference. We favor intensive induction in most fit older patients but alternatives such as hypomethylating agents and low-dose cytarabine may be considered in patients with other comorbidities. Enrollment of patients into well designed clinical trials addressing important questions remains of utmost importance in order to advance the understanding and treatment of this disease although the best means of drug development remains a challenging dilemma.

Keywords

Acute myeloid leukemia; older; 7+3; decitabine; azacitidine; hypomethylating agents; novel agents; clinical trials

Introduction

> *If you know your enemies and know yourself, you will not be imperiled in a hundred battles; if you do not know your enemies but do know yourself, you will win one and lose one; if you do not know your enemies nor yourself, you will be imperiled in every single battle*.
>
> - Sun Tzu, ancient Chinese general and military strategist, from The Art of War

Most expositions on the topic of acute myeloid leukemia (AML) acknowledge that the prognosis for older patients is poor and tangible progress has been lacking. This is unfortunate since AML is a disease of older persons – the Surveillance Epidemiology and End Results (SEER) data indicate that the median age at diagnosis is 67 years and

CONTACT Jay Yang yangj@karmanos.org.

approximately 70% of newly diagnosed patients are 55 years or older [1]. While AML is a potentially curable malignancy, only about 10–15% of newly diagnosed patients older than the age of 60 will be long-term survivors. This is a disease population with a significant unmet medical need.

The evaluation and management of older persons with AML is hardly straightforward and many variables should be taken into consideration. They can broadly be simplified into patient, disease and treatment-related factors. It is a scenario in which the art of medicine can and should be practiced by the physician with a thoughtful consideration of the goals of treatment. We would argue that these patients would often benefit from consultation with a leukemia specialist.

7 + 3 induction – the long reigning king or the emperor with no clothes?

Since the '7 + 3' combination of cytarabine and anthracycline was introduced for AML more than 40 years ago, there has been steady progress in the survival of younger patients. While there has been incremental improvement in chemotherapy, transplant techniques, and risk-stratified therapy, much of the increase in survival is attributable to supportive care measures such as antiemetics (ondansetron), antifungal agents (azoles), and blood-banking techniques. It is likely that the limits of beneficial cytotoxic therapies have already been reached. It is hoped that the acquired knowledge of the molecular structure of AML will lead to better therapies targeting the molecular and immunologic underpinnings of this disease.

Intensive chemotherapy induction with 7 + 3 remains the standard initial approach today in older persons despite remission rates of 40–60% which are inferior to the 60–80% seen in younger persons. Remission rates will be lower still with increasing age and more adverse cytogenetics. And in those patients fortunate enough to achieve remission, remissions are often brief and the large majority will expect to have their disease relapse. This reality, along with the threat of a prolonged hospitalization of 4–5 weeks and a real induction mortality rate, has discouraged many patients and their treating physicians from embarking on this therapy.

Despite this, we still consider 7 + 3 induction to be the preferred therapy for many older patients. We look for reasons to treat rather than not to treat. 7 + 3 still produces the highest complete remission rates – an important goal since it associated with safe blood counts that preclude the need for transfusions, mitigate the risk of infectious complications, and pave the way for an improved quality of life. Remissions are also requisite for the possibility of long-term disease control and cure. It is likely that intensive chemotherapy is under-utilized. Indeed, registry data from the United States has shown that only 40% of elderly patients were given any therapy for AML but that anti-leukemia treatment was associated with improved survivals [2], results that were replicated in both Europe and Sweden [3,4].

Many clinical trials have been performed through the years with the intent on improving 7 + 3-based therapy. These trials have tested numerous combinations including dose escalations, prolongations and combinations with a myriad of additional agents such as cytotoxic drugs (thioguanine, etoposide, amsacrine), P-glycoprotein inhibitors (cyclosporine,

PSC833), growth factors and targeted agents (ATRA, TKIs) to name a few. These have largely been unsuccessful. The escalation of daunorubicin to 90 mg/m^2 per dose resulted in a higher complete remission (CR) rate and survival in younger patients but failed to do so for most older patients [5,6]. Despite the therapeutic nihilism that may exist among treating physicians, enrollment of patients into rationally designed clinical trials is paramount, although the best means to do that is debatable. Here we present real-life cases followed by discussions focusing on the issues that we consider to be most valuable.

Case 1 – know thyself (the patient)

A 78-year-old female is hospitalized due to generalized weakness and fevers. She is found to be pancytopenic with a WBC of 2100 /μL, hemoglobin of 6 g/dL, and platelets 16,000 /μL. No source of infection was found. Bone marrow aspirate confirms AML with an abnormal karyotype consisting of trisomy 10. She has a history of Parkinson's disease and stroke. Upon further questioning, Parkinson's was diagnosed more than 7 years ago due to an upper extremity tremor and has never progressed or needed treatment. Her stroke was several years ago and resulted in minimal residual right arm weakness. She was living alone and taking care of herself until her recent hospitalization.

Discussion: The definition of 'elderly' has historically been defined as greater than 60 or 65 years based on arbitrarily selected inclusion criteria of many clinical trials conducted in AML. And, although increasing age has been shown to be a remarkably consistent variable predictive of an increased risk of death, there is no dichotomous age 'cutoff', and decisions about therapy should be based on the circumstances in individual patients [7]. We discourage the use of the term 'elderly' since it connotes a patient unable to tolerate treatment [8]. We prefer to use the term older and have even coined the term 'olderly' to describe patients greater than the age of ~70 years, but who can be considered for aggressive therapies.

Ultimately, the goal of the initial patient assessment is to determine whether the patient is a candidate for disease-modifying therapies – particularly, standard intensive induction. Age and performance status have consistently been found to be the most important factors predicting for outcomes [7]. Indeed, in an older SWOG analysis, patients above the age of 75 with a performance status of 3 had an early induction mortality rate of 82%. And while those patients are clearly not candidates for intensive therapy, many other older patients are. Improvements in supportive care have clearly made intensive induction therapy safer, particularly in regard to infectious causes of death [9]. Large cooperative group trials in older patients treated with intensive induction chemotherapy are now reporting early mortality rates of around 10% [6]. These data support the notion that a larger proportion of older patients should be considered for aggressive antileukemic therapies.

More comprehensive assessments that have included multiple disease and patient-related factors have been found to better predict outcomes with therapy [10–14]. A predictive model was developed by Krug et al. using variables at the time of diagnosis that were significantly associated on multivariate analysis with CR and/or early death after intensive induction therapy. These factors included body temperature, hemoglobin level, platelet count level,

fibrinogen level, age, and type of leukemia (*de novo* or secondary) [15]. Despite the validity of these algorithms, these are complex and time-consuming and unlikely to be used by oncologists on a daily basis in the clinic, although the German AML group algorithm can be accessed online at http://www.aml-score.org. We would also stress that nothing replaces a face-to-face assessment of the patient. This 'eye test' is an important, albeit admittedly subjective, measurement for a patient's fitness level.

The patient in Case 1 was offered therapy with a hypomethylating agent (HMA) at another hospital. She sought a second opinion where 7 + 3 induction therapy was discussed and recommended. She was quoted an approximate 50% chance of remission and 10% chance of mortality with induction. Her induction was complicated by febrile neutropenia and atrial fibrillation. Her blood counts completely recovered by day 35 and a bone marrow biopsy at that time was consistent with complete remission. She was allowed an additional three weeks to improve her performance status before considering additional consolidation therapy.

Case 2 – know thy enemy (the leukemia)

A 79-year-old woman presented to her physician because of fevers and shortness of breath and was found to be pancytopenic with a hemoglobin count of 6.9 g/dL, WBC 8000/μL (65% blasts, ANC 300/μL), platelets 15,000/μL. Chest x-ray showed a left lower lobe infiltrate and she improved with antibiotic treatment and did not require supplemental oxygen. She had been living at home with her husband and managing her household activities. A bone marrow was hypercellular with >75% blasts; the karyotype was normal and molecular studies showed an NPM1 mutation.

Discussion: AML in older patients is characterized by an increased resistance to chemotherapeutic drugs resulting in lower remission rates, higher rates of relapse, and shorter durations of remission compared with younger patients. Some of this can be explained by increasing frequencies of adverse karyotypes, genetic mutations, and multi-drug resistance phenotypes. Older patients are also more likely to have AML arising out of an antecedent hematological disorder, such as a myelodysplastic syndrome (MDS) or myeloproliferative neoplasm, as well as therapy-related disease. Both are associated with poor survival rates.

Chromosomal features and molecular mutations may be invaluable in the decision-making process and should not be ignored in the evaluation of the older patient. If the clinical scenario allows, it may be prudent to wait for these results before making final therapeutic choices, particularly for patients who are unsure about whether to proceed with induction. Importantly, the diagnosis of acute promyelocytic leukemia needs to be considered and excluded given its excellent prognosis with combinations of non-cytotoxic agents [16]. Patients with adverse cytogenetics have lower remission rates and dismal long-term survivals making aggressive therapy less attractive. Conversely, patients with favorable cytogenetics, such as core binding factor (CBF) leukemias, have higher remission rates and appear to preferentially benefit from chemotherapy. Older patients with disease harboring an NPM1 mutation (particularly if FLT3-ITD negative) also appear to have both higher rates of

remission and disease-free survival with induction chemotherapy [17]. These groups of patients should be treated with intensive induction whenever possible.

The assessment for NPM1, CEBP-alpha, and FLT3 mutations in AML, particularly in AML with normal karyotype, should be considered standard. The characterization of a plethora of other genetic aberrations in an individual's AML genome is now available with advances in gene sequencing. This may be of great benefit if specific mutations or combinations of mutations are found to have significant prognostic or predictive (i.e. help direct selection of specific treatments) value. For example, AML with FLT3-ITD mutations tend to have more proliferative disease with an increased risk of relapse resulting in poorer long-term survivals [18]. There is preliminary evidence that mutations in TET2 or DNMT3A may predict for a response to HMAs such as azacitidine or decitabine [19,20]. The prognostic value of a number of other mutations is less clear, particularly considering the overlapping presence of mutations. These mutations may also provide an oncogenic target susceptible to inhibition (see discussion in the later part of the article).

Given her excellent performance status and chemoresponsive molecular subtype, the patient in Case 2 was offered 7 + 3 induction. She achieved a complete remission and was offered post remission consolidation given the long-term disease-free survival of 25+ % in older patients with NPM1 mutations.

Case 3 – know thy weapon part 1 (alternatives to intensive induction)

A 74-year-old man who was being followed without treatment for MDS for the past 4 years, is referred to you because of a recent bone marrow, done because of a decrease in hemoglobin to 11 g/dL, shows 22% undifferentiated blasts; the karyotype shows trisomy 8. His performance status is 0 but he has a history of hypertension, coronary artery bypass with approximately weekly episodes of angina, and a creatinine of 3.0. His hemoglobin is 11.1 g/dL, WBC 2200/μL with ANC of 600/uL and platelets 110,000/μL.

Less intensive therapy—Less intensive therapy seems like a logical alternative for older patients who are not good candidates for the rigors of intensive therapy. The most popular therapies include HMAs and low-dose cytarabine (LDAC). Compared with supportive care, LDAC resulted in a marginal improvement in overall survival in a randomized trial with very few, if any, long-term survivors [21]. This is a result that should not be surprising given the low remission rates (approximately 15%). LDAC remains an often-used agent in Europe while physicians in the United States have been less eager to adopt this therapy.

HMAs are considered by some to be the therapy of choice for older AML patients, despite the lack of FDA approval for this indication in the United States (although both azacitidine and decitabine are approved in Europe). Both azacitidine and decitabine have been compared in randomized trials against 'physician's choice' treatment (best supportive care, LDAC or intensive chemotherapy in the azacitidine trial) for older patients with AML [22,26]. The majority of control patients in both trials received LDAC. Neither drug showed a clinically or statistically significant improvement in overall survival. Complete remission rates with HMAs in these randomized trials were 15–20%, which is similar to LDAC and clearly inferior to intensive induction (see Table 1).

Due to the low complete response rates, the limitation of durability of responses, and the lack of efficacy from randomized trials, we reserve less-intensive therapies for patients with excessive comorbidities or a poor performance status that preclude treatment with intensive therapy. HMAs may be a more suitable option for patients with adverse cytogenetics, who typically fare poorly with cytotoxic chemotherapies including LDAC, and for those patients who prefer treatment on an outpatient basis, although multiple courses of treatment are necessary and hospitalizations for complications are still common. HMAs are likely to be even less efficacious and indeed, have not been adequately evaluated, in patients with truly proliferative AML, since patients treated on the registration trials generally had lower WBC counts (median 3100/μL). The true value of HMAs may be that its limited non-hematologic toxicity profile makes it a useful agent in combination with other novel therapies. Additive or synergistic combinations would certainly be a welcome step forward.

The diagnosis in the patient in Case 3 is now technically ‘AML’ rather than ‘MDS’ because of the increase in marrow blasts to >20%. However, this dichotomous definition is arbitrary and it is absurd to consider that patients with 19% blasts are biologically different than those with 21% blasts. The blood counts are relatively stable and in a clinically safe range and this patient certainly does not require immediate treatment. We have seen many such individuals go for weeks to months before the counts deteriorate to the point where a treatment decision is needed and, given the expected poor results with any intervention, a conservative observation approach with RBC transfusions as required, would be reasonable at this time. Inevitably, unless other medical problems intervene, a recommendation about treatment will be needed. There is no absolute answer to what should be done then, but in the interim, the patient has had the opportunity to assess the pros and cons of intervention with the assistance of the physician with whom they have established a relationship.

Case 4 – know thy weapon part 2 (consolidation and transplant)

A 71-year-old man in otherwise good health is in morphologic and cytogenetic complete remission after completing induction therapy with 7 + 3 for apparently *de novo* AML. At the time of diagnosis, his WBC was 35,000/uL, the marrow was hypercellular with >70% blasts and the karyotype was monosomy 7. He has a 57-year-old HLA identical sister.

Consolidation—Patients who achieve remission with induction chemotherapy are typically considered for consolidation therapy with cytarabine alone or cytarabine-containing regimens. The preferred dose, schedule, and number of cycles are largely unknown but patients who do not receive any consolidation invariably relapse. Seminal studies from the CALGB showed that high dose cytarabine (3 g/m^2 per dose) primarily benefitted younger patients and those with CBF cytogenetics compared with lower doses of cytarabine [26,27]. Consolidation at these lower doses is typically much better tolerated than induction therapy. For these reasons, we typically offer one to three cycles of low (100 mg/m^2/d for 5 days) or intermediate (400 mg/m^2/d for 5 days) dose cytarabine for our older patients in remission. We have alternatively used cytarabine at a dose of 1–1.5 g/m^2/d for 4–6 doses for one cycle. We reserve higher doses for those with a preserved performance status and favorable cytogenetics or mutations.

Transplantation—Unfortunately, the large majority of older patients receiving consolidation chemotherapy will eventually relapse. Allogeneic hematopoietic stem cell transplantation (HSCT) has long been considered the most potent anti-leukemia therapy due to its graft versus leukemia effect. Although HSCT clearly reduces the risk of relapse, it was previously not felt to be feasible for many older patients due to the fear of complications and treatment-related mortality. With advances in supportive care and transplant techniques, such as reduced intensity conditioning (RIC) regimens and the use of non-traditional donor sources, a larger proportion of older patients can and should be considered for HSCT.

Several non-randomized analyses of younger AML patients have shown superior survivals for AML patients with adverse cytogenetics in CR1 who receive a HSCT during consolidation when compared to chemotherapy alone [28]. There also appears to be a benefit, albeit of smaller magnitude, in AML patients with intermediate risk disease. A recent analysis focusing on patients older than the age of 60 came to a similar conclusion about the benefits of HSCT in older patients [29]. RIC has clearly made HSCT considerably safer in terms of early mortality with acceptable rates of graft versus host disease. However, this comes at the expense of increased rates of relapse compared to full myeloablative regimens [30,31]. Although randomized trials showing the benefit of HSCT would be welcome, the data support the cautious application of HSCT in older patients with AML in CR1 and selected patients should be urgently referred to a transplant center for evaluation.

Given the very poor outcome associated with monosomy 7, we would recommend allogeneic transplantation for the patient in Case 4. All of the patient's surviving siblings were older and had other medical issues and an unrelated donor search was initiated. Unfortunately, he was referred to us approximately 3 months after CR, and his leukemia relapsed shortly thereafter. This is a common scenario, and a reminder of the need to begin donor searches immediately after diagnosis in older patients who might be considered for allogeneic transplantation.

Case 5 – know thy weapon part 3 (novel agents)

A 68-year-old male was diagnosed with AML with normal cytogenetics and negative for NPM1 and FLT3 mutations. He received 7 + 3 induction achieving a complete remission. He was evaluated for HSCT but did not have a matched related or unrelated donor and transplant was deferred. He went on to receive several courses of intermediate dose cytarabine for consolidation. He remained in remission for approximately 6 months at which point his disease relapsed. Karyotyping of the leukemia now reveals several abnormalities consistent with clonal evolution of his disease. Salvage chemotherapy with both salvage combination chemotherapy and then decitabine were both unsuccessful. The patient eventually was placed in hospice and died 10 months after his initial diagnosis.

Discussion: This case highlights the all-to-familiar and frustrating outcome for the large majority of older AML patients. The field of oncology has recently seen a dizzying array of breakthroughs in the understanding and treatment of various cancers. Leading the way has been the development of targeted and immunologic agents. Why this type of progress has

not been seen in AML is multifactorial, but is largely related to a disease that is ultimately more complex than previously thought [32].

In addition to the large number of molecular abnormalities that have been described in AML, a number of these mutations may be detected in the AML genome of any one patient [33]. The importance of this is twofold: it complicates the assessment of prognosis and it has implications for targeted therapy. Perhaps it is naïve to think that any one targeted agent will be able to control a disease with multiple oncogenic driver mutations. Studies of the clonal architecture have also shown that multiple malignant and pre-malignant clones exist in any one patient with AML [34]. Even if remission is obtained, relapse may due to the reemergence of any one or more of these clones or sub-clones. In order to cure the patient of leukemia, all of the clones as well as the leukemic stem cell will need to be eradicated. It has become clear that combinations of drugs will likely be necessary.

There is a litany of experimental agents for AML in various phases of clinical development including cytotoxic drugs such as clofarabine [27] and sapacitabine [35]. Perhaps the most prominent class of experimental agents is FLT3 inhibitors [36]. A number of them have been evaluated in the clinic and have produced responses of short duration when used as single agents. The specificity, schedule, and dose of any particular FLT3 inhibitor are all important factors in maximizing efficacy and limiting toxicity of these agents. A randomized study combining sorafenib with chemotherapy was ineffective in a broad cohort of older AML patients [37] but studies in younger patients have shown clinical benefit, first with sorafenib in unselected AML patients [38] and more recently with midostaurin [39] in patients with FLT3-ITD or TKD mutations. Additional studies in older patients are ongoing.

Mutations in isocitrate dehydrogenase (IDH) result in the accumulation of 2-hydroxyglutarate, altering DNA methylation patterns and ultimately blocking myeloid differentiation [40]. Mutations in IDH1 and/or IDH2 are mutually exclusive and are found in about 20% of patients with AML. Inhibitors of IDH1 and IDH2 have shown promise with a number of durable responses seen in patients with myeloid malignancies harboring IDH mutations [41]. Even more tantalizing is the preliminary observation that this class of inhibitors may promote myeloid differentiation much in the same fashion as ATRA and arsenic trioxide in acute promyelocytic leukemia. Given these exciting results, we would advocate routinely screening for IDH1 and IDH2 mutations at the time of diagnosis. Other drugs targeting mutated oncogenes include inhibitors to KIT [42] and RAS. Novel drugs targeting non-mutated but overexpressed genes include inhibitors to BCL2 [43], polo-like kinase [44], bromodomains [45], and MDM2 [46].

Antibody-based approaches include gemtuzumab ozogamicin (GO), an antibody–drug conjugate targeting CD33 on myeloid cells [25,47]. Analogous to GO, SGN-CD33A is an anti-CD33 antibody–drug conjugate with a novel payload (pyrrolobenzodiazepine) which is currently being tested in Phase I and Phase II studies [48]. Novel antibody-based approaches targeting CD33 or CD123 include naked antibodies, antibody–drug conjugates and various forms of bispecific antibodies. Although promising, these therapies targeting myeloid stem cell or progenitor cell antigens may be limited by prolonged and profound cytopenias due to the inhibition of myelopoiesis. Immunologic therapies including chimeric antigen receptor

modified T cells (CAR T-cells) and checkpoint inhibitors (i.e. PD1 or PDL1 inhibitors) are just now making their way into clinical trials.

Case 6 – a discussion on clinical trial design

A 58-year-old was diagnosed with AML when she presented with profound fatigue, a hemoglobin count of 6 g/dL and a WBC count of 14,000/μL with a large percentage of circulating myeloid blasts. Bone marrow examination confirmed *de novo* AML with normal cytogenetics. She was placed on a large cooperative group clinical trial comparing chemotherapy plus or minus gemtuzumab ozogamicin during induction and consolidation [49]. She was randomized to receive GO and achieved a complete remission which was then followed by three courses of high-dose cytarabine consolidation. She remains in remission seven years later.

Although not technically an ‘older’ patient, this case highlights some of the difficulties in conducting clinical trials in AML. This was a typical Phase 3 AML study with a large number of patients (>600). The lack of any recently FDA-approved therapies for non-M3 AML is rather remarkable. This is even more so considering the large number of clinical trials requiring the accrual of a large number of patients completed during this time. The lack of progress makes one wonder whether there is a flaw in the current approach to drug development and whether there can be a more efficient design to clinical trials.

Gemtuzumab ozogamicin was granted accelerated approval by the US FDA in 2000 based on encouraging Phase 2 results [47]. However, based on the negative results of the aforementioned randomized Phase 3 trial, the drug was withdrawn from the market in 2010 [49]. A number of additional Phase 3 trials have since been reported which have shown a benefit to GO when combined with chemotherapy in patients with favorable-risk cytogenetics and perhaps intermediate-risk cytogenetics [50]. More than 15 years and thousands of clinical trials patients since the drug was used in its first patient [47], the drug remains in regulatory limbo as many experts have clamored for its availability. This is not a saga that we would like repeated for any future promising drugs.

Randomized Phase 3 trials are costly, require large numbers of patients, and have largely been negative in the past 3 decades. Randomized Phase 2 trials with the ability to compare a number of novel agents to a standard comparator have been suggested. Within this context, if a novel agent meets a certain prespecified endpoint then the cohort can be rapidly expanded. This so-called ‘pick a winner’ approach efficiently tests a larger number of drugs in a shorter period of time and has the potential to more quickly identify drugs that appear promising [51]. This may be particularly important in AML given its molecular heterogeneity since targeted therapies will likely need to be applied to small, specific groups of patients, making randomized trials almost impossible to perform. This approach has already been applied in the UK with some success [52].

Expert Commentary and Five-Year View

The next five years promises to be an exciting period in the understanding of the biology of AML and MDS. Methodological advances in gene sequencing will allow for the rapid genetic characterization of an individual’s AML. The hope is that this knowledge will

translate to the proper selection of effective targeted therapies. The complex biology of this disease makes it likely that combinations of novel agents will be necessary to target multiple molecular aberrancies and multiple disease clones. For example, the ‘positive’ trials with FLT3 inhibitors produced relatively modest incremental improvements and although more potent inhibitors are being evaluated, it is likely that inhibition of this target alone will not be sufficient, particularly in older patients in whom other mechanisms of drug resistance are operative.

AML/MDS in older patients can be thought of as a disease of myeloid stem cells with exaggeration of the survival signals which permit these and the stem cells of other organs to escape the ravages of exposure to naturally occurring toxins. Indeed, *in vitro* studies demonstrate overexpression of virtually all mechanisms of resistance to cytotoxic agents, particularly in cells from older patients. Drugs which affect the antiapoptotic effects of p53 mutations and overexpression of the bcl-2 pathways might be of particular interest in this regard. Perhaps most promising, as evidenced by advances seen in patients with malignant melanoma and lung cancer, are treatments designed to break down the immune tolerance which permitted the proliferation of the malignant clone in the first place. The potent effects of the graft versus leukemia effect from allogeneic transplantation provided proof of principle in hematologic malignancies many decades ago. These immunologic tools are being developed and modified rapidly and are at the forefront of new therapies for cancers in general. Whether the AML progenitor will be a suitable target remains to be seen, but in our estimation, this is now the most exciting new approach which can be applied broadly to AML and not just to patients with particular mutations. It is likely that such approaches will be most effective at times of lower leukemic burden and hence, it is unlikely that 7 + 3 or other cytotoxic therapies will be replaced anytime soon.

In the interim, AML in older individuals remains a difficult challenge requiring thoughtful decisions by experienced clinicians and informed patients. The cases presented are typical of the problems in this important group of patients and demonstrate that such patients require individualized recommendations which take into account the biology of the AML and most critically, their unique social and medical circumstances.

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Key Issues

- AML in older persons has a poor prognosis.
- The optimal management of AML in older patients requires a thorough and thoughtful evaluation of patient, disease, and treatment-related factors.
- Intensive induction (7+3) should be considered the default therapy for selected patients as the risk of induction death is not as high as previously expected.
- Those who are not candidates for 7+3 can be considered for less intensive therapies including HMAs and LDAC although these are, at best, palliative in nature.
- Effective novel therapies are urgently required but considerable obstacles to drug development and clinical trials remain.

Table 1.

Reported complete remission (CR) rates for previously untreated older AML patients from selected phase 3 trials.

Study author	Treatment	Number of patients	Median WBC (per μL)	Early death (at 30 days)	CR (not including CRi)	OS
Lowenberg [6]	7 + 3	813	34% of patients with >20,000	11%	54–64%	Approx 12 mo
Burnett [21]	LDAC	103	NR	26%	18%	<6 mo
Dombret [22]	Azacitidine	241	3100	8%	20%	10.4 mo
Kantarjian [23]	Decitabine	242	3100	NR	16%	7.7 mo
Burnett [24]	Clofarabine	200	4600	18%	22%	<6 mo
Amadori [25]	Gemtuzumab ozogamicin	118	NR	11%	15%	4.9 mo

CR – Complete Remission; CRi – Complete Remission with incomplete hematological recovery; OS – Overall survival; NR – Not reported.