Current Oncology Reports (2019) 21: 71
https://doi.org/10.1007/s11912-019-0823-1

GERIATRIC ONCOLOGY (AR MACKENZIE, SECTION EDITOR)

Acute Myeloid Leukemia: Update on Upfront Therapy in Elderly Patients

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Published online: 27 June 2019

Abstract
Purpose of Review Acute myeloid leukemia (AML) disproportionately impacts elderly patients. Treating elderly patients with AML has been a challenge due to the increased prevalence of medical comorbidities and decreased performance status in this population, as well as the different biology of AML in elderly patients.
Recent Findings The care of elderly patients with AML has advanced significantly over the past few years. Our greater understanding of the biology of AML in elderly patients has led to the development of novel, lower-intensity treatment options. We present here a review of the most recent literature regarding therapeutic options available to older patients, as well as tools to help identify the right treatment for the right patient.
Summary As targeted and lower-intensity treatment options become available, developing an approach to "right size" therapy for individual elderly patients is paramount.

Keywords Acute myeloid leukemia · Elderly AML · Upfront therapy · Secondary AML · Therapy-related AML

Introduction

Although acute myeloid leukemia (AML) can be seen at any age, the disease has a disproportionate impact on elderly patients. The median age of new patients at diagnosis is 68 years with more than half (57.4%) of the newly diagnosed aged 65 or older [1]. Historically, the treatment of elderly patients with AML has been a challenge because of the increased prevalence of medical comorbidities and decreased performance status in this population, as well as the different biology of AML in elderly patients.

In contrast to the preceding decades, the care of elderly patients with AML has advanced significantly over the past few years. As newer, targeted treatment options become available, as well as those that do not involve traditional "high-dose" strategies, developing an approach to "right size" therapy for individual elderly patients is paramount. We present here a review of the most recent available literature regarding therapeutic options available to older patients, as well as tools to help identify the right treatment for the right patient.

This article is part of the Topical Collection on *Geriatric Oncology*

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Approach to Elderly Patients with AML

The population of patients over age 60 with AML is a heterogeneous group. While performance status may decrease with chronologic age, a patient's "biological age" and ability to tolerate intensive chemotherapy aimed at remission induction may vary significantly between adults born in the same year. For this reason, development of a standardized treatment approach for older patients has been controversial. The following questions have been suggested previously [2] when developing a treatment plan for elderly patients with AML:

1. Which patient of an older age can receive intensive treatment and not experience prohibitive toxicity?
2. Even in those who can tolerate such chemotherapy, would disease features make the likelihood of benefit so low that nonintensive therapy would be a better option?

Answering the first question requires tools to stratify elderly patients based on risk. Answering the second question requires understanding the biology of AML in elderly patients. As our ability to answer these questions improves over time, our ability to assign the right treatment to the right patients will also improve.

Development of Risk-Assessment Tools

Predictive models to identify patients at highest risk of adverse outcomes with intensive remission-induction therapy have been proposed [3]. These tools have included assessment of age, karyotype, ECOG performance status, and medical comorbidities. One such tool, the hematopoietic cell transplantation comorbidity index (HCT-CI), has been evaluated for its predictive ability for outcome in elderly patients with AML prior to transplant. Those patients with a score > 2 prior to induction have been shown to have lower remission rate, increased early mortality, and decreased survival [4, 5].

Clinical calculators [6, 7] have also been developed to help practitioners navigate the complex risk differential of treatment-related and disease-related mortality. Authors here suggest that standard induction therapy is reasonable for two groups of older patients [1]: those with good functional status (ECOG PS 0–2), minimal comorbidities, and good risk cytogenetic and molecular profiles; and [2] those with high (> 50,000/microL) or rapidly rising blast count who are at risk for leukostasis or tumor lysis syndrome and require timely cytoreduction that low-intensity options cannot provide. Conversely, these authors have suggested that older patients with unfavorable-risk cytogenetic and molecular features who are medically unfit due to ECOG PS > 2 or significant comorbidities should be treated with low-intensity regimens [8].

More recently, the use of geriatric assessment tools, including assessment of physical and cognitive function, has been shown to further refine the ability of predictive models to better understand the relationship between poorer performance status and decreased overall survival with patients who screened positive for cognitive impairment or who had objectively measured impaired physical function having significantly higher risk of death (HR 2.5 and 2.2, respectively) [9]. Studies evaluating the utility of geriatric interventions targeting vulnerabilities identified during a geriatric assessment are ongoing [10].

Understanding the Biology of Disease

In general, AML in elderly patients is more likely to be preceded by myelodysplastic syndrome, to have unfavorable cytogenetics, to exhibit multi-drug resistance, and to be refractory to chemotherapy [11, 12]. While it is not yet clear the extent to which each of these factors impacts survival or what additional factors contribute, increasing age contributes significantly to the biology of AML. In one analysis of 968 adults with AML who received intensive induction therapy, CR rates decreased consistently from 65 in patients aged < 56 to 33% in patients aged 75 or greater. Similarly, among those achieving remission, DFS decreased from 21.6 to 8.9 months, respectively, and OS for all patients decreased from 18.8 to 3.5 months, respectively [11].

Cytogenetic Abnormalities and Age

In an analysis of two SWOG trials [11], the percentage of patients age > 75 years with favorable-risk cytogenetics was only 4%, while poor-risk cytogenetics were seen in 51% of patients in this age group. In contrast, 17% of patients age < 56 years were found to have favorable-risk cytogenetics and only 35% had poor-risk cytogenetics. The adverse cytogenetics observed in older patients primarily consisted of loss of all or part of chromosomes 5 or 7. Even in each cytogenetic risk group, treatment outcomes were found to decrease with age, although the degree of difference in outcome between older patients and younger patients was much more significant in the favorable-risk group than the unfavorable-risk group. Complex karyotype has also shown to increase significantly after age 60, indicating that multiple genetic events, including epigenetic events, may contribute to the development of AML over a patient's lifetime [12]. The presence of any type of monosomy confers a poor prognosis. In those patients with two or more autosomal monosomies or one autosomal monosomy in combination with at least one other structural chromosomal abnormality, 4-year overall survival is only 4% [13].

Molecular Abnormalities and Age

The genetic diversity of AML is only beginning to be understood, but much progress has been made in the last decade. Many studies have evaluated the prevalence and prognostic impact of specific genetic alterations in elderly patients with AML. In a landmark publication, Papaemmanuil et al. identified thousands of driver mutations across more than 70 genomic regions [14••]. Interestingly, this analysis showed that the number of driver mutations, independent of a patient's age and total white blood cell (WBC) count, correlated with overall survival, suggesting that age may be a surrogate for the collection of mutations that develop in the hematopoietic lineage over time. With regard to historically favorable-risk prognostic markers, the proportion of patients who harbor an isolated *NPM-1*, which is associated with good prognosis in the absence of co-occurring *FLT3-ITD* mutation, tends to decrease with age after age 60 [12, 15]. Unlike younger patients, while older patients with *NPM-1* mutation who are *FLT3-ITD* negative tend to have higher complete remission (CR) rates, they do not experience a concordant increase in disease-free or overall survival [16]. In contrast, the proportion of patients

with biallelic CEBPα mutation does not appear to correlate with age [15].

Conversely, a higher proportion of elderly patients tend to harbor mutations associated with poorer prognosis. These include *ASXL1*, *TET2*, and *DNMT3A*. The *ASXL1* mutation is five times more common in patients > 60 years old than those younger than age 60 and is associated with poorer CR rates as well as decreased disease-free, event-free, and overall survival in patients who are otherwise classified in the ELN favorable-risk group [17]. The *TET2* mutation is also more prevalent in patients > 60 years of age, where it is observed approximately one fourth of the time, compared with younger patients, where it is observed < 10% of the time. In patients of all ages with intermediate-risk cytogenetics, the presence of *TET2* mutation portends a shortened overall survival [18]. While mutation in *DNMT3A* is present in approximately one third of patients both older and younger than 60 years of age with de novo, cytogenetically normal AML, the type of *DNMT3A* mutation impacts survival differently depending on a patients' age. In older patients, this mutation is known to have poor prognostic significance [19]. Older patients with R882-DNMT3A have significantly shorter disease-free (3% vs. 21% at 3 years) and overall (4% vs. 24% at 3 years) survival rates. This same variation was not seen with younger patients with *R882-DNMT3A* mutation. *R882-DNMT3A* mutations were associated with a 76% increased risk of death after adjusting for *NPM1* and *FLT3-ITD* mutation status [18].

Certain genetic mutations are highly specific for secondary AML. These include mutations in *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, or *STAG2* [20]. When these mutations occur in patients with treatment-related AML or de novo AML, the clinicopathologic features of the patient's disease and clinical course are similar to patients with secondary AML where prognosis and response to therapy are often poor [20].

Pre-Treatment Evaluation

Prior to selection of initial therapy, assessment of the following should be performed for all elderly patients with AML.

Patient Evaluation

A thorough assessment of a patient's comorbid conditions; performance status; baseline organ function; and psychosocial factors, including cognitive ability and social support should be performed on all patients. Concomitant nutritional deficiencies which may impact cytopenias should be assessed at baseline. A thorough medication review with particular attention to drug-drug interactions is essential.

Disease Evaluation

Diagnostic studies, including bone marrow aspirate and biopsy and immunophenotype by flow cytometry, should be reviewed and confirmed by an expert hematopathologist. Evaluation for cytogenetic abnormalities via karyotype and fluorescence in situ hybridization and evaluation for molecular aberrations should be performed in all patients at the time of diagnosis to guide prognosis and treatment strategy. While a multigene panel looking for the 70+ common mutations in AML is strongly preferred, mutational testing must include evaluation of *FLT3-ITD*, *IDH1*, and *IDH2* at a minimum, so that appropriate therapy may be selected.

Upfront Treatment

Selection of Initial Therapy

Until recently, options for standard of care upfront treatment for elderly patients with AML consisted of standard induction therapy with high-dose chemotherapy with continuous-infusion cytarabine and an anthracycline ("7+3") for patients who were deemed "fit," or, lower-intensity treatments such as single-agent hypomethylating agents, low-dose cytarabine (LDAC), or supportive care only for patients who were deemed "unfit." [8] Improved data on risk stratification and the development of novel combinations of therapies over recent years have begun to shift this paradigm.

In contrast to patients < 60 years of age, where CR rates to intensive induction therapy range from 60 to 85%, due to many of the patient- and disease-related factors described previously, patients > 60 years of age have sub-optimal complete response rates in the range of 40–60% [21]. This is not to say that older patients should not receive standard induction therapy. To date, it has been shown that induction chemotherapy can provide a survival advantage for elderly patients [22, 23], even in select patients > 80 years of age [24], and remission induction followed by allogeneic stem cell transplant in first CR for patients remains the only known path to cure for patients with non-favorable-risk AML. However, as a result of concerns regarding efficacy and toxicity, < 40% of patients age 65 or over receive treatment with chemotherapy [3].

While the previously discussed tools can assist in determining the most appropriate upfront therapy, establishing the goal of treatment at the time of diagnosis is paramount. Importantly, not all elderly patients may value "cure;" a goal of prolonged disease control that maximizes quality of life may be reasonable for some patients. As more novel treatment approaches become available, the ability to control a patient's disease with limited side effects and logistical impact on their daily life has significantly increased.

High-Intensity Regimens

Standard Induction Therapy

Standard induction therapy consists of 7-day continuous infusion of cytarabine 100 mg/m^2/day and 3 days of anthracycline. The choice of anthracycline (daunorubicin vs. idarubicin vs. mitoxantrone) is thought not to impact CR rates [8], but the ALFA-9801 trial did show superiority for idarubicin compared with daunorubicin 80 mg/m^2/day in patients age 50–70 years. Whichever anthracycline is chosen, the optimal dose should be used, either daunorubicin 60 mg/m^2/day or 90 mg/m^2/day, idarubicin 12 mg/m^2/day, or mitoxantrone 12 mg/m^2/day, as dose reductions have been shown to decrease response rates with similar toxicity profile [25]. With this therapy, the response rate for elderly patients (which was variably defined in different analyses) is approximately 30–40%.

The goal of standard induction therapy is remission-induction. If cure remains the goal following remission-induction, patients who achieve a CR should go on to receive consolidation therapy with chemotherapy or reduced intensity conditioning allogeneic stem cell transplant.

CPX-351 (Vyxeos) for Secondary AML or Treatment-Related AML

Vyxeos is a liposomal encapsulation of cytarabine and daunorubicin in a synergistic 5:21 M ratio, which is thought to target leukemic cells to a greater extent than normal bone marrow cells. Based on results of a randomized phase II study in patients age 60–75 with treatment-naïve AML which showed improved overall and event-free survival in patients with secondary AML (s-AML), [26] a phase III trial was performed to compare traditional "7+3" induction regimen to Vyxeos in adults age 60–75 with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplastic-related changes (AML-MRC) and ECOG POS of 0–2 [27••]. Patients could receive up to two induction cycles with Vyxeos to obtain response. The median age was 67 years with approximately 1/3 of patients in each group age 70–75 years and more than half of the patients in both groups had unfavorable-risk cytogenetics. Adverse effects were similar between the two groups with the most common being febrile neutropenia (68.0% vs. 70.9%). The median time to count recovery was longer in the Vyxeos group who achieved CR or CRi (35.0 and 36.5 days, respectively) vs. the 7+3 group (29 days). Compared with the 7+3 group, the Vyxeos group experienced decreased 30- and 60-day mortality (5.9% and 13.7%, respectively in the Vyxeos group vs. 10.6% and 21.2% respectively in the 7+3 group, although neither difference was statistically significant), greater overall remission rate across all AML subtypes (CR + CRi) (47.7% vs. 33.3%), improved median survival (9.56 months vs. 5.95 months, HR 0.69), and improved 1-and 2-year survival rates (1-year survival 41.5% vs. 27.6% and 2-year survival 31.1% and 12.3%). Importantly, this survival difference was seen irrespective of patients' age, based on pre-planned subgroup analysis.

Hypomethylating Agents + Venetoclax

It has recently been recognized that inhibition of the BCL-2 (B cell lymphoma-2) pathway has an important therapeutic role in the treatment of AML [28••]. Clinically, the addition of venetoclax, a potent BCL-2 inhibitor, to hypomethylating agents has shown promising results. Azacitidine and decitabine have been safely and successfully combined with venetoclax in a phase 1B study in elderly AML [29]. Although this data is non-randomized, the CR rates with this combination in elderly patients reached 27–35% with overall response rates of 59–65%. Subsequent analysis has shown the median overall survival of patients in this group to be 17.5 months. Importantly, rates of adverse effects are comparable with those of single-agent hypomethylating agents [30].

Based on these promising data and limited success with single-agent hypomethylating agents (as below), many providers are offering either azacitidine or decitabine with venetoclax upfront for patients who may not be considered eligible for "7+3" but who still desire cure. Randomized trials are ongoing, as are trials using venetoclax in combination with other induction regimens and with other novel agents in the relapsed and refractory setting [31].

Addition of Midostaurin to Standard Chemotherapy for FLT3-ITD-Mutated Patients

Midostaurin is a multi-targeted oral kinase inhibitor with activity against *FLT3* which has been approved for treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3-ITD positive. This is given in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation [32] based on the results of a phase III, double-blinded, randomized, placebo-controlled trial [33] comparing standard induction therapy with cytarabine and daunorubicin followed by high-dose cytarabine consolidation plus midostaurin or placebo. This study showed improved event-free (HR 0.78) and overall survival (HR 0.78) in the midostaurin group. Toxicity profiles were similar between the two groups. Whether or not this benefit holds true for older patients with *FLT3-ITD* positive AML is not known, as this study excluded patients > 59 years of age.

Lower-Intensity Regimens

In contrast to higher-intensity regimens, the goal of lower-intensity regimens is palliation of symptoms, disease control,

and improved quality of life with the hope of prolonged survival.

Single-Agent Hypomethylating Agents

Azacitidine and decitabine are hypomethylating agents that inhibit DNA methyltransferase and are approved for the treatment of MDS and AML as single agents or in combination (as above).

Azacitidine was studied in the phase III setting in patients age 65 years or older (median 75 years) with AML (with 30% or greater bone marrow blasts) in the AZA-AML-001 study. Patients with intermediate- or poor-risk cytogenetics and ECOG performance status (PS) 0–2 were randomized to azacitidine 75 mg/m [2] subcutaneously days 1–7 of a 28-day cycle vs. conventional care (either induction chemotherapy, LDAC or best supportive care). While overall response rates were similar (27.8% vs. 25.1%), compared with conventional care, treatment with azacitidine resulted in prolonged median overall survival by 3.9 months (10.4 vs. 6.5 months), particularly for patients with MDS-related changes (12.7 months vs. 6.3 months). There was no difference in 30- and 60-day mortality and, importantly, toxicity was comparable between the two groups.

Phase II data from patents greater than 60 years of age (mean 74 years) with newly diagnosed AML who were treated with decitabine 20 mg/m [2] for days 1–5 of a 28-day cycle showed a CR rate of 24% and overall survival of 7.7 months. This included patients with poor-risk cytogenetics or antecedent MDS [34], .From these promising data, a randomized, phase III trial was performed. In this study [35], patients age 65 and older (median 73 years) with AML with intermediate- or poor-risk cytogenetics and an ECOG PS of 0–2 were randomized to receive decitabine vs. patient choice of LDAC or supportive care. Here, decitabine significantly improved the CR rates compared with patient-choice treatment (17.8% vs. 7.8%), and a subsequent unplanned analysis of mature survival data showed a small but statistically significant improvement in OS (HR 0.82, 95% CI 0.68–0.99, $p = 0.037$). A randomized, phase II trial comparing decitabine on a 10-day vs. 5-day schedule in elderly or unfit patients with AML is ongoing (NCT01786343) [31].

Low-Dose Cytarabine

Prior to the development of hypomethylating agents, low-dose cytarabine (LDAC, 20 mg subcutaneously twice daily for 10 days every 4–6 weeks) was compared with hydroxyurea in patients age 51–90 (median 74 years) deemed unfit for standard chemotherapy [36]. As would be expected, LDAC showed an improved remission rate (18% vs. 1%) and improved overall survival (OR 0.60). Notably, this benefit was most seen in patients with favorable- or intermediate-risk cytogenetics (OR 0.54, 95% CI 0.36–0.82) and not observed in patients with poor-risk cytogenetics (OR 1.30, 95% CI 0.68–2.47). Median disease-free survival for those patients who achieved CR in the LDAC group was 8 months. The 30-day mortality in this group remains high at 26%. It is important to note that a significant number of patients included in this study had secondary AML (27%). The benefit was primarily seen in patients with de novo AML (OR 0.48, 95% CI 0.32–0.72) compared with secondary AML (OR 0.69, 95% CI 0.38–1.24)

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is a humanized monoclonal anti-CD33 antibody-drug conjugate with DNA-intercalater calicheamicin which targets AML blasts. It was initially approved based on phase II data showing a response rate of approximately 30% when used as a single agent for initial treatment of AML in patients unfit to tolerate intensive chemotherapy [37]. Use of GO fell out of favor when subsequent studies showed decreased benefit and increased toxicity, particularly in the older patient population [38, 39]. A subsequent phase III study of patients age 61 and older [40] utilizing an alternate dosing schedule in patients age 61 and older compared with best supportive care (BSC) showed significantly improved overall survival (HR 0.69), with the benefit increased in patients age 76–80 (HR 0.66) and 81 years or older (HR 0.55) and in those patients with favorable- or intermediate-risk cytogenetics. No improvement in OS was seen in patients with poor-risk cytogenetics. However, the absolute benefit was small (4.9 months vs. 3.6 months). Single-agent GO has never been compared head-to-head with other upfront options for elderly patients deemed unfit for induction chemotherapy, such as low-dose cytarabine (LDAC) and hypomethylating agents, but the above data is not promising. The addition of GO to LDAC improved response rates but did not significantly prolong overall survival in older patients with AML [41].

The addition of GO to induction chemotherapy has also been studied in a number of clinical trials. A recent meta-analysis of five randomized trials found that the addition of GO to induction therapy reduced the risk of relapse and improved survival in both younger and older patients with favorable- and intermediate-risk (OR 0.47 and 0.84, respectively) but not poor-risk cytogenetics (OR 0.99) [42]. The overall CR rate was 25% with 15.3% of patients achieving CR and 11.7% achieving CRi. Overall survival was 8.2 months for patients achieving CR and 5.8 months for patients with lesser responses.

GO has been studied in combination with azacitidine in elderly patients in the phase II setting and results have been encouraging in poor-risk patients (defined as patients 70 years or older with an ECOG performance status of 2–3) [43]. Here,

35% of patients achieved CR or CRi and median overall survival in this group was 11 months. A phase III trial of this combination is planned.

Targeted treatments for IDH1- or IDH2-mutated patients

Ivosidenib and enasidenib are oral small molecule inhibitors which have shown single-agent efficacy in patients harboring isocitrate dehydrogenase-1 and -2 (*IDH1* and *IDH2*) mutations, respectively. In a phase I/II, first-in-human study, ivosidenib was administered to patients 18 years or older (median 68, range 18–89) with ECOG PS 0–2 with advanced hematologic malignancies with *IDH1* mutation. Overall, the drug was found to be well-tolerated. Differentiation syndrome occurred in 10.6% of patients. Treatment resulted in an overall response rate of 41.6% and CR or CRh in 30.4% with a median duration of response of 8.2 months [44•]. Similarly, enasidenib was studied in patients 18 (median 70, range 19–100) years or older with mutant-*IDH2* advanced myeloid malignancies and ECOG PS 0–2 in a phase Ib/II study with a dose escalation phase followed by an expansion phase [45•]. The most common treatment-related adverse effect was indirect hyperbilirubinemia. Differentiation syndrome was observed in 6% of patients. The overall response rate was 38.5% and the median overall survival for patients with relapsed/refractory AML was 9.3 months with an estimated 1-year survival of 9.3 months.

While ivosidenib and enasidenib were not specifically studied in the elderly patients, they are well-tolerated options for elderly patients who are not candidates for or who prefer not to receive more intensive regimens. Studies combining these agents with induction chemotherapy and hypomethylating agents are ongoing.

Conclusions

In contrast to the preceding decades, the landscape of options for upfront therapy for elderly patients with AML is changing rapidly. The lines between the historic dichotomies of "fit" versus "unfit" and "younger" versus "elderly" are blurring as the toxicity profiles of newer regimens improve. Even so, the nuances of treating elderly patients with AML persist with the continually expanding arsenal of treatments available. The challenge of "right-sizing" treatment for elderly patients so as to maximize benefit while minimizing toxicity and impact on quality of life is ever more present.

Compliance with Ethical Standards

Conflict of Interest Gina Keiffer declares that she has no conflict of interest.

Neil Palmisiano has received research funding support from AbbVie.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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