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Emerging therapeutic modalities for acute myeloid leukemia (AML) in older adults

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Abstract

Treatment for the older adult with acute myeloid leukemia (AML) is challenging, due to both more aggressive disease biology as well as patient-related risk factors that limit tolerance of intensive chemotherapy. The use of prognostic models and comprehensive geriatric assessments can help hematologists evaluate the suitability of intensive chemotherapy for individual patients. For older patients considered fit for intensive chemotherapy, standard induction therapy should be given, followed by consideration of reduced intensity allogeneic stem cell transplantation. Patients considered unfit for intensive therapy are standardly treated with hypomethylating agents. Several new therapeutic agents have shown promising results either by improving intensive chemotherapy (CPX-351), by improving upon lower intensity therapy (venetoclax, antibody drug conjugates), or by targeting somatic mutations (FLT3 inhibitors and others).

Keywords

Acute myeloid leukemia; Older adults; Induction chemotherapy; Hypomethylating agents; Novel agents

1. Introduction

Acute myeloid leukemia (AML) is a disease of older adults, with a median age of diagnosis of 67 years and one third of patients aged ≥ 75 years [1]. Increasing age has been associated with higher treatment-related mortality (TRM), lower complete remission (CR) rates, higher relapse risk, and shorter overall survival (OS) [2–4]. Concerns about poor efficacy and high toxicity contribute to less than half of patients with newly diagnosed AML aged ≥ 65 receiving any chemotherapy in the US [5].

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Concept and design: R. Olin.
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Analysis and interpretation of data: R. Olin and L. Huang.
Manuscript writing and approval: R. Olin and L. Huang.

2. Risk Stratification

Poor outcomes in older patients are a result both of disease biology and patient characteristics. Older patients have a higher incidence of secondary AML and unfavorable cytogenetics. Older patients with favorable cytogenetics have worse prognosis than their younger counterparts [2,6]. Leukemic blasts in older patients are also more likely to be resistant to chemotherapeutic agents due to higher expression of the multidrug resistance geneMDR1 [7]. In addition to more aggressive disease biology, many older patients with AML tolerate chemotherapy poorly, due to comorbidities including age-related renal and hepatic dysfunction. Geriatric syndromes such as functional impairment, cognitive impairment, and polypharmacy also influence treatment decision-making.

2.1. Prognostic Models

To identify patients who would benefit from and can tolerate intensive chemotherapy, prognostic models have been created to estimate probabilities of TRM and CR; some of these models are available as online tools [8,9]. These models tend to rely on age and performance status (PS) as markers of treatment tolerance. However, chronologic age is simply a surrogate for physiologic age, and PS alone may not fully assess patients' functional impairment.

2.2. Geriatric Assessments

Comprehensive geriatric assessments (CGA) are standardized, in depth evaluations of physical function, comorbidity, polypharmacy, nutritional status, cognition, depression, and social support that help improve risk stratification for older patients. They are better than PS scales at identifying patients who may not be frail but nevertheless have vulnerabilities that impact treatment tolerance [10]. For example, in a prospective study of AML patients aged ≥ 60 treated with induction chemotherapy, CGA measures of objective physical performance (Short Physical Performance Battery < 9) and cognitive impairment (Modified Mini-Mental State Exam < 77) were independently associated with OS after accounting for other tumor and clinical characteristics such as age and PS [11].

3. Treatment Approach

When an older patient is diagnosed with AML, the first step in treatment decision-making is to determine whether the patient is fit for intensive induction chemotherapy (IC), which depends on the above disease- and patient-related factors as well as patient preference. One must also determine the overall goal of the therapeutic plan—curative, life-prolonging, or palliative (Fig. 1). In general, patients who are not candidates for IC due to comorbidities or other patient-related factors are likely not candidates for a curative approach. However, selecting a strategy upfront does not preclude changing course later. If a very good response is achieved and any necessary improvements in PS and organ function occur with a lower intensity regimen, patients may “crossover” to a curative strategy of reduced intensity allogeneic transplantation.

Determination of fitness is clearly a significant challenge. Our current approach is to consider PS, comorbidities, and other geriatric domains such as cognition. Social support

and a strong caregiving team are particularly critical in an older patient with any vulnerabilities. The current state of the literature does not support a consistent approach to this determination; more and larger studies are needed to clarify the best use of CGA and/or its components.

3.1. Intensive Chemotherapy

3.1.1. Induction Chemotherapy—Several studies have attempted to address whether an intensive approach (standard "7+ 3" regimen of standard dose cytarabine plus an anthracycline) improves outcomes compared to lower intensity therapy in older adults. Retrospective studies are inevitably confounded by patient selection bias. Studies from the 1980s showed improved survival with IC versus best supportive care (BSC), but a non-significant benefit of IC when compared to low-dose cytarabine (LDAC) [12,13]. However, these studies were not performed in the era of modern supportive care. The best modern data supporting the use of IC comes from the retrospective Swedish registry study assessing "real-world" outcomes in different areas of Sweden which differed in physician willingness to administer IC. IC was associated with better outcomes even in patients aged 70–79 [3]. The 7+3 regimen also appears to be superior to single agent clofarabine in patients aged > 60 [14]. Based on this data, IC remains a reasonable standard of care for older patients with AML who are considered fit enough to receive it.

It is controversial, however, whether certain subsets of patients who may be fit for IC should in fact not receive it. Some evidence suggests patients with secondary AML, poor risk cytogenetics, or AML with myelodysplasia-related change may benefit more from hypomethylating agents (HMA), or simply are less likely to benefit from 7 + 3 [14–16]. Data to answer this question is still emerging. Our practice is to continue to offer IC to fit older patients, but for patients with borderline fitness and the above high-risk disease features, we may be more likely to consider HMA.

3.1.2. Post-remission Therapy—If an intensive strategy is selected and remission is achieved, the clinician then needs to determine the optimal post-remission therapy. Several trials have examined the role of higher doses of cytarabine as part of a consolidation regimen and have consistently not shown any benefit in survival [17]. Thus, there is currently no clear standard of care for chemotherapy-based consolidation in first remission.

Given that higher intensity consolidation does not seem to improve the generally poor outcome of older AML, the development of non-myeloablative or reduced intensity conditioning (RIC) regimens has made allogeneic stem cell transplantation an increasingly attractive option for post-remission therapy. Studies show that older adults with AML who proceed to RIC allogeneic transplantation can achieve 2-year survival rates of 34–48% [18,19]. Preliminary results from a prospective biologic assignment study ("donor versus no donor") of patients aged 60–75 years in first remission suggest that, compared to chemotherapy consolidation, allogeneic transplantation results in lower relapse rates and higher disease-free survival, but higher non-relapse mortality, with a non-significant trend toward improved OS [20].

3.2. Lower Intensity Therapy

The HMAs decitabine and azacitidine represent the current lower intensity regimen of choice for older patients with AML. This is based on trials which randomized patients to receive HMA versus patient/physician choice of BSC, LDAC, or in some trials, IC (Table 1). One international phase 3 study compared azacitidine to conventional care regimens (IC, LDAC, or BSC) in patients with AML and >30% bone marrow blasts. Azacitidine resulted in median OS of 10.4 versus 6.5 months with conventional care regimens, although the primary endpoint was not met. The study was not powered to detect an OS difference in the group pre-selected for IC, though patients in this group who received azacitidine and IC had similar median OS (13.3 vs 12.2 months). Interestingly, for patients with poor risk cytogenetics or myelodysplasia-related change, azacitidine was superior to conventional care regimens, with median OS of 6.4 compared to 3.2 months [15]. Another study found that patients with unfavorable risk cytogenetics or TP53mutation treated with decitabine had higher response rates and similar OS compared to patients with intermediate risk cytogenetics [16].

4. Emerging Therapies

Whenever possible, older patients with AML should be enrolled on a clinical trial. Numerous new drugs are emerging from the drug development pipeline with the potential to greatly enrich the limited therapeutic options for older AML patients; some of these are highlighted below.

4.1. CPX351

The 7 + 3 regimen has been a standard in AML treatment since the 1970s, and multiple attempts to improve upon it have largely been unsuccessful, except in younger and favorable risk subsets [21–24]. CPX-351 is a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio, chosen based on in vitro studies showing this ratio to be maximally synergistic. Subset analysis of a phase 2 trial of CPX-351 showed an encouraging signal in secondary AML [25]. Therefore, a phase 3 trial was conducted randomizing older patients aged 60–75 with previously untreated secondary AML to receive 7+3 versus CPX-351. Results showed a higher CR rate (37.3% vs 25.6%), improved OS (9.56 vs 5.95 months, $p = 0.005$), decreased early death in ≤60 days (13.7% vs 21.1%), and more patients proceeding to allogeneic transplant (34% vs 25%) in the CPX-351 arm[26]. Although early deaths due to toxicity were similar, there were fewer early deaths due to progressive AML. Landmark analysis from time of transplant also showed that patients who received CPX-351 had better post-transplant survival. Why CPX-351 prolongs survival—decreased toxicity, better efficacy, more patients transplanted, or a combination—remains unclear. CPX-351 (Vyxeos) was approved by the FDA in August 2017 for therapy-related AML and AML with myelodysplasia-related change and will become a new standard of care for older adults with secondary AML.

4.2. Small Molecule Inhibitors

4.2.1. Venetoclax—Venetoclax is a potent BCL2 inhibitor which binds selectively to BCL2, promoting programmed cell death. Ongoing phase 1b trials combining venetoclax

with azacitidine and decitabine in adults aged ≥ 65 with untreated AML unfit for IC show overall response rate (ORR) of 62% across all treatment arms, with median duration of response of 8.4 months [27]. These results are promising compared to historical results for azacitidine alone with ORR of only 29% [15]. In 2016, venetoclax received breakthrough designation in combination with HMA for patients with AML who are unfit for IC.

4.2.2. FLT3 Inhibitors—FLT3 mutations occur in 30% of AML patients, and FLT3 internal tandem duplication (ITD) mutations are associated with poor prognosis. Small molecule FLT3 inhibitors have emerged as an attractive therapeutic option. Type II inhibitors such as sorafenib are vulnerable to the secondary development of D835 mutations, resulting in resistance. Type I inhibitors, such as midostaurin, crenolanib, and gilteritinib, are able to bind FLT3 despite the presence of the D835 mutation. Midostaurin was recently shown to prolong survival in combination with chemotherapy, but this trial did not include older patients [28]. Studies are ongoing with other FLT3 inhibitors including crenolanib and gilteritinib in combination with chemotherapy or with HMA, and as monotherapy for post-transplant maintenance.

Several drugs targeting novel small molecular targets are in development for the treatment of AML, which are summarized in Table 2. Though not specifically aimed at older patients with AML, these novel therapies represent promising treatment options for older adults whose options may otherwise be limited.

4.3. Antibody-Drug Conjugates

Antibody-drug conjugates (ADC) targeting CD33 are a promising class of agents for older adults with AML. Gemtuzumab ozogamicin (GO) is an ADC comprised of a monoclonal antibody targeting CD33 linked to the cytotoxic agent calicheamicin. GO was approved in 2000 for use in older patients with relapsed, CD33 positive AML, but was withdrawn from the market in 2010 when the confirmatory phase 3 study showed no benefit but increased toxicity, including hepatic veno-occlusive disease, when used for younger patients in combination with 7+3 [29]. However, low dose GO as first-line monotherapy significantly improved OS compared to BSC in older AML patients ineligible for IC [30], and is now being reviewed by the FDA for use in combination with 7 + 3 based on the ALFA-0701 trial showing a survival benefit for patients aged 50–70 [31].

Vadastuximab talirine (SGN-CD33A) is a new anti-CD33 ADC which in a phase 1b study in combination with HMA for older patients with treatment naïve AML showed promising CR rate of 73% [32]. However, in June 2017 all trials of vadastuximab were halted due to a higher rate of death in a phase 3 trial in older adults.

5. Conclusion

The treatment approach for older patients with AML generally consists of IC for the fit patient and HMA for the unfit. The development of CPX-351 for secondary AML and increasing utilization of RIC allogeneic transplantation may improve both the tolerability and long-term outcome of an intensive treatment strategy. Emerging novel agents such as venetoclax, ADCs, and small molecular inhibitors that are effective and tolerable, as well as

drug combinations, will be invaluable additions to the treatment landscape for older patients with AML.

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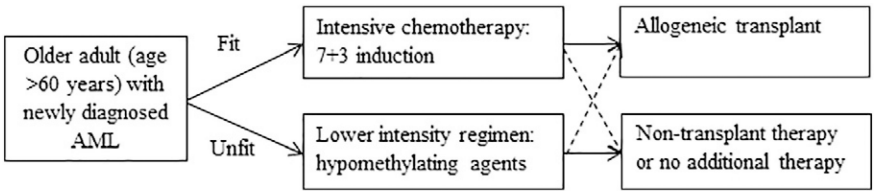

Fig. 1.
Treatment algorithm for older AML patients.

Table 1

Trials evaluating hypomethylating agents in acute myeloid leukemia in older adults. BSC = best supportive care, LDAC = low dose cytarabine, IC = intensive chemotherapy, CR = complete remission, OS = overall survival, MDS = myelodysplastic syndrome, WHO = World Health Organization, AML= acute myeloid leukemia.

Trial	No. of patients	CR (%)	p-Value	Median OS (months)	p-Value	Comments
Kantarjian [33]						
Decitabine	243	17.8	0.001	7.7	0.108	Age ≥ 65, poor/intermediate risk cytogenetics.
BSC or LDAC	242	7.8		5.0		Unplanned analysis with 446 deaths show same median OS with p = 0.037.
Fenaux [34]						
Azacitidine	55	18	0.80	24.5	0.005	Age ≥ 18 (median age 70), 20–30% blasts (subset of MDS trial meeting WHO criteria for AML).
BSC, LDAC, IC	58	16		16.0		CR rates with IC 55%, LDAC 15%, BSC 0%.
Dombret [15]						
Azacitidine	241	27.8	0.54	10.4	0.10	Age ≥ 65, >30% blasts.
BSC, LDAC, IC	247	25.1		6.5		CR rates with IC 48%, LDAC 26%, BSC 0%.

Table 2

Novel therapeutic targets for AML. BCL2 = B cell lymphoma 2, FLT3 = fms like tyrosine kinase 3, Plk = polo like kinase, IDH = isocitrate dehydrogenase, MEK = mitogen-activated protein kinase enzyme, MDM2 = murine double minute chromosome 2, HDAC = histone deacetylase, CTLA4 = cytotoxic T-lymphocyte-associated protein 4, PDL = programmed cell death ligand, BiTE = bispecific T cell engager, CAR-T = chimeric antigen receptor T cells

Therapeutic approach	Drug
Small molecule inhibitors	
BCL2	Venetoclax
FLT3	Midostaurin, sorafenib, crenolanib, lestaurtinib, gilteritinib
Plk	Volasertib, rigosertib
IDH1/2	AG-120, AG-221
MEK	Trametinib, cobimetinib
MDM2	AMG-232
HDAC	Pracinostat, panobinostat, entinostat
Antibody-drug conjugates	
Anti-CD33	SGN33A (vadastuximab), AC225 (lintuzumab)
Anti-CD123	SL-401
Immunotherapy	
Anti-CTLA4	Ipilimumab
Anti-PD1/PDL1	Nivolumab, pembrolizumab, PDR001, MBG453
BiTE and DART antibody constructs	AMG 330, MGD006
CAR-T cells	CART123