REVIEW ARTICLE

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Dose intensity for induction in acute myeloid leukemia: what, when, and for whom?

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ABSTRACT

Intensive chemotherapy has been the backbone of the treatment of acute myeloid leukemia (AML) for decades. However, an increase in novel targeted agents, which has been brought about in part by a deeper understanding of the genetic makeup of AML, has led to remission-inducing regimens that do not require traditional cytotoxic agents. Combinations of a hypomethylating agent (HMA) and venetoclax have doubled the chance of remission for patients considered unfit for induction chemotherapy who would have traditionally been offered single-agent HMA. In fact, this regimen may rival the complete remission rate achieved with induction chemotherapy for certain populations such as the very elderly and those with secondary AML, but equivalency has yet to be established. Further advances include the addition of gemtuzumab ozogamicin and *FLT3* inhibitors to induction chemotherapy, which improves survival for patients with core-binding factor and *FLT3*-mutated AML, respectively. Still, much work is needed to improve the outcomes of the highest-risk subgroups: frail patients and those with high-risk cytogenetics and/or *TP53* mutations. Promisingly, the landscape of AML therapy is shifting dramatically and no longer is intensity, when feasible, always the best answer for AML.

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Introduction

The initial data for the most widely utilized intensive induction chemotherapy regimen for acute myeloid leukemia (AML), a combination of cytarabine and an anthracycline ("7+3"), were published in 1973.[1] In the subsequent four decades the question of increasing or decreasing the intensity of induction had been asked multiple times. Various institutions adopted modified cytarabine and anthracycline platforms that included the addition of a third agent such as etoposide and/or employing time sequential therapy.[2] However, no modifications, other than variations in dose intensities of anthracycline, have been widely adopted. Hypomethylating agents (HMA) and low or intermediate doses of cytarabine have been utilized for patients over 70-75 years old or those considered unfit for intensive therapy due to comorbidity or poor performance status (PS), but intensive induction was the only AML-directed therapy with a known survival benefit. After years of stagnation in new agents, beginning in 2017 the world of AML therapy was uplifted by the approval of new therapies. However, until recently none has provided a true alternative to induction for those individuals who are otherwise induction candidates, and upfront therapy for those who were unfit was still limited. Given the survival benefit seen with venetoclax combination therapies when compared with HMA alone,[3] the question of intensity has risen again, but with no clear answers regarding whether fit patients would benefit from this intermediate intensity option. Here we will review the literature and provide our position on when to consider dose intensity in the era of novel, less intensive induction strategies.

To treat or not to treat?

While induction therapy is still considered the standard of care for younger patients with favorable- or intermediate-risk disease, not all patients are deemed

eligible for standard induction. What has been clearly demonstrated is that AML-directed chemotherapy improves survival for newly diagnosed patients when compared with best supportive care and that this benefit extends to the elderly and those with poor PS.[4,5] In 1989, Lowenberg and colleagues performed a randomized trial of intensive induction chemotherapy (IC) *versus* best supportive care combined with mild cytoreductive therapy for relief of progressive symptoms in patients 65 years and older. Despite the concern that older patients would suffer from complications of intensive therapy, survival was significantly better in those treated with IC and frequency of hospitalization was not different between the treatment groups.[6] Despite these early findings, historically the majority of older adults with AML were not offered chemotherapy. For instance, SEER data for patients with AML aged 65 years and older from 1991-1996 demonstrated that the median survival was 2.4 months with a dismal 2-year overall survival (OS) of 6%. While those receiving chemotherapy survived longer, only 34% of patients received chemotherapy.[7] From 2000 to 2009, treatment rates for older AML patients increased from 35% to 50% and leukemia-directed therapy reduced the risk of death by 33% with a median OS of 18.9 months in those receiving IC, 6.6 months in those receiving HMA, and 1.5 months in patients receiving best supportive care.[8] In a propensity matched analysis, patients 60 years and older who received IC had a median survival of 197 days whereas those receiving best supportive care had a median survival of 53 days.[9] Furthermore, a randomized trial comparing IC to best supportive care demonstrated improvement in OS for patients over 65 receiving IC.[10] The benefit of treatment also appears to extend to patients aged 70-79 years old, in whom a goal of achieving remission has been associated with improved survival.[5]

In one of the original studies of the interaction PS and age in AML, older age and poorer PS had a synergistic effect on early mortality after IC. Thirty-day mortality in patients ≥75 years old with Eastern Cooperative Oncology Group (ECOG) PS of 3 was 82% compared with 50%, 18%, and 14% for those ≥75 years old with PS of 2, 1, and 0, respectively.[11] In AML patients aged 70-79 years old with PS 0-2 the 8-week mortality was 8% in those with intermediate-risk karyotype and 22% in those with high-risk karyotype, compared with 23% and 47% if given palliative therapy only.[4] Interestingly, even in AML patients with an ECOG PS 3-4, 8-week mortality was shown to be 76% in those treated with palliation and 50% in those treated with intensive treatment,[4] which suggests that even in those with a poor PS, treatment does not necessarily increase early mortality.

Whether, patients with a poor PS would fare better with less intensive therapy remains to be seen. It is possible that the burden of their disease compromises their PS and that less intensive therapies, which take weeks or months to achieve remission, would not adequately control their leukemia in time to reduce early mortality. For the first time, we have moderate intentsity therapies that offer similar complete resmission (CR) rates compared to IC, albeit with a delay to time of acheiving remission. Studies that compare therapy intensity in patients with poor PS, by fitness level, and by proliferative disease features are needed to determine the best approach in these high-risk patients.

When to treat?

Time from diagnosis to treatment was historically tied to survival outcomes, with increased mortality associated with delays in initiation of chemotherapy. In 2009, Sekeres *et al.* published that this was true for patients <60 years old, but not for those 60 years and older.[12] For younger patients, delays beyond 5 days were associated with inferior survival. Importantly, patients with a white blood cell count at diagnosis >50x10^9/L were excluded from the analysis. The authors hypothesized that older AML patients had biologically different disease that was inherently more resistant to chemotherapy. Using chromosomal analysis to identify such patients would allow pursuit of alternatives to standard IC. With further advances in the molecular and chromosomal categorization of AML, delaying therapy to allow individualization of treatment, particularly for older patients, is becoming more common. For instance, our group demonstrated that rapid fluorescence *in situ* hybridization testing could identify 86% of patients with myelodysplastic syndrome (MDS)-defining cytogenetics,[13,14] a population that has been shown to benefit from CPX-351 (liposomal daunorubicin and cytarabine).[15] In addition, rapid identification of core-binding factor (CBF) leukemia through fluorescence *in situ* hybridization or polymerase chain reaction analysis allows incorporation of gemtuzumab ozogamicin (GO) into induction, which has been shown to improve survival. For all *FLT3*-mutated patients, the addition of an *FLT3* inhibitor to IC is now standard of care. With regard to molecular analyses, the initial management in older patients may change with the presence of an *IDH* or *TP53* mutation. Delaying therapy to allow for genetic classification is, therefore, being increasingly employed.

Given the growing role of chromosomal and molecular testing to tailor initial therapy, Rollig *et al.* reviewed the outcomes of patients whose treatment was delayed to allow for personalized treatment choices. In their study, with 0-5, 6-10, 11-15, and >15 days from diagnosis to starting treatment, the 2-year OS was 51%, 48%, 44%, and 50%, respectively, with a 30-day mortality rate of approximately 4% in each group.[16] Importantly, there was no difference based on whether the initial white blood cell count was >50x10^9/L or ≤50x10^9/L. However, patients with a high white blood cell count, high bone marrow blast count, and/or high lactase dehydrogenase had a shorter time from diagnosis to treatment.[16] The authors concluded that physicians were appropriately selecting those patients who could postpone therapy initiation and that advances in supportive care such as the use of anti-fungal agents may decrease early mortality to allow safe delays. In addition, stabilizing cytoreductive measures such as hydroxyurea and leukapharesis can be employed to allow informed treatment decisions. As such, we support rapid turnaround of fluorescence *in situ* hybridization testing for MDS-defining cytogenetics and CBF, as well as molecular analysis for *TP53*, *IDH*, and *FLT3* mutations. We anticipate that with time, as other genes become targets for leukemia therapy, the list of mutations necessary for rapid testing will grow.

Anthracycline dose

One of the often debated questions with regard to IC intensity is the ideal dose of anthracycline. In a random-

ized US intergroup trial, daunorubicin at a dose of 90 mg/m^2 compared with 45 mg/m^2 for AML patients younger than 60 years old was associated with a higher CR rate at 70% *versus* 57%, improvements in OS at 46.8% *versus* 34.6%, and event-free survival at 40.8% *versus* 28.4%, respectively.[17] However, the survival advantage was restricted to patients younger than 50 years old.[18] With longer follow-up and additional analyses based on molecular classification, it was determined that in patients 50-60 years old who had either an *FLT3*-internal tandem duplication or an *NPM1* mutation higher anthracycline dose was associated with improved OS.[19] Lowenberg and colleagues demonstrated that in patients aged 60-83 (median, 67) years old who received cytarabine 200 mg/m^2 those receiving an escalated dose of daunorubicin to 90 mg/m^2 from 45 mg/m^2 had a CR rate of 64% compared with 54%, but survival endpoints did not differ.[20] In the subgroup of patients aged 60-65 years old, the CR rate was 73% *versus* 51%, event-free survival was 29% *versus* 14%, and OS was 38% *versus* 23%, respectively, by anthracycline dose. In the Medical Research Council's (MRC) AML15 randomized phase III trial that compared induction with two cycles of daunorubicin 90 mg/m^2 to two cycles of 60 mg/m^2, CR rate, toxicity, and OS were similar except for the subgroup of *FLT3*-mutated patients, in whom the higher dose provided a survival advantage.[21,22] While toxicity increases with age for escalating anthracycline doses, higher doses should be considered for patients under 60-65 years old, particularly if *FLT3*-mutated and possibly if *NPM1*-mutated. Another important consideration is the choice of anthracycline. Idarubicin and daunorubicin have largely been used interchangeably.[23-25] However, a recent meta-analysis supports the preferential use of idarubicin over daunorubicin, particularly when utilizing a high dose of anthracycline (daunorubicin 90 mg/m^2 or equivalent).[26]

Cytarabine dose and CPX-351

The ideal dosing for cytarabine in combination with an anthracycline for induction is less controversial and appears to be 100-200 mg/m^2/day typically administered as a 24-hour infusion.[27] Dose escalations beyond 200 mg/m^2/day have not been associated with further improvements, for instance, increasing the dose to 400 mg/m^2/day did not improve survival.[28] Lowenberg and colleagues demonstrated that, when in combination with an anthracycline, high-dose cytarabine (1000 mg/m^2 every 12 hours on days 1-5) was associated with no difference in outcomes, but a higher incidence of toxicity, prolonged hospitalization, and delayed hematologic recovery when compared to cytarabine 200 mg/m^2/day as a continuous infusion for 7 days (7+3).[29] Early mortality after high-dose cytarabine without an anthracycline was higher than after 7+3 and is of particular concern in patients with renal dysfunction. Furthermore, the incidence of cerebellar toxicity is much greater with high-dose cytarabine, limiting its use to otherwise fit patients who are in need of a non-anthracycline-containing induction regimen due most often to baseline cardiac dysfunction (ejection fraction <45%[30]) or cumulative lifetime dose of anthracycline that would exceed doxorubicin 450-550 mg/m^2 or equivalent.[30,31]

In 2017, CPX-351 (liposomal daunorubicin/cytarabine) was approved for patients with secondary AML as a method to improve the delivery of cytarabine based on a fixed molar ratio. While CPX-351 did not improve survival beyond 7+3 for all newly diagnosed AML patients, a randomized trial comparing CPX-351 to standard 7+3 in patients aged 60-75 years with therapy-related AML, AML from prior MDS, or AML with MDS-defining cytogenetics demonstrated a significant improvement in median survival of 9.56 *versus* 5.95 months (P=0.003), 2-year OS of 31.1% *versus* 12.3% and, a higher CR rate of 47.7% *versus* 33.3%, (P=0.016).[15] However, the consolidation strategy for the control arm utilized cytarabine 100 mg/m^2/day for 5 days and daunorubicin 60 mg/m^2 on days 1 and 2 rather than high-dose cytarabine, which is the preferred consolidation regimen and can be utilized either as definitive therapy or as a bridge to hematopoietic cell transplantation (HCT). HMA/venetoclax, discussed more below, competes for the same population of older patients with secondary AML and produces a promising CR rate, thus we typically consider CPX-351 for patients with secondary AML in whom HMA or HMA/venetoclax has failed.

Triplet chemotherapy

We have established that chemotherapy intensity is important for treating AML with curative intent, however, until 2017, intensity beyond that established above failed to further improve survival due to improvements in relapse being offset by increased toxic deaths.[32-34] Etoposide is one of the most widely utilized chemotherapy additions to standard induction, but has not been shown to improve survival when added to 7+3[35] or when utilized as part of time sequential therapy where the 68% CR rate and median OS of 17.2 months[36] are similar to the results associated with conventional 7+3 on clinical trial.[37] The addition of cladribine, but not fludarabine, to 7+3 for AML patients aged 17-60 years was associated with improvement in OS in patients aged 50 to 60 years old, those with a leukocyte count at presentation above 50x10^9/L, and patients with an unfavorable karyotype.[38] In contrast, in patients 60-77 years old, the addition of cladribine to 7+3 did not improve OS or CR.[39] However, in a subgroup analysis of patients aged 60-65 years old with good- or intermediate-risk cytogenetics there was an OS benefit with the triplet.[39]

Although the addition of a third standard cytotoxic agent to 7+3 has not been widely adopted, two Food and Drug Administration (FDA)-approved therapies have been shown to boost efficacy in specific populations without significant increases in toxicity: GO and midostaurin. GO is a monoclonal antibody to CD33 attached to the traditional cytotoxic drug calicheamicin. Adding 3 mg/m^2 of GO to 7+3 (daunorubicin 60 mg/m^2) significantly improved the survival of patients with good-risk AML,[40] leading to its approval for CD33$^+$ AML. A subsequent meta-analysis demonstrated that adding GO to induction for CBF-AML produced a 20.7% absolute survival benefit at 6 years.[41] GO in combination with 7+3 has also been explored for *NPM1*-mutated AML in which it was associated with a reduction in relapse, but a higher early death rate (10.3% *vs*. 5.7%), which translated into no improvement in event-free survival.[42] Subgroup analyses suggested a benefit in younger female and *FLT3*-negative patients, but given that the primary endpoint was not reached, we do not routinely add GO to induction or consolidation for *NPM1*-mutated AML and instead monitor patients closely for rapid minimal residual disease clearance[43] and consider

allogeneic HCT if this is not achieved. While adding GO to induction for patients with intermediate-risk AML was associated with a small improvement in OS, we typically recommend consolidation with HCT in first CR patients. Given the potential for sinusoidal occlusive syndrome after GO and HCT, we reserve GO for patients with CBF-AML, who derive the most benefit[44] and for whom we do not routinely recommend HCT in first CR. Aside from increasing the risk of sinusoidal occlusive syndrome, GO also prolongs the duration of cytopenias after 7+3, but is otherwise well tolerated.

FLT3 (tyrosine kinase domain or internal tandem duplication)-mutated AML is another subtype in which additions to 7+3 are becoming standard of care. Midostaurin is a protein kinase inhibitor that targets *FLT3* and other protein kinases. The phase III Ratify trial demonstrated that patients receiving 7+3 in combination with midostaurin 50 mg twice daily on days 8-21 compared with 7+3 in combination with placebo had a 4-year OS of 51.4% *versus* 44.3%, respectively.[45] Like GO, midostaurin is also added to consolidation cycles. Midostaurin is well tolerated with rash, nausea, abdominal pain, and diarrhea as the most frequent, but often manageable, side effects. However, in patients over 60 years old receiving midostaurin, cardiac toxicity (22%), arrthymias (10%), and pulmonary complications (14%) were more common than antipicated.[46] Given the success of midostaurin, the addition of more potent *FLT3* inhibitors to induction is being explored in ongoing studies. For instance, 7+3 plus gilteritinib was associated with a composite CR rate of 93.9% in early trials.[47] We anticipate that additional *FLT3* inhibitors will be approved for use in combination with induction in the near future. While not yet approved in combination with 7+3 or 5+2, the addition of venetoclax to IC is also being explored, with promising early results discussed below.

The argument for intensity in older fit populations

In a Swedish registry study of older AML patients, early death was dependent on PS and age, but patients administered intensive therapy had a lower early death rate regardless of age.[48] At the time, HMA use was rare or non-existent[49] so patients treated with hydroxyurea, lower-dose cytarabine, or best supportive care comprised the majority of the comparator group.[49] In a study by Bories *et al.* the OS of patients 60 years and older between 2007-2010 who were selected by their physician to receive IC, or if unfit for IC then azacitidine, or if unfit for azacitidine then best supportive care, was 18.9, 11.3, and 1.8 months, respectively.[50] One of the limitations of such studies is that PS, disease features, and co-morbidity influence how patients are selected for a given therapy. To adjust for these differences, a propensity score matching analysis that included age, secondary *versus de novo* AML, bone marrow blast percent, and cytogenetics demonstrated an improvement in OS for IC when compared to azacitidine from 6 months after treatment initiation.[50] However, PS and co-morbidities were not different between the IC and azacitidine groups and thus not matched. This highlights the subjectivity of fitness; clinicians utilized criteria other than PS and co-morbidity to deem the patient unfit for IC. In a multicenter retrospective analysis of 1,295 patients aged 65 years and older treated between 2008-2012, Sorror and colleagues tried to account for this type of selection bias by using an AML-composite model[51,52] score and found that those who received IC had longer survival than those who received a HMA, including the subset of patients aged 70-79 years old.[53] While this study importantly demonstrates the continued role for IC, the authors acknowledge that it does not include the latest generation of moderate-intensity options. For instance, azacitidine/venetoclax was associated with a composite CR rate of 66.4%, compared with 28.3% for single-agent azacitidine, and has the potential to rival the CR rate of IC in older patients and those with secondary AML.[3]

Another potential advantage of IC is the ability to achieve cure in a small number of patients without need for ongoing HMA therapy or consolidation HCT. For instance, in a study by Heiblig *et al.* the median OS for AML patients 70 years and older receiving IC, HMA, or best supportive care was 12.4 months, 11.5 months and 2.6 months and the 3-year OS was 27%, 17%, and 6%, respectively. While median OS was similar after IC and HMA, patients receiving HMA were exceedingly unlikely to live beyond 3 years, whereas a very small number of patients receiving IC survived beyond 10 years.[54] As such, in patients who are not candidates for HCT, upfront intensive options have the potential for long-term survival and may be considered. While some may argue that patients not fit for IC upfront would by definition not be candidates for bone marrow transplantation, OS improvements associated with IC even in poor PS patients contradict this dogma. Furthermore, in older or frail patients, the prolonged stress of HCT may be more difficult to withstand than a single month of intensive treatment.

Clofarabine

Clofarabine is another moderate-intensity regimen explored in older AML patients who were considered unfit for intensive induction[55] and at doses of 20 mg/m^2 was associated with a CR/CR with incomplete hematologic recovery (CRi) rate of 48%, 30-day mortality of 18%,[56] and a median disease-free survival of 37 weeks.[55] Based on encouraging phase II results, a phase III ECOG ACRIN-led intergroup trial in newly diagnosed AML patients 60 years and older investigated the use of clofarabine 30 mg/m^2 for 5 days compared with daunorubicin 60 mg/m^2 days 1-3 and cytarabine 100 mg/m^2 days 1-7 and demonstrated similar CR rates, but significantly inferior OS for clofarabine-treated patients (HR=1.41).[57] For patients with high-risk cytogenetics there was no difference in OS between the arms. The authors reached the conclusion that 7+3 induction was still the standard for older fit patients.[57] Clofarabine in combination with daunorubicin has also been compared to cytarabine and daunorubicin, but with no significant differences in remission or survival outcomes.[58]

The argument for attenuated intensity in older or unfit patients

Attenuated doses of the combination of anthracycline and cytarabine have not been shown to be of more value in older patients who are fit for induction.[59-61] However, for patients unfit for IC, lower intensity options have been explored. One of the earliest utilized lower-intensity ther-

apies, low-dose cytarabine (LDAC), prolongs survival when compared to either hydroxycarbamide or best supportive care. However, the CR rate is only 18% with a median OS of 18 weeks and there were no responders among patients with high-risk disease.[62] In an effort to improve upon modest outcomes with LDAC alone, glasdegib, a hedgehog inhibitor that is also being studied in combination with 7+3,[63] was combined with LDAC, where it was associated with a CR rate of 17% and an 8.8 month median survival compared with 2.3% and 4.9 months for LDAC alone in that study.[64] Glasdegib is now FDA-approved for use in combination with LDAC and it could be considered in patients with renal failure or those deemed unfit for induction who have already failed HMA-based therapy. However, the widespread adoption of LDAC and glasdegib has been limited by the contemporary approval of LDAC and venetoclax discussed further below.

Azacitidine and decitabine, two HMAs in common use for myeloid diseases, were first approved for MDS in 2004 and 2006, respectively. Despite never receiving FDA approval as single agents for AML, HMAs have been commonly employed to treat unfit older AML patients since that time. The data behind this approach include those from a study of 980 AML patients 70 years and older in whom the median OS was 14.4 months after HMA, 10.8 months after daunorubicin/cytarabine, 5.9 months after LDAC, and 2.1 months with best supportive care.[65] Propensity score matching showed a significant benefit from HMA. At least two other studies retrospectively compared HMA and IC and suggested that survival was similar.[66,67] However, when compared to lower-intensity AML chemotherapy such as single-agent GO, LDAC, or best supportive care, nothing outperforms HMA.[32,68]

Venetoclax lower-intensity combination therapies

In an effort to improve on the modest CR rate associated with HMA as a single agent, HMA combination therapies, such as lenalidomide/HMA have been explored,[69,70] but none garnered much attention until venetoclax. Based on encouraging early data, venetoclax/HMA received accelerated approval in 2018 for newly diagnosed AML patients 75 years and older and/or for those with comorbidities that preclude IC.[71] Full FDA approval followed in 2020 based on the findings of a phase III study in which 431 patients were randomized to either 7 days of azacitidine and 28 days of venetoclax 400 mg daily or azacitidine and placebo.[3] The OS was 14.7 months in the azacitidine/venetoclax arm and 9.6 months in the azacitidine/placebo arm with a composite CR (CR/CRi) of 66.4% *versus* 28.3%, respectively.[3] By molecular subgroups, CR/CRi was achieved in 75.4% *versus* 10.7% of *IDH1/2*-mutated patients, 72.4% *versus* 36.4% of *FLT3*-mutated patients, 66.7% *versus* 23.5% of *NPM1*-mutated patients, and 55.3% *versus* 0% of *TP53*-mutated patients, respectively. The median OS for patients with intermediate-risk cytogenetics treated with azacitidine/venetoclax or azacitidine/placebo, was 20.8 months *versus* 12.4 months, respectively, whereas it was 7.6 months *versus* 6.0 months for those with poor-risk cytogenetics (patients with CBF-AML were excluded from the study). Febrile neutropenia occurred in 42% of patients treated with the combination. Thirty-day mortality was 7% in the azacitidine/venetoclax group and 6% in the control group.[3]

Alongside its approval in combination with HMA, venetoclax received accelerated approval in combination with LDAC based on a study of 82 patients aged 63-90 years who were treated with LDAC at 20 mg/m^2 per day on days 1-10 in combination with venetoclax 600 mg daily.[72] LDAC/venetoclax was associated with a 30-day mortality of 6%, a CR/CRi rate of 44%, and a median OS of 10.1 months. In patients not previously exposed to HMA, the CR/CRi rate was 62% with a median OS of 13.5 months.[72] Full approval was granted when subsequent phase III data from patients aged 36-93 years old demonstrated a 25% reduction in risk of death in the LDAC/venetoclax *versus* LDAC/placebo with a CR/CRi rate of 48% *versus* 13%, respectively.[73] Rates of CR/CRi were 72% in *FLT3*-mutated, 71% for *IDH1/2*-mutated, 91% for NPM1-mutated, and 47% for *TP53*-mutated AML. The median survival after LDAC/venetoclax for patients with the corresponding mutations was not reached, 24.4 months, not reached, and 7.2 months. Rates of febrile neutropenia were 32%. These data are particularly promising for AML patients with *NPM1* mutations and hint at a high response rate for *NPM1*-mutated patients treated with cytotoxic chemotherapy and venetoclax, discussed further below.

While not FDA-approved in combination, another lower-intensity option that is being explored is a combination of cytarabine, cladribine, and venetoclax. Phase II data showed a 58% CR rate with cladribine and LDAC alternating with HMA in older AML patients unfit for intensive induction.[74] In a subsequent trial, the addition of venetoclax to the prior regimen produced a 94% CR/CRi rate and is being explored as a moderate-intensity option.[75]

Venetoclax high-intensity combination therapies

Given its success in combination with lower intensity therapies, venetoclax has also been explored in patients 65 years and older who were fit for intensive chemotherapy. In this trial, venetoclax was given as a 7-day pre-phase ramp up, followed by idarubicin on days 2 and 3 (5+2), infusional cytarabine on days 2-7, then 7 additional days of venetoclax. Patients in the study were 63-80 years old and had a CR/CRi rate of 72% (97% in those with *de novo* AML and 43% in those with secondary AML).[76] Interestingly, a ≥50% reduction in blasts after just the pre-phase venetoclax was documented in patients with *NPM1*, *IDH2*, or *SRSF2* mutations. A few interesting points can be gleaned from this study: i) that secondary AML likely responds at least as well if not better to HMA/venetoclax than to 5+2/venetoclax; and ii) a strong signal exists that venetoclax is associated with high response rates in *NPM1*- and *IDH*-mutated AML, which might point towards the addition of this agent either to cytotoxic or HMA-based therapy, respectively, to improve outcomes in the future. Venetoclax is also being explored in combination with fludarabine, ara-C, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) induction. Among ten newly diagnosed patients treated with this regimen the CR/CRh rate was 91% with a high rate of minimal residual disease negativitiy.[77] Other intensive combinations such as venetoclax with cladribine, ara-C, and idarubicin induction are also showing promise.[78]

Disease-related factors

Primary predictors of response to chemotherapy in AML are molecular and cytogenetic factors and these will be used to guide selection of upfront chemotherapy in the years to come. For instance, in patients 75 years and older treated with IC in the AML Cooperative Group (AMLCG)-1999 trial, the average number of mutations was four and 83% of patients had a mutation in at least one of the following genes: *TET2*, *DNMT3A*, *NPM1*, *SRSF2*, *ASXL1*, *TP53*, and *SF3B1*.[79] While *NPM1* and *FLT3*-internal tandem duplication did not significantly affect OS, adverse-risk cytogenetics (according to the MRC) and *IDH1* mutations were associated with poor prognosis and chemorefractoriness.[79] Overall prognosis was poor with intermediate-risk patients having a 3-year survival rate of 10-15% and no patients with unfavorable-risk AML being alive at 3 years.[79] While in this study, *NPM1* mutations did not influence survival, an earlier study demonstrated that *NPM1* mutations in octogenarians were associated with improved survival after IC.[80] In addition, the CR rate for favorable-risk disease in older patients ranges from 89-95% for CBF-AML to 69% for *CEBPA*-double mutant disease, with CR rates for *NPM1*-mutated AML falling in between.[81] Furthermore, 3-year OS differs: 47% *versus* 21% for CBF-AML *versus CEBPA*-double mutant AML, respectively.[81] Given the relatively high CR rate, older patients with favorable-risk AML could be considered for intensive induction. In AML patients aged 70-79 years old with PS 0-2, worse cytogenetic risk is associated with higher early mortality, but with IC improving early mortality relative to palliation only.[4] This supports the pursuit of chemotherapy in patients over 70 years old, but unfortunately does not provide guidance as to the optimal regimen.

In older AML patients with good-risk profiles such as those with *NPM1* mutations[82] or CBF, IC may have the potential to achieve long-term survival or even cure. Early studies demonstrating high response rates of *NPM1*-mutated AML to venetoclax combinations[73,76] suggest that the addition of venetoclax to IC (7+3 or 5+2, etc.) may improve outcomes in the future. On the other hand, older patients with *IDH1*-mutated AML are unlikely to benefit from IC and have excellent response rates to azacitidine/venetoclax. In AML patients with chromosome 5 and/or chromosome 7 abnormalities,[83] MDS-related changes,[84] and in those with low blast counts,[85] HMA therapy has been associated with improved OS when compared with intensive cytarabine-based chemotherapy, supporting HMA-based therapies such as HMA/venetoclax in these populations. Similarly, those with monosomal karyotypes[86-89] or other adverse cytogenetics who are 75 years and older have essentially 0% 3-year survival with IC[79] and should be considered primarily for HMA/venetoclax. Patients with secondary AML or AML with MDS-defining cytogenetics also do poorly with standard IC and may benefit from initial therapy with azacitidine/venetoclax if they have not previously been treated with HMA. If they are refractory to HMA or HMA/venetoclax, CPX-351 rather than 7+3 induction can be considered, as can the addition of venetoclax to HMA in HMA refractory patients.

TP53-mutated AML is a particular challenge given that it is associated with a 2-year OS rate of 9%.[90] Lower-intensity therapy has been associated with equivalent response rates to those in patients treated with higher-intensity therapy, but with less toxicity.[91,92] For that reason, IC is less frequently employed in patients with *TP53* mutations and clinical trials exploring HMA combinations such as those with venetoclax, magrolimab, or eprenetapopt[93] are being pursued specifically in this population. Given the poor prognosis of this subgroup to all approved therapies, patients should consider clinical trials if available.

A subgroup of patients who should primarily be considered for IC would be those with highly proliferative AML in whom a delay to CR or effective disease control may lead to excess early mortality. Proliferative leukemia is often associated with CBF, *NPM1*-, or *FLT3*-mutated AML, which responds well to initial 7+3 alone or in combination with a targeted agent and supports the use of IC if a delay to determining molecular and cytogenetic features is not feasible. Given the risk of tumor lysis syndrome with venetoclax, cytoreduction to a white blood cell count <20x10^9/L is preferred prior to initiation and if this is achieved by hydroxyurea then the resulting mucositis may limit oral chemotherapy options and result in missed doses. Thus, if patients are candidates for IC and have proliferative disease, we generally recommend intensive IC.

In addition to age, cytogenetic and molecular risks, and features of proliferative disease, another important consideration when selecting upfront therapy is candidacy for subsequent HCT. The vast majority of older adults have intermediate- or poor-risk cytogenetics, in whom HCT is associated with a survival benefit. Yet, patients may be deemed unfit for HCT at the time of diagnosis because of disease burden affecting PS, but may become candidates for HCT once treated.[94] However, given that CR is often considered a pre-requisite for HCT, strategies with the highest rates of achieving CR are those that should be pursued. While median survival rates after HMA and IC are similar for patients 60 years and older, the CR rate is significantly lower.[67,95-99] Given that patients are more likely to undergo HCT if they reach a CR,[100] then achieving a CR should be a primary goal if HCT is the destination. However, upfront intensity may not be required if less intensive therapy can achieve a CR without affecting PS. This strategy has been associated with success in early trials of azacitidine/venetoclax in whom some patients went on to HCT.[101] However, to understand which therapy best achieves CR would require an upfront trial of 7+3 *versus* HMA/venetoclax rather than comparisons of HMA/venetoclax and HMA alone. Thus, there is more work to be done.

Patients' fitness

One of the primary reasons for a patient not being eligible for IC is being categorized as "unfit." However, lack of a widely utilized consensus definition of what fitness entails often means that this is a subjective clinical assessment. An Italian consensus group provided a definition of unfit that is similar to many criteria used in clinical trial enrollment and includes "(i) age over 75, (ii) congestive heart failure with an ejection fraction ≤50%, (iii) DLCO ≤65% or FEV1 ≤65%, lung neoplasm, or requiring oxygen, (iv) hemodialysis, or renal cancer and age over 60, (v) liver cirrhosis Child B or C or liver function tests >3 times normal values, or age over 60 with biliary or liver cancer or

viral hepatitis, (vi) resistant infection, (vii) mental illness or cognitive impairment that is uncontrolled, (viii) ECOG PS ≤3 not related to leukemia, (ix) physician judgement."[102] The ninth criteria is critical, as a clinician's gestalt judgment is often a reason that patients are felt to be ineligible for IC. However, the accuracy of this clinician assessment may differ by physician and by practice patterns. In a study by our group, we showed that in newly diagnosed AML patients over 60, a physician's gestalt assessment was less likely to categorize patients as frail and more likely to categorize patients as fit than objective measures of fitness.[103] Specifically, academic clinicians categorized 37% of newly diagnosed older AML patients as fit, whereas only 17% were fit according to Fried's frailty index.[103]

Another key component in determining fitness for IC is PS, which has been tied to early mortality after IC and has a synergistic relationship with age in predicting mortality.[11] The German cooperative group identified that the risk of early death after intensive chemotherapy was much higher (24%) in adults over 60 years old and that the CR rate was much lower (50%).[104] Kantarjian *et al.* evaluated 446 non-CBF AML patients 70 years or older receiving intensive cytarabine-based induction and found that the CR rate was 45%, with an 8-week mortality of 36% and a median OS of 4.6 months, with 28% of patients alive at 1 year.[105] They identified age ≥80 years, complex karyotype, ECOG PS 2-4, and creatinine >1.3 mg/dL as risk factors for mortality. The authors argued that a >30% 8-week mortality or a 3-year survival of <10% would prohibit the pursuit of IC.[104] Even worse, patients with a PS of 3-4 had an 8-week mortality of 77% and a CR rate of 24%. Although this analysis identified patients at high risk of poor outcomes with IC, there was no comparison to less intensive therapies.

One of the drawbacks to the use of PS at the time of AML diagnosis as a predictor of outcomes is the inability to distinguish impairment due to AML from impairment due to comorbidities. To try to distinguish these factors, Klepin and colleagues used functional status 6 months prior to treatment as recalled by patients and found that it was not predictive of survival,[106] which supports that the functional status at the moment, regardless of disease-related impairment, is relevant. If the AML is highly proliferative and limiting PS, perhaps intensive therapy to achieve a rapid reduction in disease burden is necessary. In fact, this could suggest that poor PS due to disease would be an indication for IC. We know that even in patients with poor PS, IC improves mortality when compared to best supportive care, but whether patients with poor PS would benefit from moderate intensity therapy over IC has yet to be determined.

Geriatric assessments have also been utilized to assess a patient's fitness for IC. For instance, an abridged geriatric assessment was better associated with survival than Karnofsky Performance Scale (KPS) or a physical performance test in older cancer patients[107] and a 30-item geriatric assessment for hematologic malignancy performed well in another study.[108] However, whether these metrics can be utilized to select therapy remains to be seen. In a study by Klepin *et al.*, impaired cognition (defined by a modified mini-mental status examination score >77) and a short physical performance battery score <9 were associated with worse OS and increases in 30-day mortality to 23% *versus* 9.6% in patients 60 years and over receiving treatment with cytarabine-based chemotherapy.[106] In contrast, in a randomized trial in older patients treated with chemotherapy, geriatric assessment did not influence outcomes.[109]

Comorbidity scores represent another avenue for assessing fitness or potential to support treatment toxicity. As a quick measure of comorbidity, polypharmacy (≥4 medications *versus* ≤1) has been associated with 30-day mortality in older AML patients.[110] More formal co-morbidity assessments include the hematopoietic cell transplantation- comorbidity index (HCT-CI)[111] and the Charlson comorbidity index (CCI).[112] Both of these tools were developed for patients in advanced stages of disease and may overemphasize the frailty of the AML patient at diagnosis.[102] Nonetheless, in newly diagnosed AML patients 70 years and older receiving IC with 7+3, CCI was 0 in 68%, 1 in 13% and 2 in 16%, and patients with a score of >1 had an odds ratio of 0.29 of achieving CR (P=0.05). The HCT-CI, which performs well for predicting mortality after HCT, predicted early death after IC for AML in some,[113] but not in other studies.[103,106] Sorror and colleagues found that creating a model that added albumin <3.5 g/dL, platelet count <20x10^9 cells/L, lactate dehydrogenase level, age, and cytogenetic and molecular risk to form an AML composite model outperformed the HCT-CI, augmented HCT-CI, and KPS for predicting mortality with AML induction.[114]

One of the limitations of utilizing comorbidity to assess fitness for IC is that some patients may have well-compensated comorbidities that do not strongly influence outcomes whereas other patients may have few comorbidities, but be frail due to lifestyle or genetics. We used Fried's frailty phenotype to predict outcomes in newly diagnosed AML patients 60 years and older and found that 17% of patients were fit, 33% were pre-frail, and 50% were frail. All fit and pre-frail patient survived to 100 days, but the 100-day mortality was 51% for frail patients (P=0.01).[102] In contrast, HCT-CI and clinician's gestalt judgment were not significantly associated with mortality in our study. Interestingly, many of the frail patients who died received HMA-based therapy or best supportive care, whereas all four frail patients who were treated with IC with either 7+3 or CPX-351 survived.[103] While this result needs to be validated in a larger population of patients, it is intriguing that fitness (or its inverse, frailty), while predictive of mortality, may not be the ideal way to exclude AML patients from IC.

Summary

Fortunately, the treatment of AML is evolving rapidly. Ongoing clinical trials are evaluating the role of optimizing intensive therapy with the addition of venetoclax, *IDH* inhibitors, or *FLT3* inhibitors. In addition, the National Institutes of Health and national cooperative groups are developing a study to determine the optimal approach to induction and post-remission therapy using personalized diagnostics including a comprehensive molecular and cytogenetic screening. Based on disease characteristics, risk profile, age and fitness, patients will be assigned to an initial therapy to include evaluating the role of novel therapeutics. Remissions will be assessed for minimal residual disease by flow and subsequent therapy will depend on the depth of initial remission in addition to baseline disease characteristics.

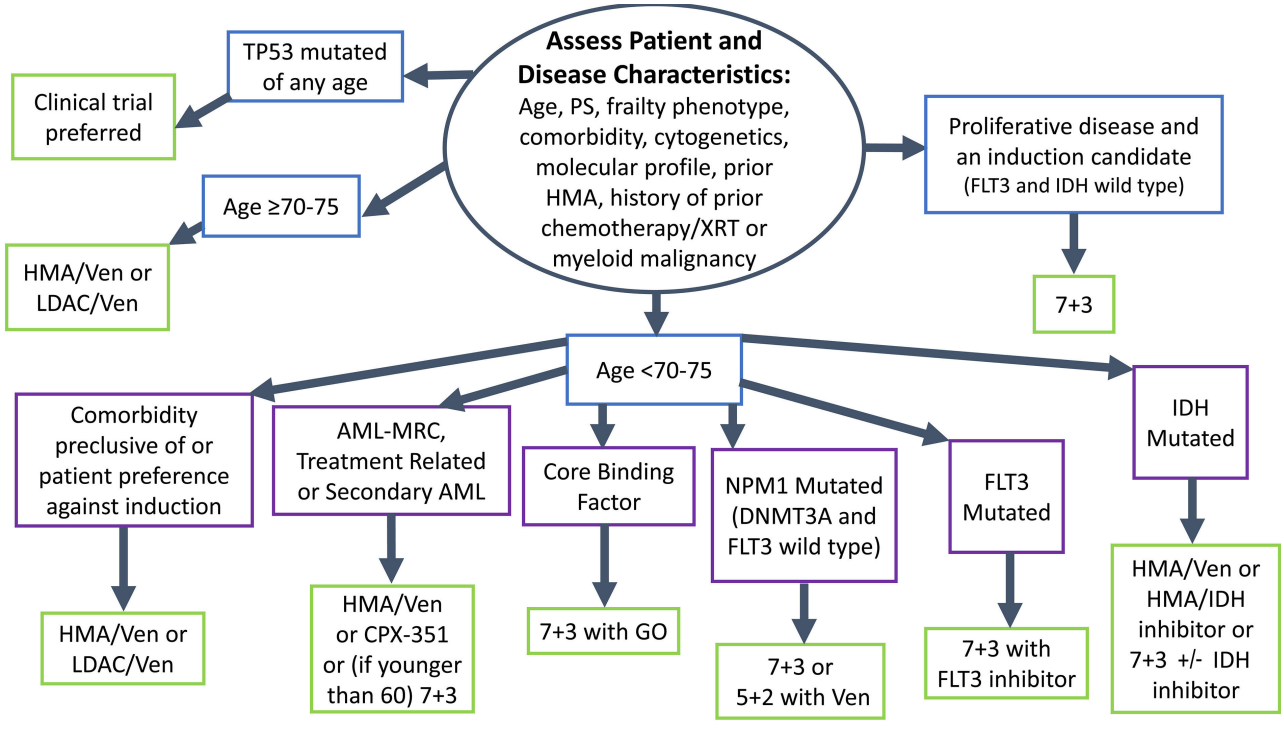

Figure 1. Selection of initial therapy for acute myeloid leukemia. *PS: Performance Status; HMA: hypomethylating agent; XRT: radiation; Ven: venetoclax; LDAC: low-dose ara-C; AML-MRC: acute myeloid leukemia with myelodysplasia-related changes; GO: gemtuzumab ozogamicin.

While looking hopefully to the future, our practice as of now (summarized in Figure 1) is to pursue IC with 7+3 in patients less than 70 years old with no criteria for exclusion from induction. We add GO to 7+3 for all patients with CBF-AML, as long as their liver function is adequate, and *FLT3* inhibitors to 7+3 from day 8-21 for all *FLT3*-mutated patients. For patients over 70 years old we prefer azacitidine/venetoclax as induction unless they have highly proliferative disease (i.e., extreme hyperleukocytosis) or have cytogenetics or mutations suggestive of chemoresponsiveness (CBF or *NPM1*). We suspect that a potential third practice-changing triplet could come in the form of venetoclax, cytarabine, and an anthracycline, which has shown early success in *NPM1*-mutated AML. For patients younger than 70 years old, we would consider azacitidine/venetoclax if they have secondary AML, adverse-risk AML including monosomal karyotype, complex karyotype or MDS-defining cytogenetics. For *TP53*-mutated AML patients we recommend a clinical trial if available until the next practice-changing treatment is approved. As leukemia physicians we are fortunate to be working in an era of remarkable progress. First and foremost, we know that the future will yield even more dramatic changes to the treatment of AML than we have been fortunate to witness in the past few years.

Disclosures

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Contributions

SML and SRM performed the literature review, evaluated the data, and wrote the manuscript.

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