

## Original Article

# Treatment of older patients with acute myeloid leukemia (AML): a Canadian consensus

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**Abstract:** Patients over age 60 comprise the majority of those diagnosed with acute myeloid leukemia (AML), but treatment approaches in this population are variable, with many uncertainties and controversies. Our group conducted a literature review to summarize the latest information and to develop a consensus document with practical treatment recommendations. We addressed five key questions: selection criteria for patients to receive intensive induction chemotherapy; optimal induction and post-remission regimens; allogeneic hematopoietic stem cell transplantation (HSCT); treatment of patients not suitable for induction chemotherapy; and treatment of patients with prior hematological disorders or therapy-related AML. Relevant literature was identified through a PubMed search of publications from 1991 to 2012. Key findings included the recognition that cytogenetics and molecular markers are major biologic determinants of treatment outcomes in the older population, both during induction therapy and following HSCT. Although disease-specific and patient-specific risk factors for poor outcomes are more common in the older population, age is not in itself sufficient grounds for withholding established treatments, including induction and consolidation chemotherapy. The role of HSCT and use of hypomethylating agents are discussed. Finally, suggested treatment algorithms are outlined, based on these recommendations.

**Keywords:** Acute myeloid leukemia, chemotherapy, cytogenetics, prognosis, hematopoietic stem cell transplantation, hypomethylating agent

## Introduction

Treatment of older patients with acute myeloid leukemia (AML) has been hampered by uncertainties. Patients over age 60, who make up more than 50% of the AML population [1], have different biological and clinical features compared to younger patients [2, 3]. Older patients are more likely to have cytogenetic abnormalities associated with poorer outcomes [2, 4-13], a history of antecedent hematological disorder (AHD) [14] and co-morbidities or poor performance status that can limit treatment options and lead to reduced dose intensity [2]. For

these reasons, there is considerable variability in how older patients are treated, specifically with respect to intensive induction chemotherapy, post-remission therapy, and hematopoietic stem cell transplantation (HSCT). The advent of newer therapies, such as hypomethylating agents, has led to further uncertainty about which treatment to offer to different subsets of patients.

In order to clarify some of these issues, a panel of ten Canadian hematologists specializing in AML undertook a review of the literature on AML in older patients. Five key clinical ques-

tions were addressed, and recommendations were formulated for each, based on the best available evidence and clinical judgment. Finally, a series of treatment algorithms was created, based on these recommendations.

### Methods

A committee of ten leukemia experts from across Canada worked on the guidelines. The committee determined the five relevant questions, and then worked in pairs to review and evaluate the relevant literature relating to each question. Initially, a PubMed search of English-language clinical trials and meta-analyses published from 1991 to 2011 was conducted to ensure that all relevant studies were included. Case reports were excluded, as were pilot studies, studies using < 30 patients, phase I studies, economic analyses and quality-of-life studies. The authors then added supplemental literature as required, and provided further insights based on personal and institutional experience and judgment. No formal evaluation of evidence was conducted. The five groups then developed written working outlines and drafted treatment recommendations for each question. These were subsequently combined into a consensus document, which was modified and approved by the Chair (JMB). Panel members subsequently met as a group and agreed on the treatment recommendations for each of the five clinical questions. Dissenting opinions were to be noted in the final document.

### Results

*Question # 1: What are the major criteria to determine who is a suitable candidate for intensive induction chemotherapy?*

#### Influence of age

Controversy persists over the upper age appropriate for intensive induction therapy [5]. Many studies have shown increasing age to be associated with a worse prognosis [6-8, 14], but the influence of performance status, co-morbidities and disease biology on these outcomes has been unclear, as these factors also worsen with increasing age. Recent evidence suggests that these factors are more important than age per se [5, 7, 14]. One retrospective study of 291

newly diagnosed AML patients receiving induction therapy compared patients aged 60-69 to those aged 70-82 [5, 9]. Patients were selected for intensive treatment on the basis of overall fitness, as determined by the treating physician, and patient preference after discussion with the physician. Patients  $\geq$  age 70 were less likely to receive induction therapy; however, among those who received induction, no significant differences were noted in terms of complete remission (CR) rate, early death (ED) or overall survival (OS) [5, 9]. A number of other recent studies support the observation that comorbidities, performance status and disease biology are more important determinants of treatment outcome than age [15-17]. These studies suggest that, if patients are pre-selected based on medical fitness and favorable disease biology, age per se is not a factor in determining suitability for induction chemotherapy. However, few patients over age 80 would meet such criteria, and some studies have indicated that patients in this age group have much higher early mortality and inferior survival with induction therapy [15, 18].

#### Complete remission (CR) achievement and duration predict survival

Achievement of CR has been considered a prerequisite for improving survival using chemotherapy [10] and thus has provided a standard point from which to compare outcomes and determine prognostic factors. Success in achieving CR with induction chemotherapy depends on both the anti-leukemic efficacy of the therapy and the patient's ability to tolerate it [11]. However, OS also depends on the duration of CR, as a brief CR duration produces only limited survival benefit.

#### Cytogenetic abnormalities as predictors of CR and survival

A number of studies, including some in the elderly, have clearly identified cytogenetics as the most powerful disease biology-related predictor of response and survival using standard induction chemotherapy. AML patients have been stratified into risk categories based on major cytogenetic scoring systems, particularly the Medical Research Council (MRC) [9, 12, 19] and Eastern Cooperative Oncology Group (ECOG) [20, 21] classifications. Although slight

differences exist, both systems have identified three major cytogenetic risk categories: favorable, intermediate and adverse. While the relative incidence of adverse cytogenetic risk profiles increases with age [8, 9, 12-14], the effect of specific cytogenetic abnormalities on clinical outcomes is independent of age. In addition, an extremely high-risk category has been identified, based on the presence of multiple monosomies [22-24]. Reported CR and survival rates associated with each of these categories are shown in **Table 1**.

For older patients with adverse-risk cytogenetics, remissions with standard induction chemotherapy are typically brief (3-6 months); median OS is in the range of 6 months [8, 9, 19], which compares with 3-4 months with supportive care alone [9, 25]. Because of this limited efficacy, there is broad consensus in the group that such patients should not be offered induction chemotherapy outside the setting of a clinical trial, unless a stem cell donor is available and there is an intention to proceed rapidly to HSCT.

Older patients with t(8;21), inv(16) and t(15;17) have demonstrated high CR rates and favorable survival and should be offered intensive chemotherapy if their functional status and medical history suggest they will tolerate the procedure [26]. Evidence in younger patients indicates that those with t(8;21) or inv(16) and a corresponding *c-kit* mutation have a high relapse rate and brief OS [27]. However, the prognostic and practical implications of *c-kit* mutations are not well studied in older patients.

For patients with intermediate-risk cytogenetics, CR rates are in the 60% range, and median CR duration is around 9 months [8, 9]; these patients are also considered suitable for standard induction chemotherapy. However, relapse rates are in excess of 80%, with a correspondingly low 3-5 year OS (see **Table 1**). These patients should therefore be considered for either HSCT, if they are eligible, or a clinical trial with an intention of prolonging survival.

Some patients present with prominent symptoms and signs due to rapidly progressive, high white cell count ( $> 100 \times 10^9/L$ ) disease and require immediate induction therapy. In such cases the physician should not wait for cytogenetic results, and induction therapy should be

initiated promptly if the patient is otherwise fit for such treatment.

### Molecular genetics in patients with intermediate cytogenetic risk

In older patients with AML arising *de novo*, 45-50% have a normal karyotype, placing the patient in the intermediate cytogenetic risk group [14, 15, 28]. In this setting, molecular genetic testing can provide useful prognostic information [13, 18, 19, 29]. The presence of a nucleophosmin (*NPM1*) mutation has been associated with superior outcomes in older patients with normal karyotype. Becker *et al* [28] found that *NPM1* mutation was associated with a higher CR rate (84% vs 48%;  $P < 0.001$ ), as well as longer disease-free survival (DFS) ( $P = 0.047$ ; 3-year rates, 23% vs 10%) and OS ( $P < 0.001$ ; 3-year rates, 35% vs 8%). Another large European study confirmed the favorable impact of *NPM1* mutations in older patients [26]. There are conflicting data suggesting that other mutations, such as *IDH1/2*, may influence prognosis in younger patients with *NPM1* mutations [30, 31]; corresponding data in older patients are lacking.

In contrast, *FLT3-ITD* mutations do not seem to affect the CR rate [32], and the influence on OS in older patients has varied among studies [28, 32]. The weight of evidence in younger patients clearly indicates that these patients are at high risk for early relapse. However, several studies in older patients undergoing induction therapy have not demonstrated an independent impact of *FLT3-ITD* mutations on OS [26, 33, 34]. These patients, as is the case with other intermediate-risk patients, may be offered induction therapy, but with an intention of proceeding to HSCT or as part of a clinical trial. The use of *FLT3* inhibitors upfront, either alone or in combination with chemotherapy, is still considered investigational. A *CEBP $\alpha$*  mutation, particularly when biallelic, has been associated with reduced relapse rates in younger patients [35], but this mutation is less common and has not yet been studied systematically in older patients. Similar to what has recently been observed in younger patients with AML, it is anticipated that in the foreseeable future, refined molecular prognostication will assume a more prominent role in the appropriate management of older patients as well.

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**Table 1.** Cytogenetic/molecular risk categories and clinical outcomes

Cytogenetic risk category	Karyotype	Complete remission	Overall survival	References
Favorable	t(15;17), t(8;21), inv(16) -OR-	75-88%	3-yr 38% 5-yr 17-38%	[8, 19, 32, 117, 118]
	Normal karyotype with <i>NPM1<sup>mut</sup>/FLT3<sup>wt</sup></i>	68-83%	3-yr 29-33% 5-yr OS 21%	[26, 28, 32]
Intermediate	Normal karyotype not associated with favorable molecular markers; cytogenetic abnormalities not included in other groups	51-63%	3-yr 18% 5-yr 11-16%	[8, 19]
Adverse	Complex (3 or more, not including a favorable abnormality), monosomy (especially complete or partial deletion of 5 or 7), inv(3), t(9;22), 11q23 or 17p abnormalities	26-40%	3-yr < 5%	[15, 18, 19, 32, 117]

**Table 2.** Clinical outcomes in five trials comparing induction chemotherapy regimens in older AML patients. Conventional regimens are shown in gray, comparators in white. Note that early death rates are consistently higher than would be expected from data in the literature on younger AML patients

Source	N	Induction Regimen	CR Rate	Early Death
Rowe <i>et al</i> (2004) [21]	235	Priming with GM-CSF 250 mg/m <sup>2</sup> x 48 hours or placebo, and DNR 45 mg/m <sup>2</sup> d1-3 + Ara-C 100 mg/m <sup>2</sup> x 7 days,	41% with DNR	16% with DNR
		Priming with GM-CSF 250 mg/m <sup>2</sup> x 48 hours or placebo, and MA 12 mg/m <sup>2</sup> d1-3 + Ara-C 00 mg/m <sup>2</sup> x 7 days, or	52% with MA	22% with MA
		Priming with GM-CSF 250 mg/m <sup>2</sup> x 48 hours or placebo, and IA 12 mg/m <sup>2</sup> d1-3 + Ara-C 100 mg/m <sup>2</sup> x 7 days	51% with IA	14% with IA
Goldstone <i>et al</i> (2001) [67]	1314	DAT → DAT → DAT → Stop ± interferon-α, → COAP → DAT → COAP +/- interferon-α (DNR 50 mg/m <sup>2</sup> d1, 3, 5; Ara-C 100 mg/m <sup>2</sup> , q12hr d1-10; TG 100 mg/m <sup>2</sup> q12hr, d1-10)	62%	16%
		ADE → ADE → DAT Stop ± interferon-α, → COAP → DAT → COAP +/- interferon-α (Ara-C 100 mg/m <sup>2</sup> , q12hr d1-10; DNR 50 mg/m <sup>2</sup> d1, 3, 5; E 100 mg/m <sup>2</sup> q12hr, d1-10)	50%	26%
		MAC → MAC → DAT Stop ± interferon-α, → COAP → DAT → COAP +/- interferon-α (MA 12 mg/m <sup>2</sup> , d1-3; Ara-C 100 mg/m <sup>2</sup> , q12hr d1-5)	55%	17%
Anderson <i>et al</i> (2002) [119]	161	Ara-C 200 mg/m <sup>2</sup> /d, d1-7 + DNR 45 mg/m <sup>2</sup> d1-3	43%	7% within 7 days of Rx
		MA 10 mg/m <sup>2</sup> /d, d1-5 + E 100 mg/m <sup>2</sup> , d1-5	56%	7% within 7 days of Rx
Van der Holt <i>et al</i> (2005) [120]	419	Two cycles of DNR 45 mg/m <sup>2</sup> /d, d1-3; + Ara-C 200 mg/m <sup>2</sup> , q12hr d1-7	48%	15%
		Two cycles of DNR 35 mg/m <sup>2</sup> /d, d 13; PSC-833 2 mg/kg → 10 mg/kg/d x 72 hours	54%	16%
Lowenberg <i>et al</i> (2009) [121]	813	DNR 45 mg/m <sup>2</sup> /d + Ara-C 200 mg/m <sup>2</sup> /d, Second cycle cytarabine 1000 mg/m <sup>2</sup> /q12h x 12 doses	54%	12%
		DNR 90 mg/m <sup>2</sup> /d + Ara-C 200 mg/m <sup>2</sup> /d, Second cycle cytarabine 1000 mg/m <sup>2</sup> /q12h x 12 doses	64%	11%

ADE = daunorubicin + cytarabine + etoposide; Ara-C = cytarabine; COAP = cylophosphamide, vincristine, cytarabine and prednisolone; d = day; DAT = daunorubicin + cytarabine + thioguanine; DNR = daunorubicin; E = etoposide; IA = idarubicin; hr = hour; MA = mitoxantrone; MAC = mitoxantrone + cytarabine; PSC = P-glycoprotein; q = every; TG = thioguanine.

### Patient-specific co-morbidity factors

Because patients with even moderate degrees of co-morbidity are often excluded from clinical studies, the proportion of older patients who might benefit from intensive induction is unclear. For similar reasons, the prognostic relevance of co-morbidity is difficult to estimate. Nonetheless, physicians must take co-morbidity into account when identifying patients likely to tolerate treatment [6, 17].

Prognostic tools developed to predict treatment-related mortality include the Charleston Comorbidity Index (CCI), which has been adapted for use in AML [36], and the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI). The latter tool, encompassing multiple organ co-morbidities [37], was evaluated retrospectively in 177 elderly patients with AML [38]. An HCT-CI of  $\geq 3$  was found to correlate with higher induction mortality (29%) and lower median OS [38]. Malfuson *et al* [39], in a retrospective analysis of 415 patients enrolled in the ALFA-9803 trial, also found that an HCT-CI of  $\geq 3$  was independently predictive of inferior survival, with a 12-month OS of approximately 11% [39]. A more recent study, using a multi-component model, found that a number of factors, including performance status, white blood cell count, serum creatinine and albumin, influenced early mortality with induction therapy [17]. Although providing useful guidance in decision making, such indices and models have not yet been validated prospectively in older AML patients.

### Relapsed AML

For relapsed patients, the duration of first complete remission (CR-1) is the strongest predictor of the likelihood of responding to re-induction chemotherapy. Patients with CR-1 duration of  $< 1$  year have a low CR-2 rate and inferior survival with re-induction [40, 41], and patients with adverse-risk cytogenetics have a CR-2 probability of only 20% [42]. These subgroups derive little benefit with intensive re-induction, particularly in older patients where tolerance of further intensive chemotherapy is poor. Patients  $\geq$  age 60 have lower CR-2 rates compared to younger patients [43]. Older patients with CR-1 duration of  $\geq 12$  months and an intermediate- or favorable-risk karyotype have a reasonable chance of achieving CR-2 and may

be considered for intensive re-induction if they are still medically fit. However, since second remissions are rarely durable, these patients should be considered for HSCT or investigative approaches in CR-2 to try to prevent relapse.

### Recommendations

1. Although overall suitability for induction chemotherapy declines with increasing age, age per se should not be the sole determinant of eligibility for induction chemotherapy. Patients  $>$  age 70 may be offered induction therapy if they meet the other criteria below.

2. Patients judged to be at high risk of induction mortality, based on the presence of major co-morbidities, should be offered non-intensive treatment options. Although co-morbidity indices are helpful in determining suitability for intensive chemotherapy, they have not been validated prospectively in the induction setting and should not replace clinical judgment. Discussion of these risks with the patient and the family are important to guide decision making.

3. For patients deemed medically fit and opting for intensive therapy, cytogenetic results are crucial to assess the potential benefit of such treatment, and should be provided in less than 1 week.

a. Patients with adverse cytogenetic profiles have low CR rates and little OS benefit compared to best supportive care alone. Therefore, in most cases they should not be offered standard induction chemotherapy outside of a clinical trial. An exception would be a potential HSCT candidate, with a suitable donor (see Q3 below), in whom induction therapy may be attempted as a means of subsequently proceeding to transplant.

b. Patients with a favorable cytogenetic profile or a normal karyotype with a favorable molecular profile (e.g., *NPM1* mutated/*FLT3-ITD* negative), should be offered induction chemotherapy with curative intent.

c. Patients with an intermediate cytogenetic profile appear to have an OS benefit with induction therapy, but outcomes are still unsatisfactory because of high relapse rates. These patients may still be offered induction chemotherapy but should also be considered for clini-

cal trials and other post-remission strategies, including HSCT.

d. Patients who are ill due to rapidly progressive, high white cell count disease should have induction therapy initiated immediately, if they are otherwise medically fit, even if cytogenetics results are not yet available, as these patients are at high risk of early death from progressive disease.

4. Molecular data (e.g. *NPM1*, *FLT3*, and other mutations) influence relapse rates and survival. However, as CR rates are > 50% in these molecular subgroups, we do not at this time recommend using these data to guide decision-making with respect to which patients to offer induction therapy.

5. For relapsed patients, re-induction therapy may be offered to fit patients with intermediate- or favorable-risk cytogenetics and a CR-1 duration of  $\geq 12$  months.

6. All older individuals with AML should receive a consultation with a physician with expertise in managing leukemia in older patients. Patients not otherwise suitable for standard therapy, based on the criteria above, should be offered the option of referral to a center that offers clinical trials for such patients.

*Question # 2: How should we treat older patients who are considered suitable for induction chemotherapy?*

### Standard chemotherapy

Standard induction chemotherapy is the so-called 7+3 regimen, consisting of cytarabine (Ara-C) 100-200 mg/m<sup>2</sup> by continuous IV infusion for 7 days, plus daunorubicin IV for 3 days. A recent phase III study in older patients demonstrated superiority of 90 mg/m<sup>2</sup> over 45 mg/m<sup>2</sup>, with a higher CR rate, and better OS in subgroups such as patients age 60-65 and those with favorable karyotype [42]. Although there have not been any studies comparing 60 to 90 mg/m<sup>2</sup>, reported CR rates and OS with 60 mg/m<sup>2</sup> in older patients appear comparable to those in the 90 mg/m<sup>2</sup> dose in this study [9].

Other anthracyclines and anthracenediones, particularly idarubicin and mitoxantrone, may also be used [21]. Optimal dosing of idarubicin is 12 mg/m<sup>2</sup>/day x 3 [44] and mitoxantrone 12

mg/m<sup>2</sup>/day x 3 [21]. In contrast, no benefit was found with higher doses of cytarabine [45], and high-dose cytarabine has been associated with neurologic toxicity in older patients [46].

According to evidence from published clinical trials, the expected CR rate with standard induction chemotherapy is 41-62% in elderly patients, and the risk of early death is 7-16% (**Table 2**). There is no evidence to show superiority of alternative regimens such as mitoxantrone-etoposide (NOVE) or topotecan-mitoxantrone as first induction [47, 48].

Although gemtuzumab ozogamicin (GO) as a single agent is not as effective as standard induction therapy [49], it may improve the efficacy of 7+3 induction therapy in some older patients. In a recent phase III clinical trial, older patients up to age 70 received GO in three fractionated doses (3 mg/m<sup>2</sup>/day on days 1, 4 and 7), in addition to standard 7+3 induction chemotherapy with 60 mg/m<sup>2</sup> daunorubicin [50]. GO-treated patients showed improved OS compared to standard induction chemotherapy alone; 2-year event-free survival (EFS) was 15.6% in the standard treatment group, compared to 41.4% in the standard treatment plus GO group ( $P = 0.0018$ ). The UK NCRI AML16 trial, a similar study using one dose of GO in combination with 7+3 in older patients (aged 51-84) also found an improved relapse-free survival and OS from CR in the GO arm. Patients with secondary AML or adverse-risk cytogenetics did not benefit from the addition of GO [51]. GO is currently not available in North America and some other jurisdictions.

### Alternative approaches to first induction

Several alternative agents, including amsacrine, clofarabine and the hypomethylating agents azacitidine and decitabine, may be considered in selected older AML patients with poor performance status or adverse cytogenetics.

Amsacrine is associated with less cardiotoxicity than anthracyclines [52] and has been used in combination with cytarabine as induction therapy for both younger and older patients with AML. Results are comparable to those using daunorubicin [53, 54]. Amsacrine represents an alternative to anthracyclines for patients with impaired cardiac function, but it

poses a risk of arrhythmia in patients with low serum potassium, low magnesium values and prolonged QTc intervals [52]. Patients' electrolytes should therefore be corrected prior to treatment.

Clofarabine, a newer-generation nucleoside analog, was administered as a single agent to patients aged  $\geq 60$  years during induction at 30 mg/m<sup>2</sup>/day and at 20 mg/m<sup>2</sup>/day during re-induction/consolidation, to a maximum of six cycles. CR rates in the presence of 1, 2 or 3 poor risk factors at baseline (age, poor performance status, adverse cytogenetics and/or AHD) were 54%, 51% and 48%, respectively. Toxicity was acceptable, and the early death rate was 9.8% [55]. Hence, clofarabine may be a useful alternative for some patients who would not be expected to respond to 7+3 induction and for those in whom anthracycline avoidance is considered desirable because of prior anthracycline use or moderate cardiac impairment [56]. Another study in patients aged  $\geq 60$  years suggested that the addition of low-dose cytarabine to clofarabine was well tolerated and improved CR rates and EFS compared to a historical group that received clofarabine alone [57]. An ongoing UK trial is comparing clofarabine plus daunorubicin with 7+3 in fit older patients.

*Hypomethylating agents:* Retrospective data [58] suggest that the use of azacitidine in selected older AML patients may produce OS rates similar to those of patients receiving induction chemotherapy (with median OS 11.2 months with intensive chemotherapy vs. 13.7 months with azacitidine). A similar study from MD Anderson also found similar survival in older AML patients receiving hypomethylating agent therapy, compared to intensive chemotherapy [59]. However, as these analyses were retrospective, the groups may not have been equivalent; in particular, patients with rapidly proliferating disease in practice are more likely to receive intensive chemotherapy rather than hypomethylating agents. There are no prospective phase III data comparing decitabine or azacitidine to standard induction chemotherapy. Thus, there are currently insufficient data to recommend hypomethylating agent therapy over induction chemotherapy in intermediate-risk older AML patients who are otherwise medically fit for intensive therapy.

### Primary induction failure

For patients failing 7+3 induction, a second induction using a non-cross-resistant chemotherapy regimen, may be used in intermediate- or favorable-risk cytogenetic patients who are still considered candidates for intensive therapy. Re-induction regimens may include mitoxantrone plus etoposide (NOVE) [47]; for more fit patients, adding intermediate-dose cytarabine (MEC or NOVE-HiDAC) may produce higher CR rates [60, 61] but with greater toxicity. Clofarabine plus intermediate-dose cytarabine is an alternative re-induction strategy [62]. However, patients with an adverse-risk karyotype have low CR rates with re-induction [62], and these patients should probably be considered for clinical trials or supportive care.

### Consolidation after CR

Unless proceeding directly to HSCT, most patients receive consolidation chemotherapy, although the magnitude of its benefit in older patients remains unclear. A variety of post-remission strategies have been employed. There is no evidence from prospective studies that intermediate- or high-dose cytarabine (HiDAC, 0.5-3 g/m<sup>2</sup>) is superior to conventional dose consolidation chemotherapy in older patients [63, 64]. Recently, a retrospective study from Princess Margaret Cancer Centre found a superior DFS in patients over age 60 with intermediate-risk cytogenetics who received 2 consolidation cycles containing HiDAC 1.5 g/m<sup>2</sup> over 3 hours x 6 doses plus daunorubicin, compared to 7+3 followed by NOVE [65]. There was no benefit to HiDAC in patients with adverse-risk cytogenetics. However, prospective studies using such a regimen are lacking. The optimal number of post-remission cycles remains unclear, and one cycle may be sufficient [66, 67].

Despite this, there is evidence in younger patients, based on retrospective data, that consolidation using repetitive cycles of HiDAC (3 g/m<sup>2</sup>) is associated with improved DFS [68] and OS [63, 69, 70] in patients with t(8;21) or inv(16). We therefore believe it is reasonable to utilize this strategy as well in older fit patients with these abnormalities. However, as HiDAC poses a higher risk of cerebellar toxicity in patients over age 60, such patients should receive a reduced HiDAC dosing schedule, e.g.

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1-1.5 g/m<sup>2</sup> every 12 hours on treatment days 1, 3 and 5 [71].

Data from two French studies suggest that, in older patients, lower-intensity, prolonged consolidation may produce results at least comparable to those of more intensive strategies [72, 73]. One study compared conventional consolidation with an outpatient regimen consisting of six less intensive consolidation cycles in 236 patients who achieved CR. Prolonged treatment was preferred to intensive chemotherapy on the basis of significantly greater OS and DFS, as well as lower toxicity [72, 73].

For patients judged medically unfit for intensive post-remission therapy following induction, low-dose cytarabine may potentially prolong remission duration, although it probably does not improve long-term survival [74]. Given the high relapse rates associated with older AML patients, novel post-remission strategies are warranted and these patients should be considered for clinical trials, particularly for those who are not candidates for HSCT.

### Acute promyelocytic leukemia (APL)

APL is rare in older patients, but has a favorable prognosis if the patient survives the initial treatment period. CR rates are in the 80% to 90% range, and 3 year OS is in the 50% range or higher, even in patients aged 70 and older [75-77]. Consequently, all patients except the very frail should be considered for treatment with curative intent.

The standard induction treatment for APL in patients > age 60 currently consists of all-*trans* retinoic acid (ATRA) plus an anthracycline, either idarubicin or daunorubicin [75-77]. Fit older patients with high WBC counts should also receive cytarabine [77]. Post-remission therapy usually consists of two cycles of treatment using similar drugs, often followed by maintenance ATRA. However, as older patients are more prone to anthracycline-induced cardiomyopathy, left ventricular function should be closely monitored [76]. Molecular monitoring for *PML-RAR* transcripts is recommended, as in younger patients. For relapsed patients, arsenic trioxide is the treatment of choice; it is usually well tolerated and may produce long second remissions [78]. Recent studies suggest that arsenic plus ATRA may be as effective as

anthracycline-based chemotherapy when given as first-line therapy [79]; it is not yet approved for this indication but may be considered in selected patients in whom anthracyclines or intensive chemotherapy are contraindicated.

### Recommendations

1. Older patients who are deemed suitable candidates should receive induction treatment consisting of an anthracycline or anthracenedione for 3 days plus cytarabine at a conventional dose (100-200 mg/m<sup>2</sup>) for 7 days. Acceptable anthracyclines/anthracenediones include:

- a. Daunorubicin 60-90 mg/m<sup>2</sup> daily x 3 days.
- b. Idarubicin 12 mg/m<sup>2</sup> daily x 3.
- c. Mitoxantrone 12 mg/m<sup>2</sup> daily x 3.

2. For patients with contraindications to anthracyclines (e.g., impaired left ventricular function or extensive prior anthracycline exposure), amsacrine may be substituted. Clofarabine, with or without cytarabine, may also be considered for such patients. Pending new phase III trial data in AML patients, there are insufficient data to recommend hypomethylating agents over standard induction therapy in intermediate-risk AML patients who are medically fit for induction chemotherapy.

3. For patients achieving CR, consolidation chemotherapy is recommended for patients who are still medically fit for such therapy:

a. For patients with t(8;21) or inv(16), modified high-dose cytarabine-based consolidation is recommended, with reduced dosing (e.g., 1-1.5 g/m<sup>2</sup> over 2-3 hours x 6 doses), to minimize the risk of central nervous system toxicity.

b. For patients with intermediate-risk cytogenetics, there are retrospective data supporting the use of modified high-dose cytarabine-based consolidation over conventional-dose therapy. However, in the absence of prospective data, no firm recommendation can be made.

c. In patients with adverse risk cytogenetics, conventional dose consolidation therapy is adequate. There is no evidence that any one consolidation regimen is superior.

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d. The optimal number of post-remission cycles in older patients is unclear. There is no evidence that additional cycles beyond the first produce superior outcomes, although this issue has not been adequately evaluated.

e. Alternatives to consolidation include:

i. Proceeding to HSCT without consolidation (see Q3 below).

ii. Low-dose maintenance chemotherapy (e.g., low-dose cytarabine) for patients who are no longer judged medically fit or decline further intensive treatment.

iii. No active treatment or supportive care only for patients who decline or are unfit for any further chemotherapy.

4. For patients aged 60-70, there is recent evidence that adding gemtuzumab in fractionated doses to standard induction therapy results in improved outcomes. It is strongly recommended that this agent be approved for use in induction therapy for these patients.

5. For primary induction failures, a non-cross-resistant regimen (e.g., NOVE +/- modified high-dose cytarabine) is acceptable therapy for patients who are still candidates for intensive therapy.

6. Older patients with APL should receive induction therapy with ATRA, with or without an anthracycline. For relapsed patients, arsenic trioxide therapy is appropriate for re-induction.

7. Given the high relapse rates in most AML subtypes, older patients should be encouraged to enroll in clinical trials using novel induction and post-remission strategies.

*Question # 3: Which older patients should be considered for allogeneic stem cell transplantation (HSCT)?*

### Cytogenetics as an independent prognostic factor

Selecting patients for HSCT depends on weighing the benefits of the procedure relative to the expected outcome with post-remission chemotherapy alone, as well as the relative risks of these options. Given the profoundly invasive nature of HSCT and the poor function of many AML patients, neither the lowest-risk nor the

frailest patients should generally be selected for HSCT. The former are excluded because their prognosis with chemotherapy alone is good, the latter because of treatment-related mortality.

### Reduced-intensity conditioning in older patients

In younger patients at high risk of relapse, HSCT in CR-1 appears to be superior to other treatments in reducing relapse risk and thus extending survival [80-82]. However, the risk of transplant-related morbidity and mortality increases with age. The introduction of non-myeloablative and reduced-intensity conditioning (RIC)-HSCT has improved the tolerability of transplantation so that it could be applied more broadly in the older AML population. This approach is being evaluated in a prospective, international phase 3 study [83]. Recent retrospective analyses indicate that for medically fit older patients, RIC-HSCT is well tolerated, with acceptable treatment-related mortality [84, 85]. Progression free survival (PFS) and OS did not differ significantly between patients in the 60-65 and 65+ age groups, according to one report [84].

Recent evidence indicates that HSCT may improve survival for patients over age 60 when compared to chemotherapy alone [86-88]. Kurosawa *et al* [87] showed a significantly improved 3-year OS of HSCT vs. no transplant ( $P = 0.012$ ) in a group of older patients (median age 60). In this study, cytogenetic risk, but not patient age, was significantly associated with RFS and OS in multivariate analysis. Although proper randomized data are lacking in the older population, there is a general consensus in the group that RIC-HSCT may be considered for appropriate candidates up to age 70.

The decision to proceed with HSCT is based on a number of factors: (1) the response to induction chemotherapy, (2) the cytogenetic and molecular genetic risk profile, (3) the patient's fitness based on co-morbidities and (4) the availability of a suitable human leukocyte antigen (HLA) matched donor.

*Response to induction:* There is general consensus that the patient must have achieved CR with induction or other therapy. RIC-HSCT for older patients not in remission are associated with prohibitively high failure rates [89] and

should not be undertaken outside of a clinical trial. For patients with relapsed disease, HSCT may be considered for those who achieve CR-2 with re-induction therapy. Gyurkocza *et al* recently documented 5-year OS of 34% in a group of 71 older patients in CR-2. However, these authors noted that the risk of relapse was 2.5 times higher than in patients treated in CR-1 ( $P < 0.001$ ) [89]. Therefore, for patients considered at high risk of relapse, it is preferable to transplant patients in CR-1.

*Risk profile:* As discussed in Q1 (above), AML patients can be stratified into favorable and unfavorable categories, based predominantly on cytogenetics [19, 90]. Patients judged to be at high risk of relapse should be considered for HSCT in CR-1 [8, 86]. These include patients with adverse-risk cytogenetics and those with intermediate-risk cytogenetics, except those with favorable molecular profiles (*NPM1* mutated/*FLT3-ITD* negative or *CEBPA* double mutants). Although older patients with favorable-risk cytogenetics (or intermediate-risk with favorable molecular profiles) have inferior survival compared to younger patients with the same characteristics, there are insufficient data to support recommending HSCT in older patients with these favorable features.

Cytogenetic risk classification is the most important determinant of outcome in patients receiving RIC-HSCT. HSCT can to some extent overcome the effects of adverse cytogenetic and molecular genetic risk [91, 92], and results from non-randomized studies appear to favor HSCT in these patients, even allowing for patient selection. However, it is recognized that most reported series in older patients are highly selected, and prospective comparative studies in older patients are needed, comparing HSCT to conventional treatment approaches.

*Comorbidity:* The HCT-CI was developed to better define those patients with an unacceptable risk of fatal outcome with HCT [37]. Compared with the CCI, the HCT-CI has refined the definition of several co-morbidities, improving the sensitivity and specificity for predicting non-relapse mortality (NRM) [37]. Recent overall improvements in HSCT and the development of reduced-intensity conditioning has permitted wider use of HSCT in patients with co-morbidities and in patients > 60 years of age, often resulting in durable leukemia-free survival [84, 85, 93-96].

*Donor availability:* HSCT is generally performed using hematopoietic stem cells (HSCs) either from an HLA-matched sibling or from a matched unrelated donor (MUD) with at least a 9/10 antigen match. Siblings and 10/10 MUDs are probably equivalent options, based on recent data [89]; 9/10 MUD HSCT is associated with higher toxicity and treatment-related mortality [89], but this option is also considered acceptable in patients at high risk of relapse.

The difficulty of finding an appropriate donor has spurred the search for alternative sources of HSCs, including haploidentical related donors with two or more antigenic mismatches, or cord blood with three or fewer mismatches [87]. Although recent data are promising, it is preferable for alternative-donor HSCT to be done within the context of prospective clinical trials until further results are available [87, 97-99].

### Recommendations

1. When an HLA-matched related or unrelated donor is available, HSCT is an appropriate treatment option for suitable patients aged > 60 with AML who are in CR-1 and have one of the following:
  - a. Intermediate-risk karyotype, with the exception of those with favorable molecular profiles.
  - b. Adverse-risk karyotype.
  - c. t(8;21) or inv(16) with *c-kit* mutation.
2. HSCT should also be considered for patients in CR-2, although efficacy data in older patients are limited, and relapse rates are higher than for those transplanted in CR-1.
3. HSCT should employ non-myeloablative or RIC regimens in patients aged > 60.
4. The HCT-CI should be used to help determine eligibility for HSCT.
5. In higher-risk patients with no available 6/6-matched sibling or 9-10/10 MUD, alternative-donor transplants (haploidentical donors and cord blood sources) may be considered but should be done as part of a clinical trial.
6. Otherwise-suitable patients with treatment-induced AML or AML arising from an antecedent disorder (AHD) should be considered eligible for transplantation (see Q5).

*Question # 4: How should we treat older patients who are not considered suitable for induction chemotherapy?*

Patients who are not being considered for induction chemotherapy or for subsequent HSCT constitute a diverse group including individuals judged too frail for these procedures and those who would not benefit from them. They may also include patients who refuse consent or who, for reasons of personal choice or access, cannot be accommodated or treated. Major treatment options for these patients include best supportive care (BSC) with or without hydroxyurea; low-dose cytarabine; hypomethylating agents; and investigational therapies. For patients receiving BSC, trial data suggest a typical OS of approximately 3.5 months, with a 1-year survival of 10% to 15% [25]. These findings provide a benchmark from which to compare outcomes with active intervention and can be used to guide clinical decision making.

### Low-dose cytarabine

The MRC AML 14 trial [10], the only randomized trial comparing BSC with hydroxyurea to low-dose cytarabine, demonstrated a significant advantage for cytarabine treatment, with 18% achieving CR. Cytarabine treatment was associated with increased OS in all age groups. However, only patients with favorable- or intermediate-risk cytogenetics achieved a CR with cytarabine. There were no remissions, and correspondingly no survival advantage, with low-dose cytarabine in the adverse-risk cytogenetics group.

### Hypomethylating agents

A phase III study of patients with AML (20-30% blasts) and multilineage dysplasia compared azacitidine to conventional care regimens (most of whom received either either BSC or low-dose cytarabine) [100, 101]. CR rates for azacitidine were similar to those observed with low-dose cytarabine. However, the azacitidine arm had a significantly greater 2-year OS (50% vs 16%;  $P = 0.001$ ) compared to the conventional care arm, most of whom received non-intensive therapy. OS was longer in patients who experienced complete or partial response or hematological improvement with azacitidine, relative to those who had no response [102].

This is in contrast to the expected findings with cytarabine treatment, namely that survival benefits are limited to patients experiencing CR [10, 101]. A recent study in older AML patients unfit for, or unresponsive to, induction therapy reached a similar conclusion regarding survival benefit with azacitidine using a 5-day-per-week schedule, even in the absence of CR [103]. An ongoing phase III trial (NCT01074047) is comparing azacitidine with conventional care regimens in older patients with higher-blast-count AML.

Cytogenetic risk group remains an important prognostic factor with azacitidine, with adverse risk groups having inferior OS and 2-year survival. However, even in patients with adverse cytogenetic risk, azacitidine treatment was associated with significantly greater survival, relative to conventional treatment (2-year OS rate 38% vs 0%;  $P = 0.01$ ) [101].

A multicentre phase III randomized trial was recently reported, comparing decitabine to either BSC alone or low-dose cytarabine in AML patients  $\geq$  age 65 [104]. Most patients in the supportive-care arm (88%) received cytarabine. This study found that the CR rate was higher in the decitabine arm (17.8% vs 7.8%;  $P = 0.001$ ). There was a non-significant increase in OS in the decitabine arm ( $P = 0.11$ ) that reached statistical significance ( $P = 0.037$ ) at a subsequent unplanned survival analysis. Subgroup analysis showed an OS benefit in the decitabine arm for patients  $\geq$  age 75 and in those with  $> 30\%$  marrow blasts, intermediate-risk karyotype, *de novo* AML and ECOG performance status (PS) 2; however, a multivariate analysis was not done. Adverse events were similar between the decitabine and cytarabine groups [104].

### HDAC inhibitors and other investigational agents

A variety of investigational agents have been used alone or in combination with hypomethylating agents and low-dose cytarabine in older, unfit AML patients. These have included histone deacetylase (HDAC) inhibitors such as valproic acid and vorinostat [105-107], tipifarnib [25], laromustine [108], temozolomide [109] and others. Despite encouraging results in some of these, none have yet been demonstrated to be more effective than either hypo-

methylating agents or low-dose cytarabine alone [110-112]. The largest phase III trial of such agents found no survival benefit to tipifarnib compared to BSC in previously untreated AML patients over age 70 [25].

### Recommendations for patients unsuitable for induction therapy

1. For patients with 20% to 30% bone marrow blasts with multilineage dysplasia, azacitidine should be offered as standard treatment. For patients not able to receive azacitidine, low-dose cytarabine is acceptable for those with intermediate- and favorable-risk cytogenetics.

2. For all other patients, consider cytogenetic risk:

a. Intermediate-risk and favorable-risk cytogenetics: Low-dose cytarabine is reasonable initial treatment based on the MRC AML 14 study. Decitabine is also a reasonable choice, if available, based on recent phase III data, and may be superior to cytarabine in patients with *de novo* AML and those  $\geq$  age 75. Data from a similar ongoing trial with azacitidine are not yet available.

b. Adverse-risk cytogenetics: No effective treatment is available. Low-dose cytarabine is ineffective in this setting and should not be offered, while decitabine was not shown to be superior. The standard treatment is BSC.

3. All patients who are unfit for intensive induction therapy should be offered participation in a clinical trial using novel therapeutic approaches, given the overall poor outcomes in such patients.

### *Question # 5: How should we treat older patients with secondary AML?*

Patients with AML arising from an AHD or from prior treatment have an inferior prognosis with standard induction chemotherapy, compared to those with *de novo* AML [113]. Such cases, sometimes described collectively as secondary AML, are also more likely to have adverse-risk cytogenetics [113]. Studies using multivariate analysis, or otherwise correcting for cytogenetic risk group, indicate that karyotype is a more important predictor of prognosis than prior disease history per se [9, 26, 39, 114]. Accordingly,

patients with AML arising from an AHD, and with an intermediate-risk karyotype, have CR rates and OS comparable to those of patients with *de novo* AML [114]. In secondary AML patients  $>$  age 60, there is no evidence that the usual molecular risk factors, *NPM1* and *FLT3* status, are of major prognostic importance [115].

In one study, patients with prior MDS previously treated with lenalidomide or hypomethylating agents appeared to have a poorer response rate to subsequent induction therapy, relative to patients receiving only supportive care or other treatment for their earlier disease [114]. While it was suggested that the prior treatment may have altered the susceptibility of the leukemic cells to subsequent therapy, it is also possible that the prognosis in these cases was intrinsically poor. These retrospective results have not yet been verified in a prospective study.

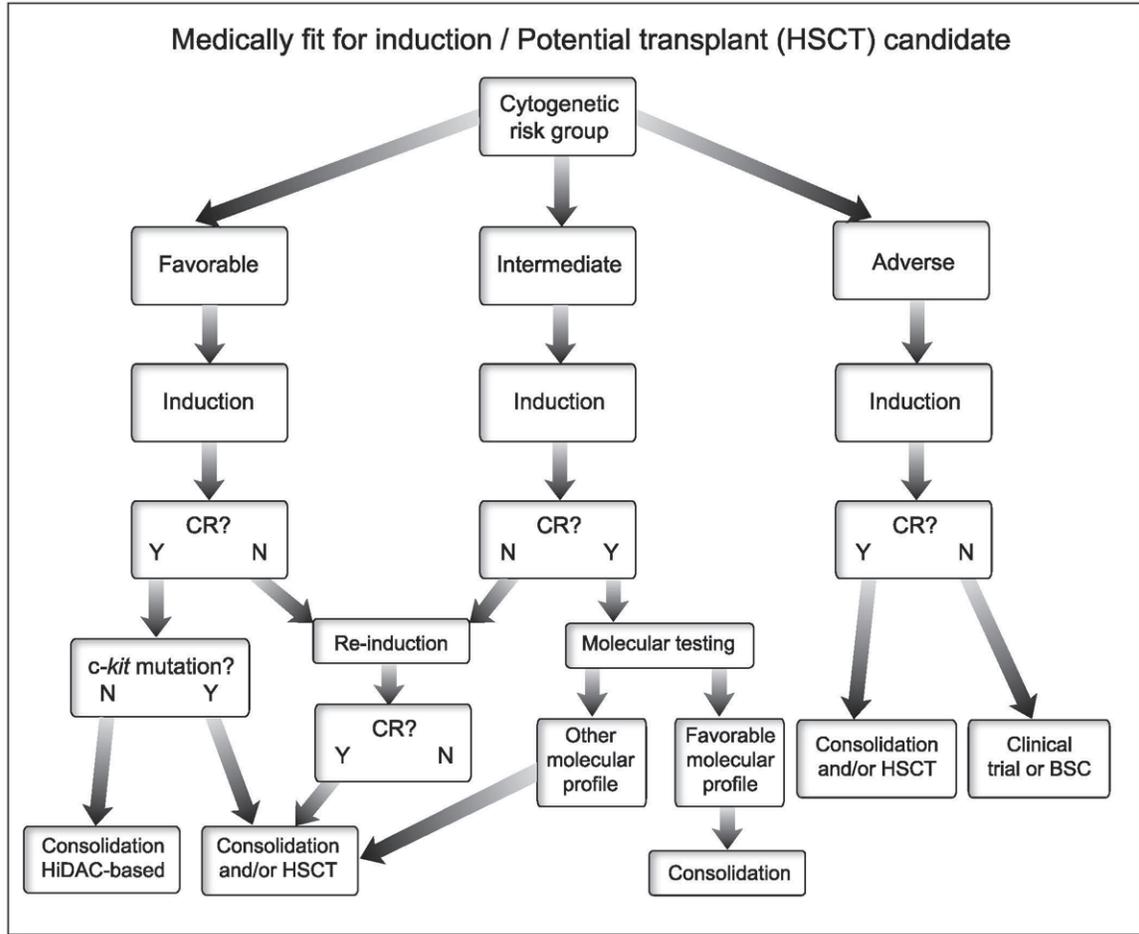
Secondary AML arising from a prior myeloproliferative disorder (MPD) is associated with a poorer prognosis with induction therapy, compared to AML arising from a prior MDS or other types of AHD [116]. A longer duration of the AHD [6], and a longer time between diagnosis of the AHD and progression to AML [114], have also been associated with shorter survival with induction therapy.

Allo-HSCT is a promising approach for secondary AML patients achieving CR. In a large cohort of *de novo* or secondary AML patients (median age 60 years) undergoing RIC-HSCT in CR, AHD was not an independent risk factor for relapse or progression [89].

### Recommendations

1. Older patients should not be denied induction chemotherapy solely on the basis of having transformed from a prior MDS or having received prior chemotherapy for another malignancy. Secondary AML patients with intermediate- or favorable-risk cytogenetics should be offered induction chemotherapy if they are otherwise medically fit, as per Q2.

2. Secondary AML patients with adverse-risk cytogenetics, or transforming from a prior MPD, should be considered for other treatment options. These may include:



**Figure 1.** Treatment of older AML patients deemed medically fit for induction who are also potential candidates for hematopoietic stem cell transplant (HSCT). BSC = best supportive care; CR = complete response; HiDAC = high-dose cytarabine.

a. Hypomethylating agent therapy, such as azacitidine, if the bone marrow shows 20% to 30% blasts with multilineage dysplasia.

b. Clinical trial, if available.

c. Supportive care alone.

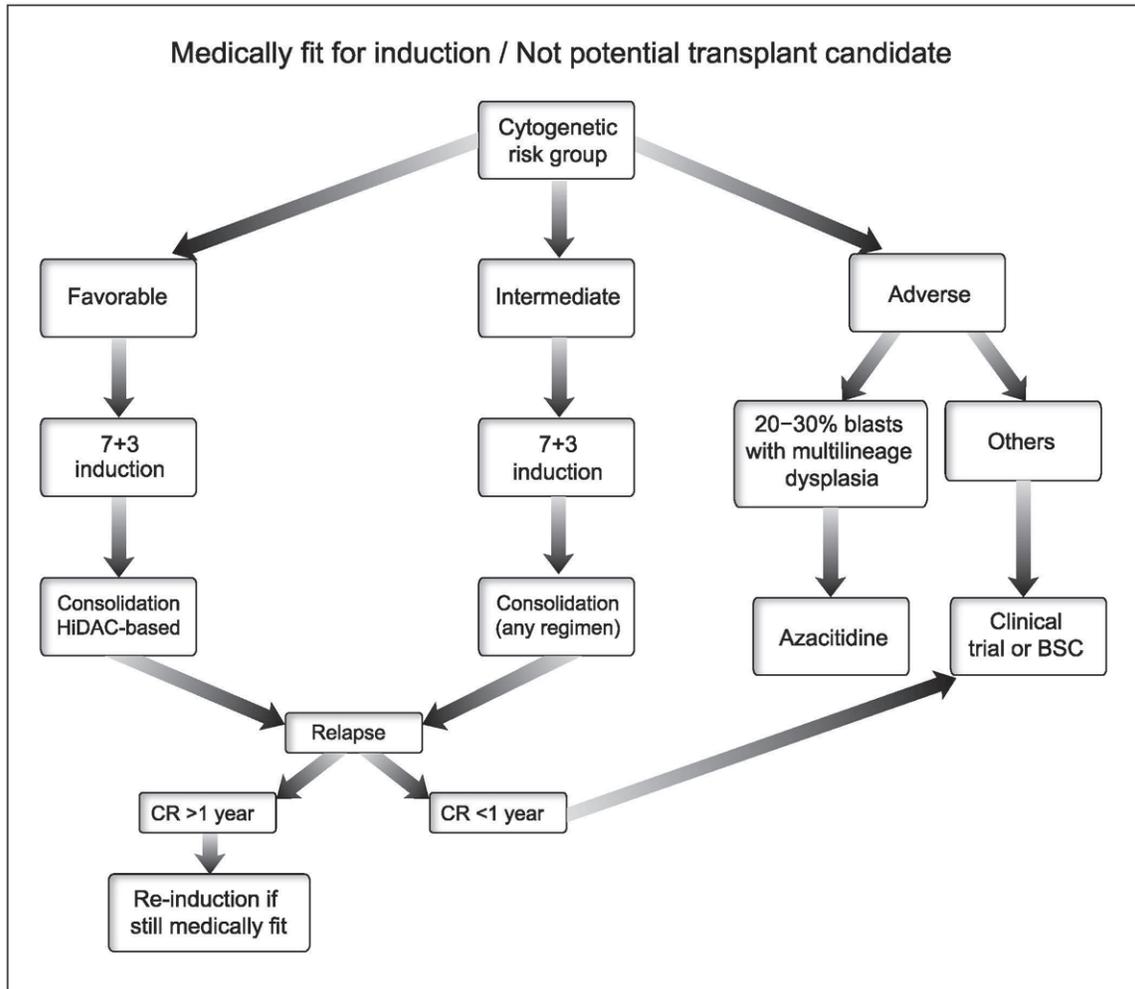
3. Potential HSCT candidates should be offered induction therapy with a view toward proceeding to HSCT if response is achieved, as in *de novo* AML. Some panel members felt that hypomethylating agent therapy is also an acceptable initial treatment for patients with 20% to 30% blasts and multilineage dysplasia, if a suitable donor has not yet been identified.

**Conclusion**

Several key recommendations evolved from this consensus. First, for older patients consid-

ered medically fit, who opt for intensive induction chemotherapy, cytogenetic information is critical in order to facilitate treatment decisions and should be provided in a timely manner. Older patients with adverse-risk cytogenetics derive little benefit from standard induction therapy, and other approaches should be considered. Conversely, patients should not be denied induction chemotherapy solely on the basis of age, having transformed from a prior MDS, or having leukemia that arose from prior chemotherapy.

For patients not suitable for induction chemotherapy, an assessment of the percentage of bone marrow blasts will guide treatment decisions. For patients with 20% to 30% blasts with dysplasia, azacitidine is the recommended agent. For patients with > 30% bone marrow blasts with intermediate-risk cytogenetics, low-



**Figure 2.** Treatment of older AML patients deemed medically fit for induction who are not candidates for HSCT. BSC = best supportive care; CR = complete remission; HiDAC = high-dose cytarabine.

dose cytarabine or decitabine are reasonable as initial treatment, pending further trial data.

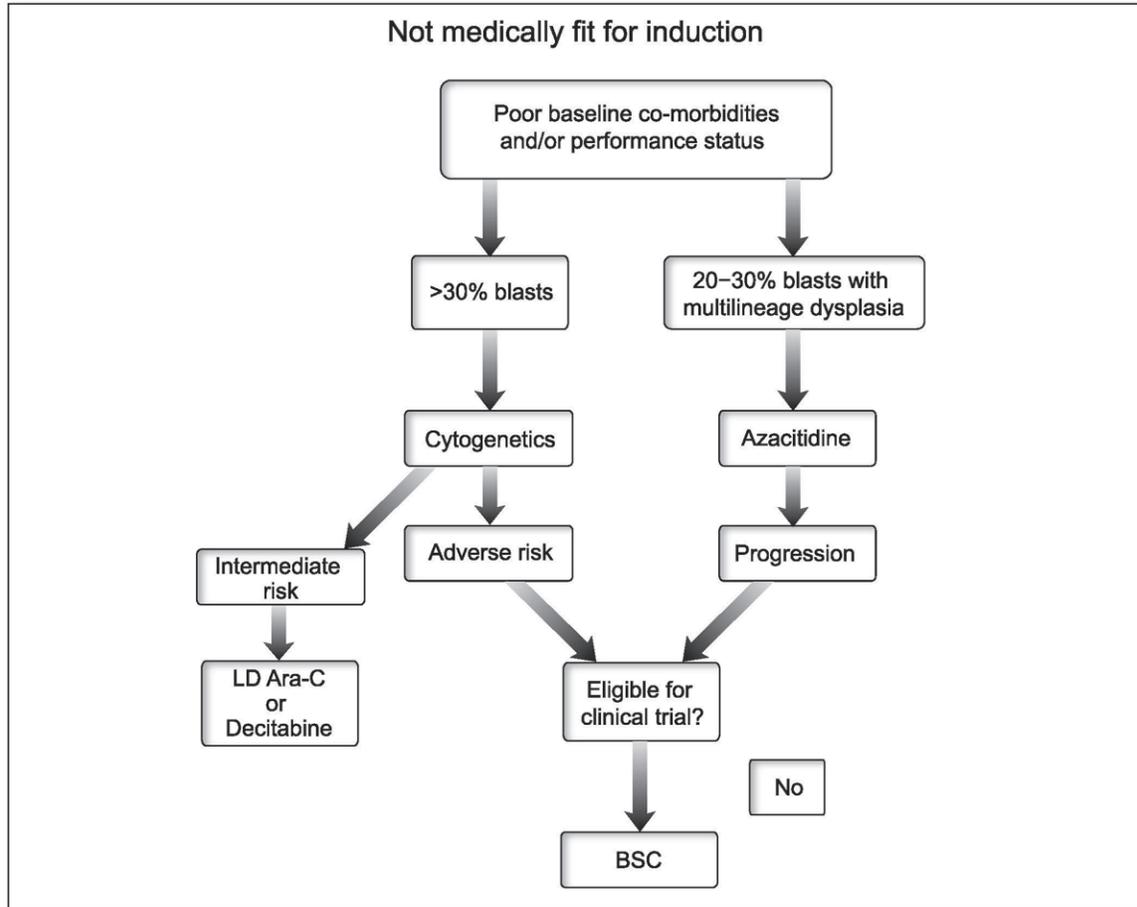
The key recommendations stemming from the discussions are summarized in the algorithms shown in **Figures 1-3**.

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**Conflict of interest**

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**Figure 3.** Treatment of older AML patients not deemed fit for induction. BSC = best supportive care; LD-AraC = low-dose cytarabine.

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