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Choosing induction chemotherapy in therapy-related acute myeloid leukemia

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ABSTRACT

Patients with AML that develops after cytotoxic therapy (tAML) have overall inferior outcomes relative to de novo AML due to both patient-related factors and the intrinsic biology of the disease. Treatment of patients with tAML is challenging. The key initial clinical decision is whether a patient is a candidate for or likely to benefit from intensive induction chemotherapy, a determination which we argue should not be predicated on chronologic age alone. For those determined likely to tolerate intensive induction chemotherapy, CPX-351 is likely superior to conventional induction with cytarabine and daunorubicin. For those deemed inappropriate for intensive induction, hypomethylating agents have the strongest evidence base in elderly adults with AML, and are an attractive option in tAML. This is particularly true in patients with *TP53* mutations who are less likely to respond to conventional induction chemotherapy. Exciting options on the therapeutic horizon for tAML include combination therapies incorporating BCL2 inhibitors, Hedgehog pathway inhibitors, and isocitrate dehydrogenase inhibitors.

1. Introduction

Therapy-related AML (tAML) can be defined as AML that develops following cytotoxic chemotherapy and/or radiotherapy for a malignant or non-malignant disease [1]. It is often grouped among the various classes of secondary AML (sAML), including AML with antecedent myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), and AML with MDS-related cytogenetic changes. The poor outcomes of patients with tAML relative to de novo AML are well-established. Patients with tAML are often older and may have more extensive medical comorbidities, as well as poor bone marrow reserve secondary to the effects of prior therapy. Patients with tAML are also more likely to present with poor-risk cytogenetics and mutated *TP53* than those with de novo AML [2–4]. Large population-based studies have suggested that even when patients with tAML are able to undergo conventional induction chemotherapy, they are less likely to achieve complete remission and have a lower overall survival (OS) [3].

A major difficulty in choosing initial therapy for tAML is the fact that, fundamentally, tAML is an epidemiologic definition which associates the development of AML with prior exposure to cytotoxic chemotherapy or radiation. For an individual patient, prior exposure to chemotherapy or radiation does not necessarily prove causation. Within the subgroup of tAML, there is substantial cytogenetic and molecular heterogeneity which similar to de novo AML affects treatment outcomes [5]. The choice of induction therapy for AML is frequently made with incomplete information as cytogenetic and molecular genetic testing can take up to 1–2 weeks to obtain results. Though better treatment options for patients with tAML are clearly needed, few trials have focused specifically on this population (Table 1) and the choice of induction therapy is based on extrapolation and subset analysis of larger studies,

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Table 1
Studies enrolling exclusively patients with sAML.

Citation	Study arms	Study type	Population	Results
Lancet et al. 2018 [14]	CPX-351 vs. conventional 7 + 3 induction	Phase III open-label study	Treatment-naïve patients aged 60–75 years with sAML[a]	Improved median OS in the CPX-351 arm (9.56 vs. 5.95 months, HR 0.69, 95% CI 0.52–0.90).
Stone et al. 2015 [36]	Cytarabine + amonafide L-malate vs. cytarabine + daunorubicin	Phase III open-label study	Treatment-naïve patients with tAML or AML after prior MDS or CMML	No improvement in CR rate in the experimental arm (negative study).

Abbreviations: AML – acute myeloid leukemia, CMML – chronic myelomonocytic leukemia, CR – complete remission, MDS – myelodysplastic syndrome, OS – overall survival, sAML – secondary AML, tAML – therapy-related AML.

[a] AML with antecedent MDS or CMML, or AML with MDS-related cytogenetic changes.

many of which excluded tAML from the initial study population.

In this review, we will first summarize the evidence base and discuss several risk stratification algorithms used to help determine which patients are appropriate candidates for intensive induction chemotherapy. We will then review available intensive and non-intensive treatment regimens for patients with tAML. We will discuss several novel agents that have shown promising results in early clinical trials and conclude with recommendations for managing patients with tAML in the current treatment landscape.

2. Choice of intensive vs non-intensive therapy

Similar to de novo AML, a key factor in treatment planning is determining whether a patient with tAML is able to tolerate intensive induction chemotherapy based on age, comorbidities, bone marrow reserve, and performance status (PS). Age has conventionally been used as an exclusion criteria in clinical trials. Data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database indicate that only 40% of adults age ≥ 65 with newly diagnosed AML in the United States receive any form of chemotherapy [6]. However, population-based data suggest that many elderly adults may derive substantial benefit from AML treatment. Analysis of data from the Swedish Acute Leukemia Registry (containing data on all patients age ≥ 16 diagnosed with AML) indicated that patients age 70–79 with newly diagnosed AML had improved OS with intensive treatment vs. palliative therapy alone regardless of PS [7].

Numerous risk-stratification models have been developed to assist clinicians in selecting appropriate candidates for intensive treatment approaches. Note, however, that none of these models has focused exclusively on the tAML population, and this caveat should be kept in mind when applying these models in clinical practice. The German AML Cooperative Group used data from a cohort of 1406 patients age ≥60 to develop an algorithm predicting likelihood of complete response (CR) and risk of early death (ED) in elderly adults treated with intensive induction chemotherapy. They then validated this prediction tool in an independent cohort of AML patients and developed a web-based interface offering their algorithm for public use. Factors associated with CR and ED were body temperature, age, de-novo vs. sAML, haemoglobin, platelet count, fibrinogen, and serum lactate dehydrogenase [8]. In another study of 3365 adults of all ages who received intensive chemotherapy for newly diagnosed AML, age and PS were the most significant predictors of treatment-related mortality (TRM) in multivariate analysis. However, multivariate models were more effective at predicting TRM than age or PS alone. Removal of age from multivariate models only modestly decreased prognostic potential, suggesting that age is largely a surrogate for other patient factors conferring a higher risk of TRM [9].

In addition, there is growing interest in using comprehensive geriatric assessment (GA) to aid in risk stratification of newly diagnosed patients with AML. In a single-institution prospective cohort study, investigators performed a standardized GA on 74 consecutively-enrolled patients age ≥60 with newly diagnosed AML. GA included measures of cognition, depression, distress, physical function (self-reported and objectively measured) and comorbidities. All had an Eastern Cooperative Oncology Group (ECOG) PS score < 3 (78.1% ≤ 1) and all were treated with intensive induction chemotherapy. In this cohort, among conventional risk factors, only cytogenetic risk group, prior MDS, and baseline serum haemoglobin were associated with inferior OS (chronologic age and ECOG PS were not). Among factors included in GA, impairment in cognition and objectively-measured physical function were also associated with inferior OS. Furthermore, in a multivariate analysis controlling for age, gender, ECOG PS, cytogenetic risk group, baseline haemoglobin, and prior MDS, impaired cognition and objectively-measured physical function remained predictors of inferior OS [10]. Similar data are available for elderly patients with AML/MDS treated non-intensively, where impairment in activities of daily living (ADLs), Karnofsky Index < 80, and high scores for 'fatigue' on a standardized quality of life assessment were associated with inferior OS [11].

A main limitation of these studies is while these scoring systems can identify patients at higher risk for poor outcomes, it does not identify patients in which a "less intensive" approach would lead to either a lower treatment-related mortality or improved patient outcomes. For these reasons, in our practice, we do not routinely perform geriatric assessment or a formal risk assessment using published tools outside of a research setting. We routinely consider patients under the age of 70 with good performance status and adequate organ function as potential candidates for intensive chemotherapy.

3. Intensive induction regimens

Induction with 7 + 3 regimens (cytarabine infused continuously for seven days with three once-daily injections of an anthracycline) has been a standard of care for patients with AML for more than 45 years. In 2017, CPX-351 (VYXEOS; Jazz Pharmaceuticals, Palo Alto, CA), a novel pharmaceutical agent consisting of cytarabine and daunorubicin at a fixed 5:1 M ratio within a liposomal carrier, was approved by the FDA for the treatment newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). CPX-351 was developed in an effort to improve the efficacy of standard cytarabine + anthracycline combination therapy. In pre-clinical studies, the cytotoxicity of a range of cytarabine: daunorubicin molar ratios ranging from 10:1 to 1:10 was tested against human and murine cell lines. A 5:1 cytarabine: daunorubicin ratio was found to exhibit maximum synergy and minimum antagonism *in vitro*. Encapsulating these compounds in a liposomal delivery vehicle allowed for longer maintenance of the synergistic 5:1 ratio in plasma and bone marrow in a mouse model of leukemia. Furthermore, administration of liposome-encapsulated vs free-drug cocktails of 5:1 cytarabine + daunorubicin extended survival in several murine leukemia models. Importantly, co-encapsulation of cytarabine + daunorubicin at a 3:1 M ratio was less effective than the 5:1 ratio *in vivo* despite a two-fold higher concentration of daunorubicin with the 3:1 product, suggesting a means to maximize efficacy while minimizing toxicities from anthracycline exposure [12]. In patients, CPX-351 likewise allowed for prolonged exposure to cytarabine and daunorubicin at the optimal 5:1 ratio, with both drugs detectable in plasma more than 7 days after administration [13].

The clinical efficacy of CPX-351 as compared to conventional induction therapy was demonstrated in a randomized, phase III trial of 309 patients with newly diagnosed high-risk and sAML [14]. The patient population for the phase III study was informed by a randomized phase II trial conducted in older, untreated adults. While CPX-351 produced higher response rates in the overall patient population, it failed to show either an improvement in event-free survival (EFS) or OS for the overall population. A planned analysis of the sAML subgroup, however, demonstrated an improved response rate (57.6% vs 31.6%, $p = 0.06$), and prolongation of EFS (HR = 0.59, $p = 0.08$) and OS (HR = 0.46, $p = 0.01$) [15]. In the phase III study, patients ranged in age from 60 to 75, and were stratified both by age and class of sAML (tAML, AML-MRC, AML with antecedent MDS, and AML with antecedent CMML). ECOG PS ranged from 0 to 2, with the majority of patients having a PS of 1 on enrollment (66% in the CPX-351 group and 57.1% in the 7 + 3 group). Patients were randomized to induction with 1–2 cycles of CPX-351 vs. 7 + 3 followed by consolidation with a similar regimen. The CPX-351 induction regimen consisted of 100 units/m^2 CPX-351 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin) administered over 90 min on days 1, 3 and 5. Bone marrow biopsy was performed on day 14 and a second induction course (100 units/m^2 CPX-351 on days 1 and 3) was administered for those who did not achieve hypoplastic marrow. Patients in complete remission (CR) or complete remission with incomplete neutrophil or platelet count recovery (CRi) went on to 1–2 cycles of consolidation, which consisted of 65 units/m^2 CPX-351 (65 mg/m^2 cytarabine and 29 mg/m^2 daunorubicin) on days 1 and 3.

In this cohort of older adults with high-risk and sAML, treatment with CPX-351 led to a significant improvement in median overall survival (OS) compared to treatment with 7 + 3 (9.56 months for the CPX-351 group vs. 5.95 for the 7 + 3 group, HR 0.69, 95% CI 0.52–0.90). Although the time to neutrophil and platelet count recovery was longer in the CPX-351 group rates of febrile neutropenia were similar between the groups with a non-significant trend towards lower all-cause mortality for the CPX-351 arm (5.9% vs 10.6% for 30-day mortality, two-sided $p = 0.149$; 13.7% vs 21.2% for 60-day mortality, two-sided $p = 0.097$). This study included 63 patients with tAML and for this subset of patients, the median OS was 12.17 months with CPX-351 vs. 5.95 with conventional 7 + 3 (HR 0.48, 95% CI 0.26 to 0.86) [14].

Limited data suggests that for those who are candidates for transplant, induction with CPX-351 is associated with better post-transplant outcomes. Of the 309 patients with sAML in the initial phase III trial comparing CPX-351 and 7 + 3, ninety-one (29.4%) of patients underwent allogeneic stem cell transplant. An exploratory survival analysis from time of transplant favored CPX-351 over 7 + 3 (HR 0.46, 95% CI 0.24 to 0.89) [14]. Among the subset of patients with tAML, those treated with CPX-351 were also more likely than those treated with 7 + 3 to achieve remission (47% vs. 36%) and to proceed to stem cell transplantation (37% vs. 27%). Furthermore, for those who received a transplant, median OS from date of transplant was not reached in the CPX-351 group vs. 6.57 months in the 7 + 3 group (HR = 0.19, 95% CI 0.04–0.97) [16]. The reasons for improved post-transplant outcomes in the CPX-351 cohort are unknown. Because CPX-351 is associated with lower induction mortality compared to 7 + 3, patients may be proceeding to transplant with less toxicity. Alternatively, CPX-351 may provide better disease control as published data has shown that achieving an MRD negative state pre-transplant has been associated with improved outcomes in the larger population of patients with AML [17].

In addition to CPX-351, two other agents, midostaurin and gemtuzumab ozogamicin, were approved by the FDA in 2017 for the treatment of newly diagnosed AML. Midostaurin is a multi-targeted kinase inhibitor active against the FLT3 tyrosine kinase which harbors activating mutations in approximately 25–30% of patients with AML [18]. Although *FLT3* mutations are more common in de novo AML than in sAML, a significant proportion (19% in one large study) of patients with sAML carry these mutations [4]. The FDA approval was based on the RATIFY study, a double-blind, placebo-controlled trial in 717 patients with previously untreated *FLT3*-mutated AML. This trial randomized patients with de novo AML to either placebo or midostaurin 50 mg orally twice daily on days 8–21 of each cycle of induction and consolidation chemotherapy followed by continuous daily midostaurin for up to 12 cycles. The trial demonstrated a significant improvement in OS for patients receiving midostaurin compared with those on the placebo-containing arm (HR 0.78, $p = 0.009$) [19]. Although this pivotal phase III study specifically excluded patients with tAML, it is likely that patients with *FLT3*-mutated tAML will similarly benefit from the addition of midostaurin to 7 + 3 induction.

Gemtuzumab ozogamicin (GO) is a CD33-calechiemicin antibody-drug conjugate which was approved in 2017 for the treatment of adults with newly diagnosed CD33$^+$ AML and for patients aged 2 years and older with CD33$^+$ AML who have experienced a relapse or who have not responded to initial treatment. Approval of GO combination treatment was based in part on the ALFA-0701 study which randomized 278 patients age 50–70 years with newly-diagnosed AML to 7 + 3 with or without 3 mg/m^2 fractionated GO on days 1, 4, and 7 during induction. Although the treatment effect on OS was not statistically significant, addition of GO improved two-year event-free survival (EFS) from 17.1% in the chemotherapy alone group to 40.8% in the chemotherapy + GO group (HR = 0.58, 95% CI 0.43–0.78, $p = 0.003$) [20]. A subgroup analysis of EFS showed comparable results among different groups except for the adverse risk cytogenetic group (HR = 1.03, 95% CI 0.5–2.13) which did not appear to benefit from the addition of GO. Similar to the RATIFY study, patients with tAML were specifically excluded from the ALFA-0701 study. In addition, the use of GO is associated with the development of veno-occlusive disease of the liver in patients undergoing allogeneic hematopoietic stem cell transplant [21]. Although fractionated regimens such as the 3 mg/m^2 on days 1, 4, and 7 used in the ALFA-0701 study appear to have less toxicity than previously used schedules of either 6 mg/m^2 or 9 mg/m^2 as a single dose used in older studies, the concern exists for using this agent in patients who have a high likelihood of proceeding to an allogeneic hematopoietic stem cell transplant.

4. Nonintensive therapy

With high-quality evidence supporting induction with CPX-351 over 7 + 3 for adults with tAML who can tolerate standard induction chemotherapy, the question remains as to the preferred first-line treatment for patients whose medical comorbidities or disease make them poor candidates for intensive therapy. Trials enrolling adults with AML not thought suitable for conventional

Table 2
Studies enrolling adults with AML "unfit"[a] for conventional induction therapy.

Citation	Study arms	Study type	Population	Results	Comments
Dombret et al. 2015 [23]	Azacitidine vs conventional care	Phase III, open-label, randomized, parallel group study	Treatment-naïve "unfit" patients age ≥ 65 with de novo or sAML[b]	Improved OS in the azacitidine group (10.4 months vs. 6.5 months, HR 0.85, 95% CI 0.69–1.03).	
Konpleva et al. 2016 [27]	Single-agent venetoclax	Phase II, open-label, single-arm study	Relapsed/refractory AML	CR or CRi noted in 6 of 32 heavily pre-treated patients.	No evidence of clinical efficacy in the 4/32 patients with tAML.
DiNardo et al. 2019 [28]	Venetoclax + HMA	Phase Ib, open-label, dose-escalation and expansion study	Treatment-naive "unfit" patients age ≥ 65 with AML	CR/CRi in 61% of patients.	Led to accelerated FDA approval for venetoclax + HMA in age ≥75 or "unfit" AML.
NCT02993523 Potluri et al. 2017 [29]	Venetoclax (400 mg daily) vs. placebo in combination with azacitidine	Phase III	Treatment-naïve "unfit" patients with AML	Completed accruing; results pending.	
Wei et al. 2017 [30]	Low-dose cytarabine + venetoclax	Phase Ib/II, open-label, single-arm study	Treatment-naïve, "unfit' patients with AML	CR/CRi rate of 62%, median OS of 11.4 months.	Lowest response rates in patients with *TP53* mutations. Led to accelerated FDA approval for venetoclax + low-dose cytarabine in age ≥75 or "unfit" AML.
NCT03069352	Venetoclax (600 mg daily) vs placebo in combination with low-dose cytarabine	Phase III	Treatment-naïve, "unfit' patients with AML	Currently accruing	
Cortes et al. 2016 [32]	Low-dose cytarabine + glasdegib vs. low-dose cytarabine alone	Phase II randomized study	Treatment-naïve patients with AML or high-risk MDS unfit for conventional induction	Improved OS for combination therapy (8.3 months vs. 4.9 months).	Led to accelerated FDA approval for glasdegib + low-dose cytarabine in age ≥75 or "unfit" AML.
NCT03416179 (BRIGHT AML 1019) Cortes et al. 2018 [33]	Chemotherapy + glasdegib vs. chemotherapy + placebo	Phase III	Treatment-naïve patients with AML (includes one arm for "unfit" patients who will receive azacitidine as chemotherapy backbone)	Currently accruing	Does not exclude sAML[b].
NCT02841540 Steensma et al. 2017 [37]	Single-agent H3B-8800	Phase I	Patients with MDS, CMML, or AML (for AML, must be unfit for conventional induction)	Currently accruing	
Amadori et al. 2016 [38]	Gemtuzumab ozogamicin (GO) vs. BSC	Phase III	Treatment-naïve "unfit" patients with de novo or sAML[b]	Improved 1-year OS rate with GO vs. BSC (24.3% vs. 9.7%).	Greater OS benefit of GO in those with CD33-positive clones and those with favorable/intermediate risk cytogenetics.
Pollyea et al. 2017 [34]	Single-agent enasidenib	Phase I	Treatment-naïve, "unfit' patients with *IDH2*-mutated AML	19% CR rate, 37.8% OR rate, OS 10.4 months, and EFS 11.3 months.	

Abbreviations: AML – acute myeloid leukemia, BSC – best supportive care, CMML – chronic myelomonocytic leukemia, CR – complete remission, CRi – complete remission with incomplete blood count recovery, EFS - Event-free survival, MDS – myelodysplastic syndrome, OR – overall response, OS – overall survival, sAML – secondary AML, tAML – therapy-related AML.

[a] Determined by investigators or treating physicians to be ineligible for standard induction chemotherapy (criteria vary based on study).

[b] AML with antecedent MDS or CMML, or AML with MDS-related cytogenetic changes.

induction therapy are compiled in Table 2. HMAs have emerged as a viable therapeutic option for adults with MDS as well as for those with AML who are unlikely to tolerate conventional induction chemotherapy [22]. A randomized, multicenter, phase III open-label trial enrolling 488 patients age ≥65 with newly diagnosed AML compared single-agent azacitidine to conventional care regimens (CRRs) [23]. Patients were pre-selected by the treating physician to receive standard induction therapy, low-dose cytarabine, or best supportive care alone (CCR), and then randomized to single-agent azacitidine vs. the physician-selected CCR. Patients randomized to azacitidine experienced superior OS compared to those randomized to CCR (10.4 months for the azacitidine group vs. 6.5 months for the CRR group, HR 0.85, 95% CI 0.69–1.03). In a pre-planned exploratory analysis, for patients whom the treating physician deemed appropriate for conventional induction chemotherapy, OS was similar in the azacitidine and conventional induction groups (13.3 and 12.2 months). However, for those whom the treating physician selected best supportive care alone, OS was significantly prolonged with azacitidine, though OS remained short (5.8 months for azacitidine vs 3.7 months for best supportive care alone; $p = 0.0288$). For those pre-selected to low-dose cytarabine, OS was 11.2 months in the azacitidine group vs. 6.4 months in the low-dose cytarabine group, though this did not reach statistical significance due to wide variability in response. This study included only a small number of patients with tAML (8 in the azacitidine group and 12 in the CCR group), making it difficult to generalize these findings to the wider population of patients with tAML.

Though most studies of HMAs as first-line treatment in AML have included only a small fraction of patients with tAML, some data suggests that the mutational profile of tAML may confer particular sensitivity to these agents. Targeted mutational analysis of bone marrow samples from 101 patients with tAML uniformly treated with conventional induction therapy revealed that 23% carried *TP53* mutations [4]. tAML patients with *TP53*-mutated clones were more likely to require multiple induction cycles, suggesting increased resistance to conventional induction therapy. Interestingly, though patients with high-risk cytogenetics and/or *TP53* mutations are known to have relatively poor responses to cytotoxic chemotherapy, this does not appear to be the case with HMAs. In a single-institution study enrolling 116 patients with AML/MDS, those with high-risk cytogenetics and/or *TP53* mutations had higher response rates than those with favorable or intermediate-risk cytogenetic profiles when treated with 10-day cycles of decitabine, though duration of responses was short [24]. In another single-institution retrospective study of 293 patients with newly-diagnosed AML, 53 (18%) were found to have *TP53* mutations. Those with *TP53* mutations were more likely to have tAML than those with wild-type (WT) *TP53* (30% vs. 13%, $p < 0.005$). In this study, there was no difference in CR to HMAs between patients with WT and mutant *TP53*. However, there was a trend toward lower CR to high-dose cytarabine-based combination therapy in those with mutant *TP53* [25]. Available data thus suggest that *TP53* mutations confer some degree of resistance to conventional induction chemotherapy, and that treatment with HMAs may be an attractive option in these patients. A randomized phase III study comparing 7 + 3–10-day decitabine in individuals ≥60 with both de novo and sAML is currently being conducted by the European Organization for Research and Treatment of Cancer (EORTC-1301-LG, NCT02172872) and may provide clarity to the situation.

5. Novel agents

Another area of active research is use of B-cell lymphoma 2 (BCL-2) inhibitors in AML. BCL-2 is a member of a class of anti-apoptotic proteins that regulate mitochondrial outer membrane permeabilization, a key step in apoptotic cell death. Family members include B-cell lymphoma extra-large (BCL-XL) and myeloid cell leukemia sequence 1 (MCL-1). Despite the above nomenclature, myeloid cells are not exclusively dependent on MCL-1, and pre-clinical data has shown that certain AML clones are highly sensitive to BCL-2 inhibition [26]. Venetoclax, a small-molecule BCL-2 antagonist, has had notable clinical success in lymphoid malignancies including chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). In a phase II trial of 32 heavily pretreated patients with refractory AML (median age 71 years), venetoclax administered as a single agent was well-tolerated and showed limited evidence of clinical efficacy, with responses noted in six of 32 patients (CR in two patients and CRi in four patients) [27]. Responses were short-lived, however, with median time to progression of 2.5 months. Furthermore, single-agent venetoclax showed no evidence of anti-leukemic effect in the four patients with tAML included in this study.

Results with single-agent venetoclax prompted further studies of combination therapy with BCL-2 antagonists in AML. A phase 1b trial examined venetoclax in combination with HMAs in 145 patients with newly diagnosed AML thought to be unfit for standard induction therapy, all age ≥65. Twenty-five percent of the cohort had sAML and all had intermediate-risk (51%) or poor-risk (49%) cytogenetics. Cytopenias and febrile neutropenia were the most common serious adverse events, and the early (30-day) mortality rate in this study was 3%. Response rates were encouraging, with a CR/CRi rate of 67% in the overall study population as well as 67% in the subset with sAML. After a median follow-up of 15.1 months, median OS was 17.5 months (95% CI 12.3 months – not reached [NR]) for the entire patient cohort and NR (95% CI 14.6 months – NR) for the subset with sAML [28]. A phase III trial of azacitidine + venetoclax (400 mg daily) vs. azacitidine alone in elderly AML patients thought unfit for intensive induction therapy has completed accruing and results are pending (NCT02993523) [29]. Similarly, the combination of venetoclax and low-dose cytarabine was examined in a phase I/II trial of 61 newly diagnosed AML patients unfit for standard induction therapy [30]. The 30-day mortality rate was again low at 3%, and encouraging results were seen, with a CR/CRi rate of 62% and a median OS of 11.4 months [30]. A phase III trial of venetoclax (600 mg daily) vs placebo in combination with low-dose cytarabine in treatment-naïve unfit AML patients is currently recruiting (NCT03069352). In the initial phase I/II data, however, response rates were lower in those with high-risk cytogenetics and/or *TP53* mutations and it is unclear how these results will translate to patients with tAML where high-risk cytogenetics and/or *TP53* mutations are prevalent. Though randomized phase III data are pending, these two phase I/II studies led to accelerated FDA-approval for venetoclax in combination with either azacitidine or decitabine or low-dose cytarabine in newly diagnosed patients with AML who are either age ≥75 or have contraindications to conventional induction chemotherapy.

Several additional options for first-line treatment of adults unfit for conventional induction chemotherapy are currently on the

therapeutic horizon. Preclinical data indicate that abnormal signaling through the Hedgehog pathway in AML and MDS and may help promote leukemic stem cell self-renewal and drug resistance [31]. Glasdegib is an orally administered small molecular inhibitor of smoothened receptor that has been combined with low-dose cytarabine (LDAC) in MDS/AML. In a phase II trial of 132 patients with high-risk MDS and AML deemed unfit for conventional induction therapy, patients treated with glasdegib + LDAC showed longer median OS than those treated with LDAC alone. For the subgroup with AML, median OS was 8.3 months with glasdegib + LDAC vs. 4.3 months with LDAC (HR 0.462, $p = 0.0004$). Cytopenias and gastrointestinal adverse events were more common in the glasdegib + LDAC group [32]. Stratification by de novo vs. sAML was not reported in this phase II study. On the basis of these results, the FDA granted accelerated approval for glasdegib + LDAC in newly diagnosed AML patients either age ≥75 or with contraindications to conventional induction chemotherapy. In the ongoing phase III BRIGHT AML 1019 trial (NCT03416179), treatment-naïve patients are classified by the treating physician as fit or unit for conventional induction chemotherapy, then randomized to chemotherapy + glasdegib vs. chemotherapy + placebo. Patient in the non-intensive group will receive azacitidine as their chemotherapy backbone [33]. Importantly, this trial does not exclude patients with sAML, and it remains to be seen whether glasdegib will prove effective in this high-risk population.

Additional agents targeting specific mutations in the relapsed or refractory population may also have some role in the upfront treatment of sAML. Inhibitors of isocitrate dehydrogenase (IDH), enasidenib (IDH2) and ivosidenib (IDH1), have been approved by the FDA for the treatment of relapsed or refractory AML based on the results of single-agent phase I studies. Mutations in *IDH1* or *IDH2* are found in approximately 20% of all patients with AML with similar frequencies in the sAML population [4]. In the phase I study of enasidenib, a dose-expansion cohort included 37 *IDH2*-mutated patients with untreated AML not eligible for standard of care treatments. Seven patients (19%) achieved a CR with an overall response rate of 37.8% (95% CI 22.5–55.2%), a median OS of 10.4 months (95% CI 5.7–15.1) and an EFS of 11.3 months (95% CI 3.9 - NR) [34]. Ongoing studies will examine the role of enasidenib in the untreated *IDH2*-mutant AML population (BEAT AML Master Trial, NCT03013998), and also ivosidenib in combination with hypomethylating agents for IDH1-mutant AML (AGILE, NCT03173248).

6. Summary

Treatment of patients with tAML is challenging. This is due to both the vulnerable nature of the patient population (comprised largely of older, multi-morbidity patients with limited bone marrow reserve) and the intrinsic biology of the disease itself, with high-risk cytogenetics and *TP53* mutations frequently present. The choice of intensive vs nonintensive approaches requires careful risk-benefit consideration and joint decision-making between patient and physician, and should not be predicated on chronologic age alone. In addition, disease-specific features that predict poor response to conventional induction therapy regardless of patient "fitness," such as mutations in *TP53* [24,25] should also be taken into consideration. Patients with highly proliferative disease or who are acutely symptomatic from their AML will tend to be treated with an intensive approach. For those with more hypo-proliferative disease typically with gradual onset of symptoms with low peripheral blast counts, we typically delay the start of therapy until we obtain additional cytogenetic and molecular data. Enrollment in clinical trials is always the preferred option when possible.

For older adults (age ≥ 60) with tAML suitable for intensive chemotherapy, particularly those who are candidates for allogeneic hematopoietic cell transplantation, our preference is to treat with CPX-351 based on the results of the phase III randomized study [14]. For younger patients with tAML, both 7 + 3 and CPX-351 are acceptable options. For younger patients treated with 7 + 3, we will add gemtuzumab using a fractionated dose schedule (3 mg/m2 on days 1, 4, 7 based on the results of the ALFA-0701 study) only in patients with favorable risk cytogenetics (i.e., core binding factor leukemias) as these are the patients who are least likely to undergo an allogeneic hematopoietic stem cell transplant. We will also add midostaurin to 7 + 3 on days 8–21 for *FLT3*-mutated AML. We do not add gemtuzumab or midostaurin to CPX-351 owing to the lack of both safety and efficacy data for the combination and the high costs associated with treating individuals with multiple newer agents. Patients who are poor candidates based on age and overall health for intensive chemotherapy are treated with a hypomethylating agent, either azacitidine or decitabine alone or in combination with venetoclax. For older adults with complex karyotypes or known *TP53* mutation, we tend to favor hypomethylating agents.

Practice Points

- Though patients with tAML often present at relatively advanced age, age alone should not be used to disqualify patients from intensive induction therapy. Published risk-assessment algorithms and geriatric assessments are available to select candidates for intensive induction regimens.
- Induction with CPX-351 is superior to conventional 7 + 3 (cytarabine and daunorubicin) in older adults with tAML.
- Hypomethylating agents are preferred for patients with tAML who are not candidates for intensive induction therapy and for older adults with mutated *TP53*.

Research Agenda:

- Clinical trials have historically excluded patients age ≥65 and patients with tAML. New trials specifically targeting this high-risk population are needed.
- tAML has a unique mutational signature relative to de novo AML, characterized by frequent mutations in genes involved in

RNA splicing and chromatin modification [4,35]. Future trials should attempt to exploit the molecular ontogeny of tAML with targeted therapies in order to develop efficacious and well-tolerated treatments.

Conflicts of interest

GLU has served on advisory boards for Jazz, Pfizer and Novartis.

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