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REVIEW

The important role of intensive induction chemotherapy in the treatment of acute myeloid leukemia

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ABSTRACT

Introduction: Intensive induction chemotherapy followed by post-remission consolidation and/or allogeneic hematopoietic transplantation has been a standard-of-care therapy for acute myeloid leukemia (AML) for decades. In recent years, a plethora of new agents have been approved for AML treatment, dramatically changing the AML treatment landscape.

Areas covered: This review provides an overview of the current role of intensive chemotherapy in the changing AML treatment landscape. PubMed-indexed publications (through 2020) and abstracts presented at major national and international conferences were reviewed for inclusion.

Expert opinion: While intensive chemotherapy is standard-of-care therapy for younger patients with AML, older patients were historically viewed as universally ineligible for intensive chemotherapy; however, several studies suggest many older patients benefit from intensive chemotherapy with a curative intent, and a more holistic approach to determining eligibility for intensive treatment is recommended. Intensive strategies have also been expanded to include novel chemotherapy designs and chemotherapy in combination with targeted agents for patients with certain disease characteristics, which may permit more personalized treatment decisions. Intensive chemotherapy continues to play a pivotal role for the management of many AML patients and can offer the best chance of long-term remission, especially when followed by transplantation.

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Acute myeloid leukemia; chemotherapy; clinical; elderly; high-dose therapy

1. Introduction

According to the Global Burden of Disease Study, in 2017 there were almost 140,000 incident cases of acute myeloid leukemia (AML) and 100,000 deaths from this disease globally, with an increasing incidence of AML largely due to population growth and aging [1]. The majority of AML cases (almost 60%) are diagnosed in persons aged ≥65 years, and 5-year AML survival decreases sharply with increasing age, from 59% for patients aged <50 years to 8% for those aged ≥65 years [2]. Increasing mortality from AML in older patients is due to more aggressive leukemia biology and a reduced tolerance for intensive therapy. In addition to poor prognosis and increased mortality, AML is associated with significant symptoms, including fatigue, pain, dyspnea, anemia, anxiety, and depression, that can impact a patient's quality of life and ability to carry out daily tasks [3,4]. Treatment is often associated with side effects that further add to the burden of AML [3].

Current treatment strategies for newly diagnosed AML typically consist of induction and post-remission consolidation with chemotherapy and/or followed by allogeneic hematopoietic cell transplantation (HCT) in sufficiently fit patients, or chemotherapy as a backbone in combination with targeted agents for patients with actionable disease characteristics. Patients not considered candidates for intensive treatment may receive lower-intensity regimens [5].

This review provides an overview of the current role of intensive chemotherapy in the changing AML treatment landscape. The literature included in this review was identified via searches of the PubMed database (through 2020) and abstracts presented at recent major national and international conferences.

2. Intensive chemotherapy as standard of care in appropriate patients

2.1. Patient assessment

Choice of initial treatment regimen for AML is typically based on both patient and disease characteristics [6,7]. Although younger adults are commonly treated with intensive chemotherapy, historically there has been a tendency to view older patients as universally ineligible for intensive chemotherapy [8,9], and clinical trials of intensive chemotherapy have often excluded older patients and those with clinically significant comorbidities. However, an increasing number of studies have demonstrated that many older patients benefit from receiving intensive induction therapy versus lower-intensity therapy or best supportive

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Article highlights

- Intensive chemotherapy, often followed by hematopoietic cell transplantation, continues to be a standard of care for AML and offers the best chance for long-term remission
- Newer intensive strategies for AML include novel chemotherapy designs and chemotherapy as a backbone in combination with targeted agents
- Many older adults with AML benefit from receiving intensive chemotherapy with a curative intent, and a more holistic approach to determining eligibility for intensive treatment is recommended

care [10–12]. For example, in a retrospective study in France of patients aged 60 to 75 years with newly diagnosed high-risk /secondary AML, intensive chemotherapy was associated with a higher rate of complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi; 69% vs 15%) and 5-year survival rate (17% vs 2%) versus hypomethylating agents (HMAs), but a similar median overall survival (OS) and early mortality rate [10]. A separate analysis of data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database for patients aged >65 years with newly diagnosed AML reported a median OS of 18.9 months for patients treated with intensive chemotherapy versus 6.6 months for those treated with HMAs and 1.5 months for those who did not receive treatment [12]. However, it should be noted that in both studies, patients who received intensive chemotherapy were more likely to be younger and have more favorable disease features.

Given these outcomes in older patients, eligibility for intensive treatment must be assessed with a more holistic approach, taking into account each patient's comorbidities, cognitive status, preferences (e.g., outpatient therapy or cultural aspects), and treatment goals (e.g., curative intent, including potential to proceed to HCT) in addition to age and performance status [7]. Patient-centric information is becoming increasingly important in treatment decision-making, and patient education surrounding treatment options is therefore important. Disease characteristics are also important factors in decision-making (i.e., antecedent hematologic malignancy, cytogenetics, mutation profile, and prior exposure to chemotherapy or HMAs) [7]. Cytogenetic classification of AML comprises three groups, regardless of age or other parameters: favorable-, intermediate-, and adverse-risk with respect to predicted treatment outcomes [6]; however, the percentage of patients with European LeukemiaNet 2010 adverse-risk categorization rises with increasing age [13]. It has been suggested that the risk of early death during induction chemotherapy (i.e., treatment-related mortality) in older patients can be calculated using seven clinical parameters, including age, AML type (*de novo* vs secondary), body temperature, and selected laboratory parameters [7,14].

It should also be noted that patient eligibility for intensive chemotherapy may shift after initial treatment, and reassessment is thus needed upon relapse (e.g., patients may become suitable for intensive chemotherapy upon recovery from leukemia-related infections).

2.2. Established intensive chemotherapy regimens

Current guidelines recommend intensive induction chemotherapy regimens in patients able to tolerate intensive treatment, optimally followed by allogeneic HCT [5,7,15], as this combination of treatment modalities represents the best potential for functional cure in AML. This approach also likely provides the greatest likelihood of achieving measurable residual disease (MRD) negativity, which has been shown in several studies to be prognostic of a reduced risk of relapse and improved survival in AML [16]. Assessment of MRD can also help to inform subsequent treatment decisions, such as the choice of consolidation regimen or pre-HCT conditioning strategy [6].

Conventional chemotherapy, such as the '7 + 3' induction regimen of cytarabine (100 to 200 mg/m^2 continuous infusion for 7 days) plus 3 days of an anthracycline (daunorubicin or idarubicin), has been a standard of care for several decades [5,7,17]. However, CR rates with 7 + 3 vary according to patient subgroups. CR is achieved in 45% to 65% of patients aged <65 years compared with 30% to 40% in those aged >65 years; younger patients also tend to have correspondingly longer OS (9.0 to 18.8 months vs 3.5 to 6.9 months) [18]. CR and survival rates also vary widely according to the type and number of chromosomal aberrations in the individual patient [19,20]. In an analysis of 126 younger adults (mean of 43 ± 18 years) with *de novo* AML who received 7 + 3, 36% achieved MRD of <0.1% cells, 51% achieved MRD of ≥0.1% to <1% cells, and 13% achieved MRD of ≥1% cells; the 3-year relapse rates for these MRD groups were 14%, 45%, and 85%, respectively [21]. In a separate analysis of 241 younger adults (aged 18 to 60 years) with newly diagnosed AML, after 1 course of 7 + 3 66% of evaluable patients had achieved MRD ≤0.1%, and patients who achieved MRD negativity had significantly longer OS ($P < 0.03$) and relapse-free survival ($P = 0.008$) [22]. Results were generally similar after a second induction course (of cytarabine plus amsacrine); the achievement of MRD negativity was more common among patients with *de novo* AML (78%) versus secondary AML (53%) and those with good- (73%) or intermediate-risk AML (82%) versus poor-risk AML (63%) [22]. With the aim of improving outcomes with intensive induction chemotherapy, modifications of the cytarabine/anthracycline combination have been evaluated (e.g., adjustments in the dose of either agent, extension of cytarabine duration from 7 to 10 days, addition of another agent such as etoposide) but have not demonstrated notably higher CR rates or longer OS [23,24].

High-dose cytarabine (HiDAC)–containing regimens represent an alternative intensive chemotherapy approach, including the FLAG/FLAG-Ida (fludarabine, HiDAC, and granulocyte colony-stimulating factor, with or without idarubicin) and CLAG/CLAG-M (cladribine, HiDAC, and granulocyte colony-stimulating factor, with or without mitoxantrone) regimens. These regimens are recommended treatment options for patients with intermediate- or poor-risk AML in the current

guidelines [5,7]; however, while these regimens have all demonstrated efficacy in AML, studies have not consistently supported the use of one regimen over another [24–28].

Further, an analysis of data from two consecutive, randomized studies by the German AML Cooperative Group in adults with previously untreated AML found no difference in remission rates or OS between standard- and high-dose chemotherapy regimens; this lack of difference between regimens was noted for both younger (<60 years) and older (≥60 years) patients, as well as across various prognostic subgroups [29]. Another randomized study designed among German AML study groups compared outcomes in older patients (≥60 years) treated with several different standard- and high-dose chemotherapy strategies and again found no clinically relevant differences in outcomes [30].

The FLAM regimen involves flavopiridol (also known as alvocidib) followed by cytarabine and mitoxantrone. Flavopiridol is a multi–cyclin-dependent kinase (CDK) inhibitor that has shown synergy with cytarabine and mitoxantrone in terms of cell cycle arrest followed by cell destruction [31]. In a randomized, phase 2 trial of 165 patients with newly diagnosed high-risk AML, FLAM demonstrated a higher CR rate compared with 7 + 3 (70% vs 47% after 1 cycle of treatment; $P = 0.003$); however, there was no difference between groups in terms of OS [32]. Notably, the cytotoxicity of FLAM was dependent on timed sequential therapy (i.e., sequential exposure of cancer cells to cell cycle–dependent agents to achieve synergistic activity) [31].

2.3. Alternative forms of intensive chemotherapy

A key issue with conventional intensive induction chemotherapy regimens, which typically include administration of >1 therapeutic agent, is the need for different treatment schedules for the individual drugs. Novel chemotherapy formulations may address this need, as well as improve upon efficacy and/or tolerability.

CPX-351 (Vyxeos® in the United States; Vyxeos® Liposomal in Europe) is a nanoscale liposomal dual-drug encapsulation of daunorubicin and cytarabine at a synergistic 1:5 molar drug ratio [33] and is approved by the U.S. Food and Drug Administration and the European Medicines Agency as induction and consolidation therapy for adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (AML-MRC; e.g., AML with antecedent myelodysplastic syndromes [MDS] or MDS/myeloproliferative neoplasms, *de novo* AML with certain MDS-related changes, and multilineage dysplasia in the absence of *NPM1* or biallelic *CEBPA* mutations [34]); current management guidelines for AML also recommend CPX-351 for patients with these AML subtypes [5,7]. In contrast to the administration of separate agents that compose conventional chemotherapy regimens, the CPX-351 liposome coordinates the pharmacokinetics of daunorubicin and cytarabine, thereby maintaining the synergistic drug ratio in plasma following administration, and prolongs drug exposure relative to the free drugs [35]. Further, the CPX-351 liposome is preferentially taken up by leukemia cells versus normal cells in the bone marrow, followed by intracellular release of the encapsulated drugs [36,37]. These properties differentiate CPX-351 from the conventional 7 + 3 regimen of cytarabine and daunorubicin despite containing the same active drugs.

In a randomized, open-label, phase 3 trial, CPX-351 induction (100 units/m^2 [daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2] administered as 90-minute infusions on Days 1, 3, and 5) followed by consolidation was compared with 7 + 3 in 309 patients aged ≥60 years with high-risk/secondary AML [38,39]. CR was achieved by significantly more patients in the CPX-351 group relative to the 7 + 3 group (37.3% vs 25.6%; $P = 0.04$) [38]. The primary endpoint analysis, which included a median follow-up of 20.7 months, found significantly longer median OS with CPX-351 versus 7 + 3 (9.56 vs 5.95 months; hazard ratio [HR] = 0.69 [95% confidence interval (CI): 0.52, 0.90]; 1-sided $P = 0.003$) [38]. A final analysis of the study, which included up to 5 years of follow-up, confirmed the improvement in OS observed with CPX-351 versus 7 + 3, with an HR that was consistent with the primary endpoint analysis and Kaplan-Meier–estimated 5-year survival rates of 18% versus 8% [39]; of note, this analysis represents one of the few randomized, controlled trials with robust, long-term survival data for an intensive chemotherapy regimen. In subgroup analyses from the primary endpoint analysis, higher CR rates and longer median OS were reported for CPX-351 versus 7 + 3 across AML subtypes [38]. Patients with prior HMA exposure were eligible for this study, and 40.5% and 45.5% of patients in the CPX-351 and 7 + 3 arms, respectively, had previously received HMAs [38]. Among patients with prior HMA exposure, the CR rate was higher with CPX-351 (25.8% vs 15.5%); median OS was similar in all patients with prior HMA exposure (5.65 vs 5.90 months; HR = 0.86 [95% CI: 0.59, 1.26]) but higher among responders (CR or CRi) with prior HMA exposure (14.72 vs 10.17 months; HR = 0.55 [95% CI: 0.26, 1.15]) [38,40]. In addition to the improvement in OS, more patients who received CPX-351 subsequently underwent HCT (35% vs 25%), and in this subgroup 3-year OS landmarked from the date of HCT was 52% with CPX-351 versus 23% with 7 + 3 [39]. Overall, the safety profile of CPX-351 was comparable to that of 7 + 3, including the frequencies of grade ≥3 infections (83.7% vs 86.1%), febrile neutropenia (68.0% vs 70.9%), pneumonia (19.6% vs 14.6%), and hypoxia (13.1% vs 15.2%) [38]. CPX-351 treatment was associated with prolonged myelosuppression, but lower early mortality rates versus 7 + 3 (30 days: 5.9% vs 10.6%; 60 days: 13.7% vs 21.2%) [38]. Together, these data suggest CPX-351 represents an advancement in intensive chemotherapy for the treatment of adults with therapy-related AML or AML-MRC, and studies of CPX-351 in other AML populations are ongoing.

A different nanoscale liposomal intensive chemotherapy formulation – EnFLAM – is also in development. EnFLAM liposomes encapsulate a combination of flavopiridol and mitoxantrone; it has been suggested EnFLAM could enable achievement of synergistic activity through the modification

Table 1. Selected studies of conventional intensive chemotherapy induction in older patients with AML.

Reference		Trial design	Regimen	Patient population	Complete remission	Median OS
Kahl et al, 2016	[43]	Single-arm, open-label trial	Cytarabine 1 g/m^2 BID on Days 1, 3, 5, 7 + mitoxantrone 10 mg/m^2 on Days 1–3	Adults aged ≥60 y with newly diagnosed *de novo* or secondary AML (n = 471)	67%	11 mo
Burnett et al, 2017	[44]	Randomized, open-label trial	Cytarabine 100 mg/m^2 every 12 h on Days 1–10 + daunorubicin 50 mg/m^2 on Days 1, 3, 5 (10 + 3) vs Daunorubicin 50 mg/m^2 on Days 1, 3, 5 + clofarabine 20 mg/m^2 on Days 1–5	Adults aged >60 y with newly diagnosed *de novo* or secondary AML (n = 806)	Cytarabine + daunorubicin: 64% Daunorubicin + clofarabine: 58%	*5-y rates* Cytarabine + daunorubicin: 14% Daunorubicin + clofarabine: 15%
Röllig et al, 2018	[45]	Randomized, open-label trial	7 + 3 vs Cytarabine 1,000 mg/m^2 over 3 h BID on Days 1, 3, 5, 7 + mitoxantrone 10 mg/m^2 bolus on Days 1–3	Adults aged >60 y with newly diagnosed AML (n = 485)	7 + 3: 39% Cytarabine + mitoxantrone: 55%	7 + 3: 10 mo Cytarabine + mitoxantrone: 10 mo
Röllig et al, 2010	[46]	Single-arm, open-label trial	7 + 3	Adults aged >60 y with newly diagnosed AML (n = 909)	50%	9 mo

AML, acute myeloid leukemia; OS, overall survival; BID, twice daily.

of drug delivery kinetics [31]. However, clinical data for EnFLAM are not yet available.

2.4. Intensive induction chemotherapy in older patients and patients with comorbidities

It has often been reported that response rates with 7 + 3 are poorer for patients aged ≥60 years than for younger patients [17,18,41,42]. However, many of these studies were conducted several years ago and, more recently, a number of European trials have shown intensive induction chemotherapy can be associated with positive outcomes in this population (Table 1). Based on such studies, the American Society of Hematology recommends older patients with newly diagnosed AML who are eligible for intensive induction therapy should receive intensive therapy rather than less-intensive therapy or palliative care [15].

Allogeneic HCT after intensive induction chemotherapy is generally considered the best chance for cure in the majority of patients with AML, and the frequency of HCT among older patients has increased in recent years. An analysis of data from four trials conducted between 2001 and 2010 that enrolled patients aged ≥60 years who received 1 to 2 cycles of intensive induction chemotherapy compared allogeneic HCT following reduced-intensity conditioning with autologous HCT, gemtuzumab ozogamicin (Mylotarg™), further chemotherapy, or no further treatment [47]. When compared with no further treatment, 5-year OS was significantly longer with allogeneic HCT (HR = 0.71 [95% CI: 0.53, 0.95]; P = 0.017); however, there was no significant difference between allogeneic HCT and the other active treatments. At 5 years, the cumulative incidence of relapse was 50% in patients who received allogeneic HCT versus 66% in those who received nonallogeneic HCT post-remission therapy. Notably, there was a survival benefit of allogeneic HCT over other HCT post-remission therapy in patients with adverse-risk disease (HR = 0.39 [95% CI: 0.21, 0.73]) [47].

The presence of comorbidities has historically been a reason for deciding against intensive induction chemotherapy, and clinical trials have often excluded many patients with comorbidities. However, in an analysis from a large Danish cohort study, although patients with a greater number of comorbidities were less likely to receive intensive chemotherapy, CR was achieved in 63% of those with ≥2 comorbidities, and the number of comorbidities was not predictive of poor response, unlike performance status [48]. Early mortality was also not increased in patients with more comorbidities [48]. Similarly, in a single-center cohort study, the presence of comorbidities was not associated with CR, OS, or early mortality in patients of any age receiving intensive induction chemotherapy [49].

Moreover, several studies suggest that not all older patients or those with comorbidities fare better with less-intensive treatments. In an analysis of data from U.S. electronic medical records for patients aged ≥60 years with newly diagnosed AML, for the whole patient cohort, OS was significantly longer following 7 + 3 induction than with an HMA [50]. Notably, even in patients with a Charlson Comorbidity Index score ≥4 (albeit only a small number of patients received either treatment), a similar benefit of 7 + 3 versus HMAs was observed (median OS: 6.7 vs 4.1 months; 1-year OS: 36.9% vs 15.9%; 2-year OS: 28.7% vs 5.3%) [50]. Similarly, in the United Kingdom, Hospital Episode Statistics have provided information regarding treatment patterns and outcomes in specific subgroups of patients with AML [9]. The use of intensive chemotherapy followed by HCT rather than less-intensive treatment was much less common in patients with therapy-related or other secondary AML versus *de novo* AML, and also in patients aged 70 to 79 years relative to younger patients. However, across all age groups, treatment with intensive chemotherapy with or without HCT was consistently associated with higher 5-year OS than either azacitidine or low-dose cytarabine (LDAC), regardless of AML subtype [9]. In a single-center, retrospective study, patients with AML aged ≥70 years and good performance status received 7 + 3 or less-intensive treatment (LDAC, azacitidine, or decitabine) between 2000 and 2014 [51]. The CR rate was much higher in the intensive chemotherapy group than in the low-intensity treatment group (61% vs 12%; P < 0.0001), and 3-year OS was significantly greater (34% vs 18%; P = 0.005) [51].

Table 2. Selected studies of intensive induction chemotherapy in combination with targeted agents in AML.

Reference	Trial design	Regimen	Patient population	Complete remission	Median OS
Gemtuzumab ozogamicin					
Castaigne et al, 2012 [61]	Phase 3, randomized, open-label trial	7 + 3 with placebo (control) vs 7 + 3 + gemtuzumab ozogamicin 3 mg/m^2 on Days 1, 4, 7	Adults aged 50–70 y with newly diagnosed AML (n = 280)	Control: 72% Gemtuzumab ozogamicin: 73%	Control: 19 mo Gemtuzumab ozogamicin: 34 mo
Petersdorf et al, 2013 [63]	Phase 3, randomized, open-label trial	7 + 3 with placebo (control) vs 7 + 3 + gemtuzumab ozogamicin 6 mg/m^2 on Day 4	Adults aged 18–60 y with newly diagnosed AML (n = 595)	Control: 69% Gemtuzumab ozogamicin: 70%	Control: 61 mo Gemtuzumab ozogamicin: 41 mo
Midostaurin					
Stone et al, 2017 [66]	Phase 3, randomized, double-blind trial	7 + 3 with placebo (control) vs 7 + 3 + oral midostaurin 50 mg BID on Days 8–21	Adults aged 18–59 y with *FLT3*-mutated newly diagnosed AML (n = 717)	Control: 53.5% Midostaurin: 58.9%	Control: 26 mo Midostaurin: 75 mo
Sorafenib					
Röllig et al, 2015 [58]	Phase 2, randomized, double-blind trial	7 + 3 with placebo (control) vs 7 + 3 + oral sorafenib 400 mg BID on Days 10–19	Adults aged 18–60 y with newly diagnosed AML (n = 276)	Control: 59% Sorafenib: 60%	Control: NR Sorafenib: NR
Serve et al, 2013 [59]	Phase 2, randomized, double-blind trial	7 + 3 with placebo (control) vs 7 + 3 + oral sorafenib 400 mg BID on Days 10–19	Adults aged ≥60 y with newly diagnosed *de novo* or secondary AML (n = 197)	Control: 60% Sorafenib: 48%	Control: 15 mo Sorafenib: 13 mo
Uy et al, 2017 [60]	Phase 2, single-arm, open-label trial	7 + 3 + oral sorafenib 400 mg BID on Days 1–7	Adults aged ≥60 y with *FLT3*-mutated newly diagnosed AML (n = 54)	74%	*FLT3*-ITD: 15 mo *FLT3*-TKD: 16 mo
Glasdegib					
Cortes et al, 2018 [68]	Phase 2, single-arm, open-label trial	7 + 3 + oral glasdegib 100 mg for 28 days	Adults aged 55 y with newly diagnosed *de novo* or secondary AML (n = 69)	40%	15 mo

AML, acute myeloid leukemia; OS, overall survival; BID, twice daily; *FLT3*, fms-like tyrosine kinase 3; NR, not reached; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

Furthermore, while intensive chemotherapy is typically associated with severe short-term side effects that can substantially impact quality of life [3], these typically resolve over time. In a study of younger and older patients with AML who received 7 + 3, there was a consistent improvement over time, up to 1 year, in overall well-being, fatigue, physical function, and cognitive function, while depressive symptoms decreased [52]. It has been suggested that outcomes with intensive induction chemotherapy in older patients may be improved by better supportive care and more personalized treatment [51]. A longitudinal study of patients aged ≥60 years with newly diagnosed AML explored the relative impact of 7 + 3 or less-intensive treatment on quality of life [53]. Over a 12-month period, quality of life improved in both cohorts, including fatigue, with no differences between groups. However, consistent with institutional guidelines, it was noted that medically fit patients were typically recommended for intensive therapy, while older and less fit patients were typically recommended for less-intensive therapy [53].

Together, these data reinforce the need to holistically evaluate patients for eligibility to receive intensive chemotherapy for AML, beyond individual factors such as age and presence of a comorbidity. They also highlight the survival benefits that some older and less fit patients may experience by receiving intensive chemotherapy that has a curative intent. Given the observed benefits of treatment on quality of life and disease-related symptoms in this patient population, it may be important to focus clinical trial endpoints on measures such as disease-free survival (DFS) in addition to OS.

2.5. Maintenance treatment following intensive induction chemotherapy

Recently, there has been interest in intensive induction chemotherapy followed by lower-intensity maintenance treatment to help further prolong disease control. In a small phase 2 study, patients aged ≥60 years received maintenance azacitidine following CR with intensive induction and consolidation chemotherapy [54]. Median OS was 20.4 months, and estimated 1-, 2-, and 3-year OS rates were 75%, 46%, and 15%, respectively [54]. In a separate study, patients aged ≥60 years who achieved CR following intensive induction chemotherapy were randomized to maintenance treatment with azacitidine or observation only [55]. Although DFS was significantly prolonged with azacitidine treatment (12-month DFS: 64% vs 42%; $P = 0.04$), there was no OS benefit (12-month OS: 84% vs 70%; $P = 0.69$) [55]. In contrast, a phase 3 trial of 472 older patients (aged ≥55 years) in CR or CRi after induction chemotherapy and who were considered ineligible for HCT reported improved survival in those randomized to receive maintenance therapy with CC-486 (Onureg®), a novel oral formulation of azacitidine, versus placebo [56]. CC-486 maintenance therapy resulted in significantly improved OS (24.7 vs 14.8 months; $P < 0.001$) and relapse-free survival (10.2 vs 4.8 months; $P < 0.001$) [56]. Based on data from this study, CC-486 was recently approved by the U.S. Food and Drug Administration for the continued treatment of adults with AML who achieved first CR or CRi following intensive induction chemotherapy but are not able to complete intensive curative therapy [57]. Further studies on the role of maintenance therapy following intensive induction chemotherapy are needed

to better understand the impact of maintenance therapy on long-term outcomes, particularly for patients who are not candidates for HCT.

2.6. Intensive chemotherapy in combination with other agents

In patients with certain disease characteristics (e.g., genetic mutations), targeted agents and other newer inhibitors may be recommended as treatments added to an intensive chemotherapy backbone (Table 2) [5,7]. To date, only a few targeted therapies have been approved in combination with intensive chemotherapy; therefore, depending on their other disease characteristics (e.g., leading to a diagnosis of therapy-related AML or AML-MRC), many patients with mutations may be good candidates for clinical trials of targeted agents in development.

Gemtuzumab ozogamicin, an antibody–drug conjugate of a humanized anti-CD33 antibody and calicheamicin, is approved in combination with 7 + 3 for patients with CD33-positive AML and favorable cytogenetics [5,7,61]. In a randomized, open-label, phase 3 trial, gemtuzumab ozogamicin plus 7 + 3 was compared to 7 + 3 alone as induction therapy in 280 patients aged 50 to 70 years with previously untreated AML; the majority of patients had expression of CD33 [61,62]. Although CR was achieved by a similar percentage of patients in both groups (72% and 73% in the control and gemtuzumab ozogamicin plus 7 + 3 arms, respectively), at a median follow-up of 15 months median OS was significantly longer in the gemtuzumab ozogamicin arm (34.0 vs 19.2 months; $P = 0.0368$) [61]. However, in the final analysis, there was no significant survival benefit observed in patients randomized to gemtuzumab ozogamicin plus 7 + 3 versus 7 + 3 alone (27.5 vs 21.8 months; $P = 0.16$) [62]. The safety profile was similar between treatment arms in terms of grade 3 to 4 nonhematologic adverse events (AEs), although the duration of myelosuppression was longer with gemtuzumab ozogamicin [61]. In a separate randomized, phase 3 trial, gemtuzumab ozogamicin plus 7 + 3 (with low-dose daunorubicin, 45 mg/m^2) was compared with 7 + 3 alone in 595 patients aged 18 to 60 years with *de novo* AML [63]. CR was achieved by approximately 70% of patients in both groups, and although median OS was shorter with gemtuzumab ozogamicin plus 7 + 3 (41 months) versus 7 + 3 alone (61 months), no significant difference was observed between treatments. In addition, the rate of grade 4 or fatal nonhematologic induction toxicity was higher in patients randomized to gemtuzumab ozogamicin [63]. A single-arm, single-institution pilot study is also examining gemtuzumab ozogamicin in combination with CPX-351 in patients with CD33-positive relapsed/refractory AML, post-HMA failure high-risk MDS, or newly diagnosed secondary AML with prior HMA therapy [64]. Preliminary results showed the achievement of CR or CRi in 6 of 19 (32%) evaluable patients; the most common AEs were infectious complications [64].

Midostaurin (Rydapt®) is an oral multikinase inhibitor that targets AML with fms-like tyrosine kinase 3 (*FLT3*) mutations, which are typically associated with intermediate- or adverse-risk disease profiles [6,65]. The combination of midostaurin plus 7 + 3 was compared with 7 + 3 alone in 717 patients aged 18 to 59 years with previously untreated, *FLT3*-mutated AML in a randomized, phase 3 trial [66]. While CR was comparable between treatment groups (58.9% and 53.5% in the midostaurin and control groups, respectively), OS was significantly improved in patients randomized to midostaurin plus 7 + 3 versus 7 + 3 alone (74.7 vs 25.6 months; $P = 0.009$). The frequency of grade ≥3 hematologic AEs was similar between treatment arms with the exception of anemia, which was more common with the addition of midostaurin to 7 + 3; grade ≥3 nonhematologic AEs were also comparable, although rash was more common in the midostaurin group (14% vs 8%) [66]. On the basis of these results, midostaurin plus 7 + 3 is recommended in current guidelines as a treatment option in patients with *FLT3*-mutated AML [5,7].

Hedgehog pathway signaling has been implicated in numerous leukemias, including AML, most notably those associated with acquired drug resistance and poor prognosis [67]. Glasdegib (Daurismo™) is an oral small-molecule inhibitor of the Hedgehog signaling pathway, which has been evaluated in combination with 7 + 3 (100 mg/day in continuous 28-day cycles) in a phase 2, open-label trial in 69 patients aged ≥55 years with *de novo* or secondary AML or high-risk MDS [68]. Patients with prior HMA exposure were eligible for this study, and 7 (10%) patients had previously received HMAs. A total of 40% of patients achieved CR, and 1-year OS probability was 67%. The most common grade >3 AEs included febrile neutropenia, anemia, hypokalemia, and hyponatremia [68]. An ongoing randomized, phase 3 study is further evaluating glasdegib plus 7 + 3 versus 7 + 3 alone in adults with previously untreated AML (ClinicalTrials.gov Identifier: NCT03416179). Also ongoing is a phase 2 study evaluating the combination of glasdegib and CPX-351 in patients with therapy-related AML or AML-MRC (NCT04231851).

The B-cell leukemia/lymphoma-2 (BCL2) inhibitor venetoclax (Venclexta® in the United States; Venclyxto® in Europe) is being evaluated in a single-center study in combination with CPX-351 in adults with newly diagnosed or relapsed/refractory AML, although only preliminary results for the dose-finding phase in relapsed/refractory AML (n = 18) are available at this time [69]. In this cohort, 7 (39%) patients achieved CR or CRi, 7 (39%) patients proceeded to HCT, and the median OS was 6.1 months. The combination was tolerable when venetoclax was administered as a 7-day regimen in combination with CPX-351 but was associated with dose-limiting myelosuppression when venetoclax was administered as a 21-day regimen [69].

There are several ongoing phase 2 and 3 trials assessing the efficacy and safety of other newer agents in combination with conventional intensive chemotherapy, including venetoclax (NCT02115295); the FLT3 inhibitors quizartinib (NCT04107727, NCT02668653, NCT04047641), gilteritinib (Xospata®; NCT04027309), and crenolanib (NCT02283177); and the isocitrate dehydrogenase 2 (IDH2) inhibitor enasidenib (Idhifa®; NCT02632708, NCT03839771). In addition, CPX-351 is being evaluated as novel backbone chemotherapy in combination with

gemtuzumab ozogamicin (NCT03904251), venetoclax (NCT04075747), quizartinib (NCT04128748, NCT04209725), midostaurin (NCT04075747), gilteritinib (NCT04293562), and enasidenib (NCT03825796, NCT04075747).

2.7. Additional targeted therapies

Bispecific antibodies are a novel class of antibody designed to recognize two different antigens and can be used to simultaneously target antigens present in cancer cells, such as CD33 (e.g., AMG 330) and CD123 (e.g., flotetuzumab) in AML cells, and immune cells (e.g., CD3 on T cells), leading to immune-mediated death of the cancer cells. Results from a phase 1, dose-escalation study suggest AMG 330 has an acceptable safety profile and antileukemic activity in patients with relapsed/refractory AML [70]. In an open-label, phase 1/2 study in patients with relapsed/refractory AML, flotetuzumab, showed acceptable safety and antileukemic activity, with an overall response rate of 30% at the recommended phase 2 dose of 500 ng/kg/day [71]. Future clinical trials will further evaluate the potential of bispecific antibodies in the treatment of AML.

3. Options for patients not receiving intensive induction chemotherapy

Although intensive chemotherapy should be the mainstay induction modality for patients considered appropriate candidates, some patients may have comorbidities and/or poor overall fitness that precludes the use of intensive therapy [7,72]. Other patients may prefer a less-intensive treatment regimen for personal reasons, for example, choosing to prioritize quality over quantity of life remaining, if there are concerns about treatment toxicity [72,73]. However, these concerns should be balanced against an understanding that more intensive regimens hold the greatest potential for achieving MRD negativity and long-term remission.

There are several less-intensive treatment options for such patients, representing a spectrum of intensities. Such therapies include HMAs (e.g., azacitidine, decitabine) and LDAC, as well as the BCL2 inhibitor venetoclax and several targeted agents (e.g., glasdegib, gemtuzumab ozogamicin, ivosidenib [Tibsovo®], and enasidenib) that may be given as monotherapies or in combination with HMAs or LDAC [5]. Time to response with these agents is often longer than with intensive chemotherapy and can require prolonged treatment durations [74], with oral therapies typically requiring long-term continuous dosing [75–77]; this differs from most intensive chemotherapy regimens, which typically involve a discreet and comparatively short treatment duration followed by the potential for an extended treatment-free period. Additionally, lower-intensity therapy is often not given with a curative intent, and many patients achieve only stable disease rather than remission. However, the achievement of stable disease does indicate a delay in disease progression and can be associated with a reduced need for transfusions and a decreased risk of infection [74]. Remissions achieved with lower-intensity therapies have traditionally been of short duration, and to achieve long-term survival these regimens should be followed by a potentially curative treatment such as HCT. Several newer agents may induce durable remissions in subsets of patients; studies are ongoing.

In a phase 3 study, decitabine and LDAC or best supportive care achieved a CR of 15.7% versus 7.4% (median time to response: 4.3 months) and OS of 7.7 versus 5.0 months, respectively [78]. The combination of venetoclax and LDAC was compared with LDAC alone in 211 patients with newly diagnosed AML who were considered ineligible for intensive induction chemotherapy in a phase 3 randomized trial [79]. This combination did not significantly improve median OS (7.2 vs 4.1 months with LDAC alone; HR = 0.75 [95% CI: 0.52, 1.07]; $P = 0.11$); however, CR was attained in more patients receiving venetoclax (27% vs 7%) [79]. In a separate phase 3 study of 431 patients with newly diagnosed AML who were considered ineligible for intensive chemotherapy, median OS was 14.7 months with venetoclax plus azacitidine versus 9.6 months with azacitidine alone (HR = 0.66 [95% CI: 0.52, 0.85]; $P < 0.001$) and the CR was 37% versus 18% ($P < 0.001$) [80]. However, it should be noted that the addition of venetoclax to either HMAs or LDAC increased the frequency of grade ≥3 hematologic AEs, and the majority of patients in both phase 3 studies experienced a serious AE (venetoclax with LDAC: 66%; venetoclax with azacitidine: 83%); thus, although these regimens are generally considered less intensive, they are not without safety risks [79,80]. In addition to this concern, data have also suggested that patients relapsing after treatment with venetoclax and HMAs fare poorly [81], with shorter OS in patients failing the venetoclax combination compared with those failing upfront intensive chemotherapy [82].

In a comparison of glasdegib in combination with LDAC versus LDAC alone in 132 patients aged ≥55 years with newly diagnosed AML, the addition of glasdegib resulted in a significantly longer median OS (8.3 vs 4.3 months; HR = 0.46 [80% CI: 0.35, 0.62]; $P = 0.0002$) and a higher CR rate (17.0% vs 2.3%; $P < 0.05$) [75].

A phase 1 trial subanalysis of 34 patients with newly diagnosed *IDH1*-mutated AML who were considered ineligible for standard therapy found that ivosidenib monotherapy resulted in a CR of approximately 30% (with a 12-month duration in 78% of these patients) and a median OS of 12.6 months [76]. Similarly, in a phase 1/2 trial subanalysis of 39 patients with newly diagnosed *IDH2*-mutated AML who were considered ineligible for standard therapy, enasidenib monotherapy was associated with a CR rate of 18%, with a median CR duration not reached; median OS was 11.3 months [77].

4. Expert opinion

Intensive induction chemotherapy continues to play a pivotal role for the management of many patients with AML and can offer the best chance of achieving MRD negativity and long-term remission, especially when followed by allogeneic HCT [83]. The development of new chemotherapy agents and novel formulations of existing regimens, such the CPX-351 dual-drug liposomal encapsulation of daunorubicin and cytarabine at a synergistic ratio, can help to

improve outcomes for patients with AML who are treated with a curative intent. Intensive chemotherapy also plays an integral part of the current AML treatment landscape when used as a backbone in combination with targeted agents, and such combinations may permit more personalized treatment for patients with specific disease characteristics [5,7]. However, AML remains a relatively rare disease that requires treatment by specialized teams, as extensive cytogenetic and molecular tests are needed to efficiently diagnose AML subtypes and treat patients based on their specific molecular/genetic characteristics. While academic and other large, specialized hematology/oncology centers have teams trained to efficiently diagnose AML subtypes, it is not expected that targeted agents should be rapidly adapted into community use. Access to rapid results to provide a differential diagnosis prior to initiating treatment and again upon relapse is needed within the community setting to facilitate personalized treatment decisions. In addition, training on the clinical profiles, including toxicity management, of newer agents is needed for clinicians in a community setting, where experience with some newer agents is currently limited, in order to ensure the best outcome for patients.

Holistic patient assessment for appropriateness to receive intensive chemotherapy is also important, particularly among older patients and those with comorbidities. Recent studies have indicated that many older patients benefit from receiving intensive induction therapy with a curative intent instead of lower-intensive therapy or best supportive care [10–12], and thus older patients should not automatically be assumed as ineligible to receive intensive treatment [7,15] or excluded from clinical studies. However, standardized objective assessments to holistically determine a patient's fitness to receive a particular therapy are lacking. Several multiparameter geriatric assessment tools have been developed to provide a more comprehensive evaluation of patient fitness, but there is currently no consensus with regard to the ideal domains for inclusion, these assessments can be time-consuming, and they need to be evaluated in clinical trials to determine their ability to identify patients who are appropriate to receive individual regimens. Meanwhile, the continued incorporation of novel agents, which represent a spectrum of treatment intensities and may have improved toxicity profiles for some patients, into the AML treatment landscape should help to improve outcomes for older patients with AML, as well as younger patients. Outcomes with intensive chemotherapy in older patients may also be improved with better supportive care [51].

Given the plethora of recently approved drugs for the treatment of AML, clinical trials should continue to look at new combination regimens, including the combination of targeted agents with novel chemotherapy formulations (e.g., CPX-351), to optimize intensive therapy for the treatment of AML. Ideally, large multicenter, randomized clinical trials would be designed to evaluate these novel combinations; however, the longer the field progresses with only data from single-institution studies and case series, the more the window for feasibly performing multicenter, randomized clinical trials closes. Additional experience in combining agents will lay the foundation for new standards of care in the coming years. Randomized trials that compare less intense but efficacious regimens versus more intensive regimens in specific AML subpopulations are also needed to optimize induction chemotherapy for all age ranges and subtypes of AML. In addition, the assessment of MRD should be integrated into clinical trials as a standardized measure to evaluate the depth of response across treatment regimens. Together, it is hoped these efforts will guide the AML treatment landscape toward a more personalized treatment approach in which patients are treated with a curative intent whenever possible, irrespective of the clinical setting.

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