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Post-remission therapy in acute myeloid leukemia: Are we ready for an individualized approach?

Benjamin A. Derman*, Richard A. Larson

Section of Hematology Oncology, Department of Medicine and Comprehensive Cancer Center, University of Chicago, Chicago, IL, USA

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ABSTRACT

Recent advances in remission induction treatment strategies for acute myeloid leukemia (AML) have improved the rates of complete remission (CR) and overall survival (OS), owing to a concerted effort to tailor therapies toward specific AML subtypes. However, without effective post-remission therapy, most patients will relapse. The extent to which post-remission therapies is individualized in the current paradigm is quite varied. Core binding factor (CBF) AML is typically treated with post-remission high-dose cytarabine (HiDAC) without allogeneic hematopoietic stem cell transplantation (HSCT), whereas those with intermediate or adverse-risk cytogenetics are treated with post-remission cytarabine followed by allogeneic HSCT in CR1 when feasible. A lack of clarity regarding the proper dosing of post-remission cytarabine has made consensus building on dosing and schedule a challenge. CBF AML benefits most from high-dose cytarabine (HiDAC), and dasatinib appears promising as an adjunct for those for *KIT*-mutated CBF AML. Other than series using CPX-351 or lomustine in older adults, multiagent chemotherapy approaches have resulted in excess toxicity without a survival benefit. Neither hypomethylating agents nor gemtuzumab ozogamicin have shown a material OS benefit. Targeted agents such as FLT3 inhibitors and IDH1/IDH2 inhibitors show potential for the patients who harbor these druggable targets, but few data are available. Many studies evaluating post-remission strategies to target AML in the MRD-positive state are already underway, and these remain a promising area of investigation.

Introduction

The goal of remission induction in acute myeloid leukemia (AML) is to restore normal hematopoiesis by a 2- to 4-$\log_{10}$ cytoreduction of the roughly 10^{12} leukemic cells present at the time of diagnosis. This sets the stage for post-remission therapy, whose goal is to eliminate the initial leukemia stem cells as well as the remaining, relatively more drug-resistant, daughter clones and ultimately lead to a cure.

Of course, post-remission therapy in AML is predicated on the success of induction therapy, and advances in remission induction treatment strategies for AML have led to modest but significant improvements in achievement of complete remission (CR) and overall survival (OS) [1–3]. Though the mellifluous term 'individualized therapy' has recently taken hold with the introduction of targeted therapies, clinicians have already been practicing a personalized approach to therapy for quite some time. Age and comorbidities have played an important role in selection of induction regimens, with hypomethylating agents, CPX-351, lomustine, glasdegib, and venetoclax recently serving as important adjuncts that result in improved CR, disease-free survival (DFS), and OS rates in older adults

* Corresponding author. University of Chicago, 5841 S. Maryland Avenue, MC-2115, Chicago, IL, 60637, USA.
E-mail address: bderman@medicine.bsd.uchicago.edu (B.A. Derman).

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with AML. Though the influence of age on post-remission strategies is an underexplored area, cytogenetics has played a key role in tailoring post-remission therapy. Patients with core binding factor (CBF) AML have typically been treated with post-remission cytarabine while forgoing allogeneic hematopoietic stem cell transplantation (HSCT); those with intermediate or adverse-risk cytogenetics have been treated with intensive multi-agent chemotherapy followed, if feasible, by allogeneic HSCT while in CR1 [4].

Without post-remission therapy, nearly all patients in their first CR will relapse [5]. Nevertheless, the optimal post-remission strategy for an individual patient has not yet been established, owing to a paucity of randomized trial data and the heterogeneity of studies that have investigated this important question. We summarize here the current state-of-the-art and discuss future directions for post-remission therapies.

What is the optimal dosing of the most commonly used post-remission therapy cytarabine?

Identifying the minimum effective cytarabine dose and schedule has taken center stage as clinicians and patients alike seek to attain durable disease responses while mitigating toxicity. Of particular concern are the incidences of hematologic, neurologic (cerebellar and ocular), gastrointestinal, and cutaneous toxicities from cytarabine.

A spectrum of post-remission cytarabine dosing schedules has been investigated; the considerable heterogeneity of these studies has made it difficult to arrive at a unified recommendation. High-dose cytarabine (HiDAC) is not consistently defined, but a typical cycle as developed by the Cancer and Leukemia Group B (CALGB) is 2–3 g/m^2 infused twice daily on alternate days for 6 doses (cumulative dose, 12–18 g/m^2 per cycle). Early studies showed that HiDAC yielded superior disease-free survival (DFS) compared to the continuous infusion of lower doses of cytarabine for 5 days [6]. However, data suggest that intermediate-dose cytarabine (IDAC; 1 g/m^2) is sufficient to achieve maximal antileukemic effects with a plateau in the dose-response relationship above this dosing level [7–10].

A meta-analysis by Magina et al. comparing the efficacy of post-remission HiDAC to intermediate/low-dose cytarabine (IDAC/LDAC) included 9 studies ranging over a period of nearly 25 years. They concluded that there was no statistically significant difference between HiDAC regimens (defined as total cumulative doses per course between 20 and 72 g/m^2) and IDAC/LDAC (0.7–18 g/m^2) with respect to relapse-free survival (RFS; HR 0.90, 95% CI 0.80–1.01) or OS (HR 0.98, 95% CI 0.87–1.09) [11]. There was a benefit in RFS for HiDAC in the favorable cytogenetic risk group (HR 0.57, 95% CI 0.33–0.99), but this did not translate into an OS benefit. Similarly, a meta-analysis by Wu and colleagues compared the benefit and safety of HiDAC (2–3 g/m^2 twice daily), IDAC (1–2 g/m^2 twice daily), and LDAC ($<$ 1 g/m^2 twice daily) within 10 randomized phase III trials with 4008 AML patients from 1994 to 2016 [12]. They found that HiDAC improved both DFS and OS in comparison to LDAC. Compared to IDAC, HiDAC showed a benefit in DFS (HR 0.43, 95% CI 0.33–0.57, $P < .00001$) with the advantage driven solely by those with favorable cytogenetics (ie, CBF AML). No OS advantage was found. HiDAC and IDAC both resulted in higher risks of grade 3 or 4 non-hematologic toxicity [12].

Prior data in CBF AML have suggested that 3 or 4 cycles of HiDAC is associated with a significant decrease in the relapse rate over 5 years compared to 1 cycle (43% vs 70%, $P = .03$); however, significant differences in RFS or OS were not observed [13]. A more recent study identified that among patients with favorable cytogenetics, 2 cycles of HiDAC did not lead to lower RFS or OS compared to 3 cycles when censored for receipt of allogeneic HSCT [14], suggesting that 2 cycles of HiDAC is sufficient for this subset. The phase Ib/IIa AMLSG 11–08 trial investigated the addition of the KIT inhibitor dasatinib to conventional induction therapy and 4 cycles of HiDAC post-remission therapy and 1 year of maintenance; the 4-year OS was an impressive 74.7% (95% CI, 66.1–84.5%) with a favorable toxicity profile [15]. Similar benefit was observed using dasatinib in CALGB study 10801 [16,17]. The 3-year DFS and OS rates were 75% and 77%, respectively.

What is the evidence for other chemotherapeutic agents in post-remission therapy?

Attempts to intensify post-remission therapy with multiagent chemotherapy have largely shown no improvement in survival over conventional HiDAC. Five randomized trials—the CALGB 9222, ALFA-9802, AML2003, AML15, and AML201 studies—compared various multiagent chemotherapies to HiDAC in AML patients < 60 years old, and all failed to show a survival benefit (Table 1) [18–22]. In most cases, intensification of post-remission therapy often resulted in added toxicity without added benefit. However, the LAM-SA 2007 FILO trial that investigated the addition of lomustine to conventional idarubicin and cytarabine during both induction and post-remission in older AML patients without unfavorable cytogenetics did show a significant 2-year OS benefit after induction (56% vs 48%, $P = .02$) [3]. However, randomization to lomustine occurred prior to induction therapy, making it difficult to make conclusions about its impact in the post-remission setting. The pivotal CLTR0310-301 phase 3 trial compared CPX-351 as induction and post-remission therapy to conventional cytarabine and daunorubicin in patients aged 60–75 with high-risk or secondary AML. Median OS was significantly improved with CPX-351 (9.56 vs 5.95 months; HR 0.69, 95% CI 0.52–0.90, $P = .003$), though it did lead to prolonged time to neutrophil and platelet recovery [2]. Randomization again occurred prior to induction therapy, making the benefit of CPX-351 in the post-remission setting unclear. However, it is feasible to give CPX-351 in the outpatient clinic to many patients in first CR, and thus avoid hospitalization for chemotherapy administration.

There has been interest in using hypomethylating agents for post-remission maintenance based on their single-agent activity in newly diagnosed AML and the myelodysplastic syndromes. Most recently, post-remission therapy with azacitidine was shown to improve DFS but not OS in older patients with AML when adjusted for cytogenetic risk and platelet count [23]. The CALGB conducted a prospective phase 2 trial with decitabine as maintenance therapy for 134 adults < 60 years old in first CR [24]. Decitabine was given IV over 1 h at 20 mg/m^2 for 5 days every 6 weeks for 8 cycles. The DFS at 1 year and 3 years was 79% and 54%, respectively. However, these results were similar to outcomes in a historical control, and it was concluded that decitabine maintenance was not

Table 1
Summary of post-remission therapy phase 3 trials and meta-analyses in AML.

Post-Remission Therapy	Study Type and Size[a]	Population	Improved DFS?	Improved OS?
Cytarabine Alone				
CALGB 8525: HiDAC (3 g/m^2 BID) vs Infusional Ara-C [6]	Phase 3, n = 596	Age 16-86	**Yes**	**Yes**
HiDAC (20–72 g/m^2) vs IDAC/LDAC (0.7–18 g/m^2) [11]	Meta-analysis, n = 4224	Age 1-73	**No**[b]	**No**
HiDAC (2–3 g/m^2 BID) vs IDAC (1–2 g/m^2 BID) vs LDAC (< 1 g/m^2 BID) [12]	Meta-analysis, n = 4008[c]	Age 15-86	HiDAC vs LDAC: **Yes**[d] HiDAC vs IDAC: **Yes**[d] IDAC vs LDAC: **No**	HiDAC vs LDAC: **No** HiDAC vs IDAC: **No** IDAC vs LDAC: **No**
Multiagent Chemotherapy Regimens				
CALGB 9222: HiDAC/EC/DM vs HiDAC [18]	Phase 3, n = 309	Age 15-59	**No**	**No**
ALFA-9802: Timed Sequential Therapy vs HiDAC [19]	Phase 3, n = 237	Age 15-50	**No**	**No**
AML2003: Mitoxantrone/ara-C + amsacrine/ara-C vs HiDAC [20]	Phase 3, n = 442	Age 16-60	**No**	**No**
AML15: MACE or MidAC vs HiDAC [21]	Phase 3, n = 1440	Age 0-73	**No**	**No**
AML201: MAC/MAMAC/MAC vs HiDAC [22]	Phase 3, n = 781	Age 15-64	**No**	**No**
LAM-SA 2007 FILO: ICL vs IC [3]	Phase 3, n = 338	Age 60-81	**Yes**	**Yes**
CPX-351 vs DA [2]	Phase 3, n = 81	Age 60-75	**Yes**	**Yes**
Epigenetic Modulators				
HOVON97: Azacitidine vs Observation [23]	Phase 3, n = 116	Age 60-81	**Yes**	**No**
Targeted Agents				
Gemtuzumab Ozogamicin vs Observation [31]	Phase 3, n = 232	Age 60-78	**No**	**No**
Midostaurin + HiDAC vs HiDAC [1]	Phase 3, n = 441	Age 18-59	**Yes**	**Yes**

BID = twice daily; DA = Daunorubicin and Ara-c (cytarabine); HiDAC/EC/DM = First cycle with HiDAC, second cycle with etoposide and cyclophosphamide, and third cycle with diaziquone (AZQ) and mitoxantrone; HiDAC = high dose cytarabine; IC = idarubicin and cytarabine; ICL = idarubicin, cytarabine, and lomustine; IDAC = intermediate dose cytarabine; LDAC = low dose cytarabine; MACE = amsacrine, cytarabine, and etoposide; MidAC = mitoxantrone and cytarabine; MAC/MAMAC/MAC = Two cycles of mitoxantrone plus high-dose cytarabine and one cycle of amsacrine plus HiDAC.

[a] n = number of patients who proceeded to consolidation.
[b] RFS benefit was seen only in those with favorable cytogenetics.
[c] n = 3932 for OS analysis.
[d] Driven by patients with favorable cytogenetics.

beneficial in young AML patients. A randomized phase 2 trial examining evaluating the use of azacitidine at various time points in the course of AML treatment, including a proposed 2 years of maintenance azacitidine, was limited in that only 15 of 104 patients reached the maintenance phase and only 2 patients received the intended 24 cycles of azacitidine [25]. CC-486, an oral form of azacitidine, offers the potential advantage of delivering a hypomethylating agent over a more prolonged schedule than is feasible with parenteral azacitidine [26]. The randomized, placebo-controlled phase 3 QUAZAR trial (NCT01757535) is currently underway investigating the efficacy of CC-486 as maintenance therapy in older patients (≥55 years) with AML in first CR [27].

Can targeted agents be used in post-remission therapy?

As targeted agents have made their way into induction and re-induction regimens for AML, their utility in the post-remission setting is now under investigation.

The anti-CD33 drug-antibody conjugate gemtuzumab ozogamicin (GO) has received FDA approval as part of induction therapy for newly diagnosed CD33-positive AML [28–30]. However, in a randomized phase 3 trial comparing GO to observation as post-remission therapy in older adults with AML in first CR, GO did not provide a benefit in any of the endpoints of DFS, OS, or probability of relapse [31]. Moreover, caution must be exercised in using GO as a bridge to allogeneic HSCT given its heightened risk of hepatic sinusoidal obstruction syndrome [32].

Approximately 30% of AML patients have an activating mutation in the fms-related tyrosine kinase 3 gene (*FLT3*), with the majority representing a *FLT3* internal tandem duplication (ITD) mutation and less commonly a *FLT3* tyrosine kinase domain (TKD) mutation [33,34]. While these mutations carry a poor prognosis when the variant allele fraction (VAF) is high, *FLT3*-ITD and TKD mutations are druggable targets that have already led to improved outcomes in this subset of AML. The phase 3 RATIFY trial (CALGB 10603) randomly assigned patients to standard induction therapy with daunorubicin and cytarabine and consolidation with high-dose cytarabine with or without the FLT3 inhibitor midostaurin 50 mg twice daily on days 8–21 of a 28-day cycle during each course of induction and consolidation, and then continuously for 12 months of maintenance. In this landmark trial, the midostaurin group experienced an OS benefit (HR 0.78, p = .009), even when censored for patients who underwent transplantation [1]. Given that randomization occurred prior to induction therapy and that the median exposure was 3 months, the additional benefit of midostaurin in the post-remission setting is unclear.

Several second-generation FLT3 inhibitors are currently in development, which have the potential advantage of higher potency and selectivity with fewer off-target effects in preclinical studies [35]. In November 2018, the FDA approved gilteritinib for relapsed/

refractory *FLT3*-mutated AML, and in that same month, they granted a priority review designation to quizartinib for relapsed/refractory *FLT3*-ITD-mutated AML [36,37]. Both gilteritinib and quizartinib have shown a statistically significant survival benefit in relapsed/refractory *FLT3*-mutant AML [38]. The efficacy of these second-generation FLT3 inhibitors as part of post-remission therapy either alone or combined with chemotherapy is not yet known. The disease-free plateaus on the survival curves when these drugs are used as single agents for relapsed disease or after allogeneic HSCT are not high. Similar strategies are now being applied to AML with other targetable driver mutations such as *IDH1* (ivosidenib) and *IDH2* (enasidenib). A phase I trial (NCT02632708) adding the appropriate inhibitor to conventional chemotherapy with induction and consolidation followed by continued use into maintenance therapy is currently underway.

Can measurable residual disease be used to guide post-remission therapy?

Measurable residual disease (MRD) in AML marks the presence of leukemia cells detectable at a level of 10^{-4} to 10^{-6} sensitivity (i.e., 1 leukemic cell detected out of 10,000–1,000,000 cells analyzed), a substantial improvement compared to traditional morphology-based assessments [39]. MRD can be measured by multiparametric flow cytometry (MFC) for many cases, real-time quantitative polymerase chain reaction (PCR) for cases with a fusion gene such as acute promyelocytic leukemia (APL) or CBF AML, or next generation sequencing (NGS) specifically for *NPM1*-mutated AML. In a retrospective analysis, Walter and colleagues investigated the significance of MRD prior to myeloablative allogeneic HSCT in 253 patients with AML in first or second CR. They found that MRD-negativity by MFC prior to transplantation was associated with a significant increase in DFS and OS ($P < .001$) and a significant decrease in risk of relapse ($P = .001$) and non-relapse mortality ($P = .017$) [40]. Several other studies have shown that both MFC and NGS MRD-negativity carry strong prognostic significance, regardless of transplantation [41–44]. Some have argued that these results mean that MRD-negativity should be attained prior to proceeding with allogeneic HSCT [44]. However, it can be argued that the MRD-positive patients are the ones who might gain the most relative benefit from allogeneic HSCT, as persistent disease reflects chemoresistant clones and thus the need for more potent therapies with alternative mechanisms of action. MRD-negative patients likely represent a chemosensitive population that might be spared a transplant procedure.

Though the utility of MRD as a treatment decision-making tool is presently unknown, achieving MRD-negativity in the post-remission setting is a worthy goal and appears necessary for long-term remission. MRD-negativity could also serve as a useful guide to introduce new modalities or determine the duration needed for post-remission chemotherapy. The open-label phase 2 RELAZA2 study investigated the use of azacitidine in older adults who had post-remission MRD-positive disease; those who responded to azacitidine appeared to have 1- and 2-year survival rates that were much improved but still inferior to those patients who were already MRD-negative without post-remission treatment [45]. Many strategies to target AML in the MRD-positive state are already underway. The anti-CD123 monoclonal antibody SL-401 is under investigation in an open-label phase 1/2 trial for patients in first CR or with MRD-positive disease (NCT02270463) [46]. The *anti*-PD-1 checkpoint inhibitor nivolumab is the subject of phase 2 studies in patients with AML in first or second remission at high risk for relapse, including patients with MRD-positive disease (NCT02275533 and NCT02532231). A list of select trials for MRD-positive AML can be seen in Table 2.

Nevertheless, several challenges with MRD testing remain, including false negatives from hemodilution of the aspirate samples and patchiness of residual disease as well as shifting immunophenotype, and a lack of harmonization with respect to measurement of MRD by MFC. It should also be noted that the detection of persistent mutations commonly associated with clonal hematopoiesis (*DNMT3A, TET2, ASXL1*) do not carry prognostic significance [43].

Conclusions

AML is a heterogeneous disease and we do not yet have sufficient arrows in our quiver to hit the critical target in each individual

Table 2
Selected trials for AML patients who are MRD-positive.

Interventions	Mechanism	Identifier	Accrual[b]	Characteristics
Actinium-225-Lintuzumab	Anti-CD33 mAb linked to α particle emitter	NCT03705858	Not yet recruiting	Phase I
DCP-001	Allogeneic dendritic cells	NCT03697707	Recruiting	Phase II
Azacitidine	HMA	NCT01462578	Not yet recruiting	Phase II
Azacitidine and Avelumab	HMA and checkpoint inhibitor	NCT03699384	Recruiting	Phase I/II
Daratumumab and DLI[a]	Anti-CD38 mAb and donor lymphocytes	NCT03537599	Not yet recruiting	Phase I/II
Decitabine	HMA	NCT03793517	Recruiting	Phase II/III
FlySyn	*Anti*-FLT3 Fc-optimized antibody	NCT02789254	Recruiting	Phase I/II
Gemtuzumab Ozogamicin	Anti-CD33 mAb linked to calicheamicin	NCT03737955	Recruiting	Phase II
Lenalidomide[a]	Immunomodulatory imide drug (IMID)	NCT02370888	Not yet recruiting	Phase I
Nivolumab	Checkpoint inhibitor	NCT02275533	Recruiting	Phase II
		NCT02532231	Recruiting	Phase II
SL-401	Anti-CD123 mAb	NCT02270463	Recruiting	Phase I/II

DLI = donor lymphocyte infusion; HMA = hypomethylating agent; mAb = monoclonal antibody.
[a] Post-allogeneic HSCT.
[b] Current as of January 2019.

patient. For the majority of AML patients in CR, it is reasonable to administer 2–3 cycles of IDAC 1–2 g/m^2 twice daily for 6 doses. For patients with CBF AML, we continue to use HiDAC 2–3 g/m^2 twice daily for 6 doses based on its track record of tolerability and effectiveness. We also add dasatinib for inhibition of KIT based on our CALGB experience. Multiagent chemotherapy approaches mostly result in additional toxicity without a survival benefit, except in the cases of CPX-351 in older adults with adverse risk cytogenetics, and lomustine in those without unfavorable cytogenetics. Hypomethylating agents such as azacitidine or decitabine have not shown a material OS benefit. Though GO has increased the CR rate, its adjunctive use post-remission is uncertain. Targeted agents such as FLT3 inhibitors and IDH1/IDH2 inhibitors show great potential for the patients who harbor these druggable targets. Despite the enthusiasm around these agents, there is uncertainty as to the nature and quality of a CR achieved by the use of a targeted agent alone as compared to cytotoxic chemotherapy in the induction setting; should post-remission therapy be different in these cases? The next generation of clinical trials in this arena needs to focus on rigorously evaluating the benefit of targeted agents specifically in the post-remission setting in a randomized fashion.

The impact of MRD-status on post-remission therapy has yet to be delineated, though there are three potential avenues to confirm its utility. Clinical trials need to be constructed where MRD status is used to (1) determine the duration of post-remission treatment (ie, longer duration for MRD-positive patients) or (2) prompt a change in the modality of therapy for MRD-positive patients (eg, introduce immunotherapies earlier), or (3) determine if allogeneic HSCT provides any benefit over conventional chemotherapy in the MRD-negative population. The timing for measurement of MRD is likely to be critical, as MRD-negativity immediately after induction is more likely to correlate with long remission durations than MRD-negativity developing only after 3–4 intensive consolidation courses.

Though a great deal has been learned in the 25 years since the landmark CALGB 8525 study establishing HiDAC as the standard of care in AML post-remission therapy, the approach to AML treatment has not changed much in that time. An armada of novel agents sits ready to be deployed—it is time that AML post-remission therapy experiences the renaissance that patients so richly deserve.

Declaration of competing interest

Dr. Larson discloses consulting fees from Novartis, Ariad, CVS Caremark, Pfizer, Celgene, and Abbvie.
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