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Therapy of Core Binding Factor Acute Myeloid Leukemia: Incremental Improvements Toward Better Long-Term Results

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Abstract

Despite being considered as good prognostic acute myelogenous leukemia (AML), the long-term survival rate in core binding factor AML leaves room for substantial improvement. We discuss treatments that have improved outcome in this group of patients with AML and ongoing/future strategies that might contribute toward incremental gains.

Background—Despite being considered as good prognostic acute myelogenous leukemia (AML), the long-term survival rate in core binding factor (CBF) AML leaves room for substantial improvement.

Materials and Methods—We reviewed relevant English language literature related to treatment of CBF AML available in PubMed. Review also included meeting abstracts.

Results—Multicycle high dose cytarabine in consolidation improves remission duration but larger groups report overall survival in the range of 40% to 50% at 5 years or longer.

Conclusions—Concerted effort is needed toward improving outcomes in CBF AML through clinical trials and risk-adapted approach.

Keywords

Chemotherapy; High-dose cytarabine; Inversion (16); Response; Translocation (8:21)

Introduction

Core binding factor (CBF) acute myeloid leukemia (AML), characterized by the presence of either translocation (t)(8;21) (q22;q22) or inversion (inv)(16) (p13q22)/t(16;16) which leads to the formation of *RUNX1/RUNX1T1 (AML1/ETO)*[1] or *CBFB/MYH11*[2] fusion gene, respectively, is more often seen among patients aged younger than 60 years where it comprises up to 12% to 15% of all AML cases.[3–6] These cytogenetic aberrations are associated with ‘favorable’ response and increased sensitivity to cytarabine (ara-C),

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however, long-term follow-up reports from larger groups show median overall survival (OS) of approximately 5 years or less,[3,7–9] indicating need for improved therapy.

Both t(8;21) and inv(16) AML have similar complete remission (CR) rates, however, the 2 subgroups have important difference in outcomes.[7,10–12] Patients with t(8;21) have inferior response to salvage therapy after relapse, contributing to inferior OS.[10,13,14] Patients with t(8;21) present with lower white counts and blast percentage and higher frequency of secondary cytogenetic abnormalities. The nature of secondary cytogenetic abnormalities also varies: -X, -Y, and del(9q) are more common among t(8;21) and trisomies 22 and 21 are more frequent in inv(16)[7,9,10]; some of these differences in 2 subgroups such as white count,[9,15,16] blast percentage,[7] complex cytogenetics, -Y in t(8;21),[9,16] and trisomy 22 in inv(16),[9,10] etc, have been shown to influence outcome. Furthermore, a recent retrospective analysis[14] has shown that *KIT* and *RAS* mutations are more common in inv(16) and *FLT3/ITD* mutation is more common in t(8;21). Both groups considered together, the cumulative incidence of relapse was higher and OS was lower in the presence of *KIT*, *RAS*, or *FLT3/ITD* mutation. Considered apart, presence of these mutations trended to increase the risk of relapse in t(8;21); in the inv(16) group it negatively affected response to salvage after relapse.[14]

Presence of *c-KIT* mutations in exons 8 and 17 have been shown to be associated with increased relapses and inferior OS in CBF AML.[17–20] However, the adverse impact of *KIT* mutation was not seen in a pediatric patient cohort[21] suggesting that therapy and other variables might overcome its impact. Old age,[7,10] secondary CBF AML,[22,23] gene expression profiling[24] and CD56 expression [in case of t(8;21)][25] are other variables with bearing on prognosis.

Optimizing Chemotherapy of CBF AML

Induction with ara-C/anthracycline-based combination chemotherapy and consolidation with high dose ara-C based regimen is considered as the standard of care for AML. Given the high CR rate of ara-C/anthracycline-based induction regimen, many of the studies have focused on the optimization of postremission consolidation therapy. Whether intensification of induction therapy can be of benefit is still an open question.

Is Optimization of Anthracycline Dose in Induction Necessary?

A phase 3 Eastern Cooperative Oncology Group (ECOG) trial randomized AML patients younger than 60 years of age to receive 3 once-daily doses of daunorubicin at 45 mg/m^2 (standard) (n = 318) or 90 mg/m^2 (high) (n =315) combined with 7-day infusional ara-C (100 mg/m^2). Consolidation therapy consisted of allogeneic stem cell transplantation (allo-SCT) or autologous (auto)-SCT (these patients also received 2 cycles of high-dose Ara-C [HDAC]). Among patients with CBF AML (n = 89), median OS was not significantly different between high-dose (n = 51) and standard-dose daunorubicin (n =38) (hazard ratio [HR], for death =0.30–1.27; P =.19).[4]

A Dutch Belgian Austrian group study among patients older than 60 years of age with untreated AML or refractory anemia with excess blasts, had similar randomization of conventional dose (45 mg/m^2 per day; n = 411) or escalated dose (90 mg/m^2 per day; n = 402) daunorubicin combined with 7-day infusional ara-C (200 mg/m^2 per day). All patients subsequently received 1 consolidation with high-dose ara-C. Subgroup analysis revealed that CBF AML patients treated with escalated dose daunorubicin (n =14) had higher rate of CR (93% vs. 74%), 2-year event-free survival (EFS) (57% vs. 29%), and OS (71% vs. 51%) compared with patients treated with conventional dose (n = 19)[26] but the low number of

CBF patients precluded adequate statistical power. Thus, the role of anthracycline dose escalation in CBF AML induction is not established.

Fludarabine and Cytarabine-based Induction and Consolidation: Can We Do Away With Anthracycline?

Fludarabine positively modulates intracellular ara-C accumulation.[27] A report from M.D. Anderson Cancer Center (MDACC) included 114 CBF AML patients treated with the following induction regimens: (1) fludarabine (30 mg/m^2 per day) followed by ara-C (2 g/m^2 per day) (FA) for 5 days (n = 45); (2) FA with granulocyte colony-stimulating factor (G-CSF) subcutaneously daily on days −1 through 5 (FLAG) (n = 22); (3) idarubicin (12 mg/m^2 per day) for 3 days and ara-C (1.5 g/m^2 per day for 4 days or 3 days if age greater than 65 years) (IA) only or with G-CSF (IAG) (n = 47). Postremission therapy for patients treated with FA or FLAG regimen included alternate cycles of ara-C (2 g/m^2 twice daily on days 1, 3, and 5) and FA or FLAG, respectively for 4 days. For patients treated with IA or IAG, consolidation included alternate cycles of 5-day infusional ara-C (100 mg/m^2 daily) and IA (idarubicin 8 mg/m^2 on days 1 and 2, and ara-C 1.5 g/m^2 per day for 2–3 days). Six to 12 cycles of postremission therapies were administered as tolerated. Multivariate analysis showed that EFS was longer than IA/IAG with a relative risk (RR) of 0.47 (FLAG vs. IA/IAG; P = .07). EFS was comparable between FA and IA/IAG group (RR, 0.84; FA vs. IA/IAG, P =.58). At a median follow-up of 159 weeks, the frequency of relapse was 32% in the FLAG group, 33% in the FA group, and 52% in the IA/IAG group. Forty-four percent of the patients with relapsed disease achieved second CR with HDAC-based salvage therapy, which possibly accounted for no significant difference in OS among different treatment groups.[28] Thus, fludarabine and ara-C based combinations (FA or FLAG) are alternates to anthracycline and ara-C options for CBF AML patients.

Gemtuzumab Ozogamicin in First-Line Combination Regimens

Medical Research Council (MRC) AML15 trial randomly assigned 1113 AML patients predominantly younger than 60 years to single dose of gemtuzumab ozogamicin (GO) (3 mg/m^2) or none on day 1 of induction with 1 of the following chemotherapies: daunorubicin and ara-C with or without etoposide, or FLAG-idarubicin. Patients who achieved remission were subsequently randomized to GO in course 3. A predefined subgroup analysis showed a significant improvement in 5-year OS (79% vs. 51%; P = .0003) among CBF AML patients allocated to GO in induction therapy (n = 72) compared with patients not allocated to GO (n = 65).[29,30]

Acute Leukemia French Association (ALFA)-0701 trial randomly assigned 280 AML patients aged 50 to 70 years to receive GO (3 mg/m^2 on days 1, 4, and 7) with 3 +7 induction regimen of daunorubicin and ara-C. Patients in remission received 2 consolidation courses of daunorubicin and ara-C with or without GO (3 mg/m^2 on day 1). A subgroup analysis showed improvement in 2-year EFS (HR, 0.50; confidence interval [CI], 0.30–0.82) and relapse free survival (RFS) (HR, 0.51; CI, 0.29–0.90) among favorable (14 patients each in GO and control group) and intermediate risk AML in the GO group compared with the control group. There was a trend toward benefit in OS (HR, 0.59; CI, 0.32–1.09).[31]

A recent comparison of an ongoing phase 2 study of FLAG regimen with gemtuzumab ozogamicin (FLAG-GO) (median follow-up >2 years) to historical data with IA/IAG at MDACC, also showed that first-line therapy with FLAG-GO was associated with significantly better event-free survival (P =.01; HR for IA/IAG, 3.20; 95% CI, 2.04–4.36).[32]

Cumulative evidence argues strongly in favor of adding GO in induction/consolidation in CBF AML if this agent becomes available for clinical use.

Postremission Therapy

Optimization of Ara-C in Postremission Therapy

A Cancer and Leukemia Group B (CALGB) study of patients with de novo AML (n =285) included 57 patients with CBF AML (Table 1). Induction comprised 3 days of intravenous daunorubicin and 7 days of infusional ara-C (200 mg/m^2 per day) (3 + 7 regimen). Patients in remission were randomly assigned to 4 courses of 1 of the 3 different consolidation regimens of single-agent ara-C: (1) 5-day infusion of 100 mg/m^2 per day, (2) 5-day infusion of 400 mg/m^2 per day, or (3) 3 g/m^2 bolus over 3 hours every 12 hours on days 1, 3, and 5. Maintenance therapy was 4 monthly treatments with 5-day ara-C (100 mg/m^2 subcutaneously twice daily) and 45 mg/m^2 intravenous daunorubicin on day 1. Ara-C dose intensification in consolidation had the greatest effect on long-term remission in the CBF AML group.[33] This established the standard that consolidation therapy for CBF AML should include HDAC.

How Much of Ara-C as Postremission Therapy is Optimal?

A retrospective analysis included 50 patients with t(8;21) who achieved remission in 1 of the 4 successive CALGB trials. As consolidation, either ≥3 cycles of HDAC or 1 cycle of HDAC was administered, followed by additional non–ara-C based postremission therapy. Patients who received consolidation therapy consisting of ≥ 3 cycles of HDAC (n = 21) had lower disease relapse rate and higher OS compared with patients treated with 1 course of HDAC (n = 29).[34] A similar report from the CALGB group (n = 48) of patients with inv(16)/t(16;16) AML younger than 60 years showed significantly lower 5-year relapse with 3 or 4 cycles of HDAC (n = 28) compared with 1 course of HDAC (n = 20) in consolidation.[35] A more recent report from CALGB confirmed that among CBF-AML patients (younger than 60 years), the ones assigned to multicourse HDAC (n = 149) in remission were less likely to relapse ($P < .001$) compared with single-course HDAC (n = 48). This report combined patients receiving 3 to 4 courses of HDAC (3 g/m^2 every 12 hours on days 1, 3, and 5) and patients receiving 4 courses of intermediate-dose ara-C (IDAC) (400 mg/m^2 per day for 5 days) as the one with multicourse HDAC. As an aside, although the CR did not differ, after multivariate analysis, patients with t(8;21) had shorter OS ($P = .045$) and shorter survival after relapse ($P = .009$) compared with inv(16).[10]

An Australasian leukemia and lymphoma group study attempted to answer the question whether incorporating HDAC in both induction and consolidation is beneficial in AML (not limited to CBF AML). All patients (n = 292) received identical induction regimen (ICE): idarubicin (12 mg/m^2 on days 1–3, later reduced to 9 mg), high-dose ara-C (3 g/m^2 twice daily on days 1, 3, 5, and 7), and etoposide (75 mg/m^2 on days 1–7). Patients were then randomized to receive 1 of the following consolidation regimens: a second identical cycle of ICE therapy or 2 cycles of attenuated IcE therapy, which included the same doses of idarubicin and etoposide and lower dose ara-C (100 mg/m^2 daily on days 1–5). As was true for all AML patients in the study, there was no statistical difference in 3-year RFS (76% vs. 69%) or 3-year OS (88% vs. 79%) among CBF AML patients treated with ICE (n = 17) versus IcE (n = 16) consolidation therapies. Thus, patients with CBF AML did not benefit from HDAC in postremission therapy when HDAC-based therapy was used in induction but the overall number of patients was small.[36]

Another way of answering the question of postremission ara-C could be to consider total cumulative dose. The Dutch-Belgian Hemato-Oncology Cooperative Group and the Swiss

Group for Clinical Cancer Research (HOVON-SAKK) cooperative trial showed no difference in survival outcomes between cumulative doses of ara-C; 13.4 vs. 26 g/m^2 in AML patients. The 5-year EFS (P =.19) and OS (P = .94) among 88 favorable-risk AML patients were similar in the 2 groups.[37] Pooled data from multiple German trials also could not demonstrate outcome difference among cumulative doses of ara-C that ranged from 20.8 to 56.8 g/m^2.[9] In the CALGB report referenced in the previous paragraph, the outcomes of patients receiving 4 cycles of IDAC consolidation (cumulative infusional ara-C dose of 8 g/m^2) and 3 to 4 cycles of HDAC (cumulative bolus ara-C dose of 54–72 g/m^2) were similar.[10] A French AML Intergroup study also did not show any difference in outcome between IDAC and HDAC groups.[38] Thus, it appears that even though postremission multicycle HDAC is considered standard for CBF AML, the optimal dose of ara-C remains to be determined.

Stem Cell Transplant

SCT vs. Chemotherapy in First Remission

Numerous studies have failed to show any outcome advantage of allo-SCT over chemotherapy among CBF AML patients in first CR.[9,11,12,15,16,38–40] Furthermore, a systematic review and meta-analysis of 10 prospective clinical trials that included 6007 patients (547 good risk patients) concluded that there is a lack of RFS (combined HR of 1.06; 95% CI, 0.80–1.42) or OS (combined HR of 1.07; 95% CI, 0.83–1.38) benefit associated with allo-SCT among cytogenetically good-risk AML.[41] Although allo-SCT can result in lower leukemia relapse, the increase in cumulative treatment related mortality offsets any survival advantage.[16] A Southwest Oncology Group/ECOG study, however, showed that patients with favorable cytogenetics AML had better survival after receiving postremission auto or allo-SCT compared with intensive chemotherapy (RR, 2.04). However, in this study, favorable cytogenetics AML patients included both CBF AML patients and patients with t(15;17).[42] Thus, the current standard is not to send patients with CBF AML to allo-SCT in first remission.

Autologous Versus Allogeneic SCT

There is no randomized comparison between auto-SCT versus allo-SCT in CBF AML. However, available studies show similar outcomes with auto-SCT and allo-SCT among CBF AML patients in first CR.[9,12,39]

Core Binding Factor AML in Elderly Patients

Patients older than 60 years comprise between 5% and 15% of total adult CBF AML patients[7,10,34] and have worse OS.[7,10] A French AML Intergroup study evaluated the outcome of CBF AML patients aged 60 years or older (n = 147). Ara-C and anthracycline-based induction chemotherapy resulted in 80% CR with first course, 88% CR with second course, 10% induction death rate, and 2% failed induction even after second course. Postremission therapy included either maintenance chemotherapy (low-dose ara-C, methotrexate, and mercaptopurine; n = 72), or intensive therapy (IDAC/HDAC-based regimen for at least 2 days; n = 48), or high-dose melphalan followed by auto-SCT (n = 8). Five-year disease-free survival was significantly longer with use of intensive consolidation compared with maintenance chemotherapy (P = .05) and the most benefit was seen in patients with t(8;21) (P = .007) but not in patients with inv(16)/t(16;16) (P = .78).[13]

From the Dutch Belgian Austrian group study described above, it appears that in older fit patients with CBF AML older than 60 years of age, escalated-dose daunorubicin in induction and limited HDAC in consolidation could be an alternative to multiple cycles of

HDAC to reduce duration of cytopenia.[26] Ideally these patients should be enrolled in clinical trials.

Monitoring for Minimal Residual Disease

Multiparameter flow cytometry,[43,44] Wilms' tumor (WT1) gene transcript level[45–49] and quantitative real-time reverse transcriptase polymerase chain reaction (RT-PCR)[50,51] of disease-specific fusion transcript have been shown to be useful to monitor minimal residual disease (MRD). RT-PCR to detect *AML1-ETO* and *CBF-MYH11* fusion transcript levels can be used to assess the response to therapy, monitor MRD, and detect impending relapse.[50,51] Analysis of CBF AML patients enrolled in MRC AML15 trial has shown that reduction in transcript levels after course 1 and 3 were significant variables for prediction of relapse.[52] However, standardization across laboratories in quantitative measurement of fusion transcripts needs to be established to develop broadly applicable cutoffs.

Current Standard Therapy

The National Comprehensive Cancer Network guidelines (version 2.2011) suggests that current standard induction therapy for AML patients (including CBF AML) younger than 60 years is infusional ara-C (standard dose) for 7 days and anthracycline (idarubicin or escalated daunorubicin) for 3 days (3 + 7 regimen) (category 1 recommendation). HDAC and anthracycline is an alternative regimen (category 2B recommendation). Postremission consolidation therapy for CBF AML includes 3 to 4 cycles of HDAC (category 1) followed by maintenance therapy (category 2B) or auto-SCT after 1 to 2 cycles of HDAC (category 2B).[53] Similar recommendations are put forward by European Leukemia Network.[54] However these recommendations are based on studies not specifically designed for CBF AML.

Considering that reports from larger groups using therapies close to these recommendations show OS in the range of 50%, it is imperative that patients should be encouraged to participate in clinical trials designed at improving outcomes. Improvement in EFS using FLAG-based regimens have made clinical trials with such regimens first-line treatment options for patients with newly diagnosed CBF AML at our institute. Benefits of incorporation of GO in induction and consolidation as demonstrated in multiple reports warrant trials specifically focused in CBF AML, provided this agent can be made available for clinical trials.

Patients with CBF AML with *c-KIT* mutations have increased relapse rate and poorer OS,[17–20] and trials targeting this population are only feasible with cooperation of larger groups. We also need to answer the question if more intensive induction therapy can overcome the adverse effect of *c-KIT* mutations as suggested by the pediatric experience. Alternatively these patients can be considered within the framework of a clinical trial for SCT as consolidation strategy provided they are low transplant risk. Older patients with poor PS or significant comorbidities should be offered clinical trial investigating novel agents alone or with low intensity regimens.

Future Directions

Treatment strategies and outcome analysis should ideally be separate for t(8;21) and inv(16) groups because outcomes differ. Because patients with t(8;21) have lesser success with salvage therapy,[10,13,14] one might argue that patients with t(8;21) will benefit from intensification of first-line therapy. Addition of fludarabine to ara-C with or without an anthracycline might provide the necessary intensification. Risk-adapted approaches that

incorporate clinical data, mutation analysis, and standardized monitoring of MRD levels in a comprehensive manner to make treatment decisions need to be developed.

A retrospective study (http://ClinicalTrials.gov number, NCT01 066286) is being conducted to detect microcytogenetic lesions and *KIT*, *FLT3/ITD*, and *NPM1* gene mutation, correlate with clinical outcomes and construct a prognostic predictive model; this study is hoped to provide a better prognostic tool to design risk-adapted trials. Targeting *KIT* mutations in CBF AML, Phase Ib/II studies (NCT00850382 and NCT01238211) are evaluating the outcome from dasatinib administered after standard induction and consolidation therapy and followed by maintenance therapy for 1 year.

The favorable data from MRC AML15 study and our phase II study (NCT00801489) of FLAG-GO in CBF AML supports the use of GO as a part of induction and consolidation therapy. Two phase II studies are ongoing to explore the role of auto-SCT in CBF AML patients in first CR (NCT01050036 and NCT01146977). Furthermore, a phase III study (NCT00428558) is comparing systematic versus response-adapted timed-sequential induction therapy with ara-C and daunorubicin in CBF AML patients.

Conclusion

Long-term results in patients with CBF AML leaves substantial room for improvement. Effort toward enrolling patients in clinical trials is thus essential. Improvement in first-line induction-consolidation therapy with a risk-adapted approach including mutation and MRD data are likely to improve outcome.

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Table 1

Doses of Ara-C Used in Different Studies and the Study Outcome

Study	Type of CBF AML (n = Number of Patients)	Dose of Consolidation Ara-C	Median Follow-Up	Median CR Duration (Months)	Cumulative Incidence of Relapse	Relapse Free Survival	Overall Survival
Bloomfield 1998[33]	t(8;21), inv(16) t(16;16) and del(16) (n = 57)	4 Courses of 1 of the 3 regimens: 100 mg/m^2 per day for 5 days vs. 400 mg/m^2 per day for 5 days vs. 3 g/m^2 over 12 hours on days 1, 3, and 5	> 7 Years	14.3 vs. NR vs. NR[a]		5-Year CR estimate of 78% vs. 57% vs. 16%[a]	
Byrd 1999[34]	t(8;21) (n = 50)	3 g/m^2 over 12 hours on days 1, 3, and 5; single vs. 3–4 courses	4.7 Vs. 5.6 years for single vs. 3–4 courses	10.5 Vs. > 35[a]		38% Vs. 71% at 5 years[a]	44% Vs. 76% at 5 years[a]
Byrd 2004[35]	Inv(16) and t(16;16) (n = 48)	3 g/m^2 over 12 hours on days 1, 3, and 5; single vs. 3–4 courses	> 7 Years		70% Vs. 43% at 5 years[a]	30% Vs. 57% at 5 years[a]	70% Vs. 75% at 5 years[b]
Bradstock 2005[36]	t(8;21) and inv(16) (n = 33)	High-dose ara-C based induction therapy followed by ara-C (100 mg/m^2 per day on days 1–5) vs. ara-C (3 g/m^2 over 12 hours on days 1, 3, 5, and 7)[c]	3.8 Years from consolidation randomization			69% Vs. 76% at 3 years	79% Vs. 88% at 3 years
Marcucci 2005[10]	t(8;21) (n = 96)	Single[d] course vs. multicourse[e] of high-dose ara-C	5.7 Years		64% Vs. 38% at 5 years[a]		43% Vs. 56% at 5 years
	Inv(16) (n = 101)		5.7 Years		70% Vs. 43% at 5 years[a]		70% Vs. 69% at 5 years
Prebet 2009[13]	t(8;21) (n = 56)	Low-dose ara-C vs. ara-C ≥ 500 mg/m^2 per day for ≥ 2 days[f]	4 Years			Median 10 months vs. NR[a]	
	Inv(16) (n = 73)		4 Years			23 Months in both arms	

Abbreviations: AML = acute myelogenous leukemia; Ara-C = cytarabine; CBF = core binding factor; CR = complete remission; ICE = idarubicin (12 mg/m^2 on days 1–3, later reduced to 9 mg), high-dose ara-C (3 g/m^2 twice daily on days 1, 3, 5, and 7), and etoposide (75 mg/m^2 on days 1–7); IcE = attenuated ICE; OS = overall survival; NR = not reached; SCT = stem cell transplantation.

[a] Signifies statistically significant difference.

[b] The similar OS is the result of the higher salvage rate with SCT in patients receiving single course of high-dose ara-C therapy versus patients receiving multiple courses.

[c] Ara-C was delivered as a part of ICE or IcE regimen (see text for details).

[d] Single course of ara-C (3 g/m^2 over 12 hours on days 1, 3, and 5) was followed by 1 course each of etoposide/cyclophosphamide and diaziquinone/mitoxantrone.

[e] Multicourse high-dose ara-C group included 3 to 4 courses of ara-C 3 g/m^2 over 12 hours on days 1, 3, and 5; or 4 courses of ara-C 400 mg/m^2 per day for 5 days: these 2 regimens did not differ in OS or cumulative incidence of relapse.

[f] Ara-C was delivered as a part of combination chemotherapy (see text for details).