Therapy-related core binding factor acute myeloid leukemia

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Practice points

Background

- Core binding factor acute myeloid leukemia (CBF-AML) is considered a favorable risk AML and is characterized by t(8;21) (q22;q22) or inv(16) (p13.1;q22)/t(16;16).
- Therapy-related (t-)CBF-AML is rare favorable subtype of t-AML usually seen in patients with prior exposure to DNA damaging cytotoxic chemotherapy or radiation.
- The genomic and clinicopathological features of *de novo* CBF-AML and t-CBF-AML are different.
- The t-CBF-AML is usually seen in older patients and have a lower leukocyte counts than those with *de novo* CBF-AML.
- Secondary cytogenetic abnormalities are less frequently seen in t-CBF-AML when compared with *de novo* CBF-AML and is an adverse prognostic factor.
- Pathogenic mutations are less commonly seen in t-CBF-AML but it has no impact on survival.

Treatment & prognosis

- High-dose cytarabine- and gemtuzumab ozogamicin-based induction and consolidation therapies are the important pillars of CBF-AML therapy and this can be extrapolated to t-CBF-AML as well.
- Quantitative PCR allows for close monitoring for measurable residual disease clearance and provides an opportunity for risk adapted therapy.
- The outcomes of patients with t-CBF-AML tends to be worse when compared with *de novo* CBF-AML.

Therapy-relatedacute myeloid leukemia (t-AML) usually stems from exposure of the bone marrow to cytotoxic chemotherapy and/or radiation therapy. t-AML is usually associated with poor overall survival, but occasionally t-AML can involve favorable-risk cytogenetics, including core binding factor AML (CBF-AML), which shows a recurrent chromosomal rearrangement with t(8;21) (q22;22) and 'inv(16) (p13.1;q22)/t(16;16)(p13.1;q22)', leading to '*RUNX1::RUNX1T1 and CBFB::MYH11*' fusion genes, respectively. Therapy-related CBF-AML (t-CBF-AML) accounts for 5–15% of CBF-AML cases and tends to have better outcomes than t-AML with unfavorable cytogenetics. Although CBF-AML is sensitive to high-dose cytarabine, t-CBF-AML has worse overall survival than *de novo* CBF- AML. The objective of this review is to discuss the available data on the pathogenesis, mutations, and therapeutic options in patients with t-CBF-AML.

Plan language summary: Acute myeloid leukemia (AML) is a type of cancer of the white blood cells. AML can rarely arise from prior treatment with radiation and/or chemotherapy and are referred to as therapy-related AML (t-AML). Usually t-AML is associated with poor outcomes; however, rarely you may see favorable outcomes with therapy related core binding factor AML. In this paper, we discuss about t-CBF-AML, which is a favorable subtype of t-AML.

Core binding factor (CBF) is a heterodimeric DNA binding transcription regulator that regulates transcription of hematopoietic genes associated with myeloid self-renewal, differentiation, proliferation, and apoptosis. As a

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heterodimer, it contains three alpha subunits encoded by *RUNX1*, *RUNX2*, and *RUNX3* and one beta subunit encoded by *CBFB*. Nearly 15% of cases of acute myeloid leukemia (AML) show a recurrent chromosomal re-arrangement with t(8;21) (q22;22) and inv(16)(p13.1q22)/t(16;16)(p13.1;q22), leading to *RUNX1::RUNX1T1* and *CBFB::MYH11* fusion genes, respectively. Although, most of the CBF-AML cases arise *de novo*, it can rarely (9–25%) be seen as a part of therapy-related AML (t-AML) [1–4]. CBF-AML is considered to have a favorable prognosis, as it is extremely sensitive to high-dose cytarabine (HiDAC)-based chemotherapy, resulting in a high complete remission (CR) rate [5,6].

t-AML, as recognized by the WHO, arises as a complication from bone marrow exposure to radiation and/or cytotoxic chemotherapy, especially chemotherapy involving alkylating agents and topoisomerase II inhibitors. t-AML is a very challenging subgroup to manage with consistently poor outcomes [6]. In t-AML with unfavorable cytogenetics, the estimated median overall survival (OS) is 14.6 months [7–10]. In general, t-AML carries a worse survival than *de novo* AML, and the median OS is strongly determined by cytogenetics [8].

Individuals who receive radiotherapy or alkylating agents (e.g., melphalan or cyclophosphamide) usually develop t-AML around 5–10 years after exposure and are genetically characterized by complex cytogenetics with a partial or complete loss of chromosomes 5 and 7 [2,6,11]. Patients who receive topoisomerase II inhibitors (e.g., anthracyclines or etoposide) have a shorter latency period of 1–3 years, sometimes as short as months, until the development of t-AML [12]. These cases are most often associated with balanced translocations involving "*KMT2A (MLL)* gene" at chromosome 11q23, the "CBF genes *(CBFB and RUNX1)*", and t(15;17). Given that the latter of these is associated with acute promyelocytic leukemia, these key driver genes could be the cause of early leukemogenesis [13].

An abnormal karyotype is seen in nearly 70–90% of t-AML cases, while favorable cytogenetics, including t(8;21), inv(16), and t(15;17), are observed in 7–22% of cases. Not all t-AML results in poor OS as patients with favorable cytogenetics have a median OS of more than 2 years [8]. The current treatment recommendation for patients with unfavorable risk cytogenetics is allogeneic stem cell transplant (allo-sct) during the first CR (CR1). Although this may be the best approach at present for patients with unfavorable cytogenetics, it is questionable whether this is the optimal strategy for t-CBF-AML as allo-sct during CR1 has not improved survival in patients with CBF-AML [14,15].

Pathogenesis & mutational landscape of AML with t(8;21) & AML with inv(16)/t(16;16)

A subset of AML with t(8;21) is found in 5–12% of *de novo* AML cases [16]. WHO classification of AML with inv(16)/t(16;16)/*CBFB::MYH11* is recognized as a separate entity, representing 5–7% of *de novo* AML cases. Multiple studies have shown that 3–15% of inv(16) and 5–25% of t(8;21) AML cases are t-CBF-AML [2,17,18].

CBF-AML involves multiple oncogenic steps, and disruption of the CBF α/β gene subunit interferes with normal hematopoiesis and differentiation; more understanding about the pathogenesis of CBF-AML is needed, although it is believed to require the cooperation of fusion genes and additional mutant genes. Initially there is impaired myeloid differentiation due to CBF aberration as a result of class I mutations, subsequently resulting in unopposed proliferation and survival led by class II mutations, leading to AML [19,20]. Kelly and Gilliland proposed the two-hit model in which the *RUNX1::RUNXITI* fusion gene generates the t(8;21) translocation and *CBFB–MYH11* fusion gene, resulting in inv(16) rearrangements that constitute the class II mutations. However, this is not sufficient to induce AML in animal models. Mutation in class I events, such as *RAS, FLT3*, and *KIT*, are necessary to confer proliferation and survival [21–23]. There is a shift in the prognosis of CBF-AML when receptor tyrosine-kinase mutations such as *KIT, FLT3*, and *N/KRAS* are involved inducing antiapoptotic and pro-proliferative signals [4].

Most patients diagnosed with t(8;21) are classified under French–American–British (FAB) type M2, and approximately 10% as FAB M1. AML with inv(16) has distinctive morphological features, including eosinophilia and monocytic predominance; hence, it is usually subclassified as FAB M4Eos. CBF leukemias share multiple common features, including younger age at presentation and frequently present with extramedullary disease [4]. inv(16) disease can likely affect lung and skin, and patients with t(8;21) are prone to gingival hyperplasia, lymphadenopathy, and hepatosplenomegaly [3].

T-CBF-AML accounts for 5–15% of CBF-AML cases, affecting an older population and the hallmarks include fewer peripheral blood (PB) monocytes and white blood cells, higher hemoglobin and less incidence of extramedullary disease in comparison to *de novo* CBF-AML, especially the t(8;21) subset [3,6,24]. The peripheral blood eosinophil count tends to be similar when comparing t-CBF-AML and *de novo* CBF AML [24].

Occasionally, CBF can present with <20% blasts in the PB and bone marrow, suggesting a myelodysplastic or atypical chronic myeloid leukemia diagnosis until cytogenetic results are obtained. As per the 5th edition of WHO, the blast cutoff of 20% has been eliminated for AML types with recurrent genetic abnormalities; however, AML with *CEBPA* mutation and AML with *BCR::ABL1* fusion remains an exception [24,25]. Sometimes, conventional cytogenetics may fail to diagnose CBF-AML, and the cytogenetic anomaly may remain cryptic, thus, FISH for CBF is a valuable diagnostic tool and should be performed on all newly diagnosed AML patients [24].

Additional mutations can be identified in *CBFB::MYH11* and RUNX1::RUNX1T1 *rearranged patients*, but their impact, including on prognosis, is not fully understood. The mutational profile with t(8;21) AML is often associated with chromatin modulator/cohesion mutations/epigenetic mutations. inv(16) AML is commonly associated with MAPK pathway mutations and, commonly, kinase mutations [4,19,26]. *DNMT3A* gene has been implicated in the regulation of methylation and is almost exclusively seen in t(8;21) and considered to have a negative impact on prognosis [27]. Similarly, mutations in other genes involved in methylation such as *TET2* is associated with inferior survival [27]. *KIT* mutation in CBF-AML, especially in the t(8;21) subset, has contradictory [2–4,28] reports. In t(8;21) AML *FLT3-ITD*, *KIT* exon 17, and trisomy 8 were confirmed to be associated with poor outcomes, whereas *WT1* and *NRAS* mutations were associated with favorable prognosis [27]. *FLT3-ITD* mutation is more common with t(8;21), whereas *FLT3 TKD* was more prevalent with inv(16) AML (27). In a recent report, mutations are less common in t-CBF-AML (57%) than in *de novo* CBF-AML (80%), with no difference in the frequency of the commonly occurring mutations between each cohort. *TP53* mutations, which are common in t-AML, are rare in t-CBF-AML. Mutations are more frequent in inv(16) than t(8;21) [24,29]. It is common to encounter multiple mutations along the same signaling pathway in CBF-AML, and it is well understood CBF-AMLs are frequently associated with tyrosine kinase pathway mutations, including *FLT3*, *KIT*, and *NRAS*/*KRAS* mutations [4,30]. On flow cytometric analysis, aberrant B-cell markers, predominantly CD19 and, rarely, CD20, CD79a, and CD22, were seen in 71% of t(8;21) and 5% in inv(16) AML cases; however, they were encountered in 78% of t-CBF-AML cases [24]. inv(16) AML has been reported to express T-cell markers, including CD2 [2,3]. In a recent study, no difference in immunophenotype antigen expression was noted by flow cytometry between t-AML and t-CBF-AML [24].

Secondary cytogenetic abnormalities are more often demonstrated in *de novo* CBF-AML than in t-CBF-AML, while the occurrence of a complex karyotype (≥3 cytogenetic abnormalities) is seen equally in both entities. One or more secondary abnormality is more common in t(8;21): this is observed in 65% of t(8;21) patients, whereas it occurs in only 40–45% of inv(16) patients [31,32]. The secondary cytogenetic abnormalities profile differs between t(8;21) and inv(16) AML. Loss of X or Y and del(9q) is more frequent in t(8;21), while trisomy 22, trisomy 21, trisomy 8, and del(7q)/monosomy 7 are more common in inv(16) [1,26,27,33,34] The prognostic value of secondary cytogenetic abnormalities in CBF-AML has been evaluated previously and studies have shown conflicting results. Rogers *et al.* reported that CBF-AML patients without secondary cytogenetic abnormalities have an inferior OS when compared with those with abnormalities (median 87 vs 190 months, p = 0.021) [24]. Some studies have shown that trisomy 22 is associated with better outcome [35] whereas other studies have refuted this claim [31]. Similarly, the prognostic value of trisomy 8 is controversial with some studies claiming a favorable outcome [36] whereas others suggesting an adverse impact on survival [27]. Chen *et al.* showed that loss of X chromosome predicts a favorable prognosis in female patients with t(8;21) [37]; however, Schlenk *et al.* and Han *et al.* found no survival advantage [14,31]. Zhou *et al.* showed that loss of Y chromosome was associated with a higher relapse rate and inferior OS in males with t(8;21) [38]; however, these observations were not replicated in other studies [31]. The prognostic value of del(9q) is also controversial with discordant results in two large studies [14,31]. In addition, the prognostic value of secondary cytogenetic abnormalities in t-CBF-AML is unknown.

In general, complex karyotype (≥3 cytogenetic abnormalities) is associated with poor survival in most AML subtypes. However, multiple studies have shown that complex karyotype ((≥3 cytogenetic abnormalities) has no impact on outcomes in CBF-AML [27,39]. In contrast, Mosna *et al.* showed that complex karyotype as defined by 4 or more cytogenetic anomalies is an adverse prognostic marker in CBF-AML [40].

Treatment options

As alluded to earlier, treatment of t-AML largely depends on cytogenetics and patient fitness level. However, other comorbidities, including age and molecular features, do influence response to treatment. Per WHO and European Leukemia Net (ELN) classification, unfavorable- and intermediate-risk AML usually benefits from CPX-351 (a

fixed liposomal encapsulation of daunorubin and cytarabine in a 1:5 molar ratio), which demonstrated better OS of 16 months versus 5 months seen with the 7 + 3 regimen [41].

The treatment of t-CBF-AML is similar to *de novo* CBF-AML. Although CBF-AML have high remission rates of around 90%, there is a relatively high relapse rate as well. The relapse rates among *de novo* CBF AML and t-CBF-AML are similar. The post-remission 5-year OS of *de novo* CBF ranges between 50%–65% [35]. Event-free survival (EFS) at 5 years is considered to be 40%–50% [1,14,42], but more recent reports have indicated improved results [43] (39). Reported 5- and 10-year OS of t(8;21) is 45% and 43%, and that for inv(16) is 48–50%. Survival is shorter in patients >60 years old [1,35].

CBF-AML is considered to be sensitive to cytarabine; hence, a cytarabine/anthracycline (7 + 3) regimen followed by HiDAC consolidation results in high CR rates of around of >85% [35]. The addition of fludarabine prior to the administration of cytarabine can enhance the intracellular accumulation of arabinosylcytosine triphosphate [44]. The UK medical research council (MRC) AML 15 trial showed an improved 8-year survival of 66% after two cycles of fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) induction followed two courses of consolidation of HiDAC (1.5 g/m^2 or 3 g/m^2 twice on days 1,3, and 5) [45].

Gemtuzumab ozogamicin (GO) is an anti-CD33 monoclonal antibody linked to calicheamicin. The MRC AML 15 trial reported a higher response rate and OS with 2 courses of FLAG-Ida with GO in course one, followed by two courses of consolidation. This regimen showed an 8-year OS rate after CR of 72% (favorable risk, 95%: intermediate risk, 63%) [45,46].

A patient-based meta-analysis of initial trials with addition of GO to chemotherapy showed a substantial survival benefit in CBF leukemia with favorable-risk cytogenetics (76% vs 54%) at 5 years and a modest but significant improvement in intermediate-risk patients (40% vs 35%), but unfortunately no benefit in patients with poor-risk cytogenetics [47].

It is unclear at present what the best dosing schema is for GO, as the approved dosing schedule has not been yet tested in the context of CBF [46,48,49]. Randomized data from the Acute Leukemia French Association (ALFA-0701) trial, which led to the approval of GO in September 2017, had only 9 CBF leukemia cases, of whom only 3 received GO [48]. The trial demonstrated improvements in OS and EFS in frontline therapy of older patients with the addition of GO to chemotherapy in the favorable- and intermediate-risk AML patients [48].

Borthakur *et al.* reported improved EFS in patients with CBF-AML with a frontline regimen of FLAG in induction/consolidation compared with idarubicin and cytarabine (IA). The available data motivated a study of a FLAG-GO (low-dose GO of 3 mg/m^2 at induction on days 1 and 2 of the planned post-remission cycles) regimen with the omission of idarubicin. The reported 5-year OS was 71% and 5-year relapse free survival (RFS) of 87% with FLAG-GO versus 68% for FLAG-Ida, but OS was not significantly different between the regimens. The presence of *KIT* or kinase mutations did not impact RFS [49].

Multiple studies have shown the importance of deeper remission, which correlates to an early reduction (3 log reduction at the end of induction and 4 log reduction at mid consolidation) in CBF fusion transcripts and thus to improved RFS [34,50]. Patients treated with FLAG-GO (76%) achieved an optimal reduction in fusion transcripts by mid-consolidation compared with 42% for those treated with FLAG-Ida (p < 0.001) [43,51].

Relapses and long-term survival are worse in patients with t(8;21) translocation, with an estimated survival of 0.7 years in comparison to 1.2 years in patients with inv(16) post-relapse from CR, dictating a higher response to salvage therapy in inv(16) AML [1,35], despite the fact patients with t(8;21) AML translation tend to be younger than those with inv(16) [1]. In a recent study, the median OS of patients in first relapse with t(8;21) and inv(16) was 9 months and 15.6 months, respectively [52]. A second CR (CR2) was achieved in 60–85% of patients with salvage therapy, and the median OS at 5 years was 50%, which is similar to the OS in CR1 [53] and is better than outcomes in CR2 in patients with intermediate- and poor-risk AML. The FLAG-Ida regimen showed a favorable effect on relapsed AML over all demographic subgroups, including older patients, those with poor-risk disease, and subgroups with *FLT3–ITD* mutation [45].

The OS in t-AML is dismal, with a 5-year OS of 10%, often associated with multiple cytogenetic abnormalities [8]. Given these poor OS data, allo-sct is recommended in CR1. Reports of t-CBF-AML have shown better outcomes than intermediate- and poor-risk t-AML. In an analysis of 13 patients with t(8;21) t-AML, the OS was 19 months at a median of 13 months of follow-up. The CR rate was high at 91%; however, 70% of patients relapsed [2].

The outcomes of patients with t-CBF-AML are inferior to those with *de novo* CBF-AML. In a study of 188 patients with CBF-AML, 17 had t-CBF-AML, 13 had inv(16), and 4 cases had t(8;21); 15 (88%) of the 17 t-CBF-AML patients achieved CR and complete remission with incomplete platelet recovery (Cri). None of the

patients had myelodysplastic syndrome prior to their diagnosis of t-AML. Additional cytogenetic abnormalities were similar in t-CBF-AML and *de novo* CBF-AML. The OS for t-CBF-AML was 100 weeks, versus 621 weeks for *de novo* AML. The most common therapeutic regimen was induction with HiDAC to intermediate-dose cytarabine, followed by consolidation with cytarabine (median, 6 cycles; range 1–14) in patients who achieved CR [6].

Rogers *et al.* reported a multi-center retrospective study evaluating the genetic and clinicopathological features of CBF-AML. It was observed that there was no difference in OS between therapy-related t(8,21) and *de novo* t(8;21) patients; however, patients with *de novo* inv(16) CBF-AML patients had a superior OS when compared with those with therapy related-inv(16) [24].

In general, the outcomes of t-CBF-AML are much better than those of patients with poor- or intermediate-risk t-AML. The FLAG regimen, single-agent low-dose cytarabine, and hypomethylating agents alone or in combination with venetoclax are some of the therapeutic options for t-AML [54–60]. As the overall response rate of t-CBF-AML is similar to that of CBF-AML, therapeutic options for t-CBF-AML are similar to those of CBF-AML. T-CBF-AML has a high overall response rate and hence these patients are not considered candidates for allo-sct during CR1 [11].

Quantitative monitoring of measurable residual disease in CBF-AML

The presence of unique translocation makes CBF-AML amenable to molecular monitoring for measurable residual disease. Quantitative monitoring of the transcripts by real-time reverse transcriptase polymerase chain reaction (qRT-PCR) is one of the most effective prognostic factors in CBF-AML and provides risk stratification and predicts relapse, with the ability to detect early relapse with high sensitivity [34,50,61]. This is tool is highly useful for the early identification of patients at high risk of frank relapse, especially since CBF-AML patients are not usually transplanted during CR1. The limitation of qRT-PCR is a lack of standardization of MRD-based monitoring across all institutions. More studies are required for a better understanding of whether peripheral blood MRD monitoring is sufficient, or bone marrow is required to provide reliable information [34,50]. MRD monitoring by flow cytometry is useful in CBF-AML, although most published data prefer qPCR-based MRD monitoring. The AML-MRC 15 study reported that a >3 log reduction in *RUNX1::RUNX1T1* transcripts in the bone marrow at the end of induction was suggestive of improved RFS; 47% of the patients who achieved MRD had a cumulative incidence of relapse (CIR) of 4%, compared with 32% who did not achieve the MRD level. In inv(16) AML, a >10 *CBFB::MYH11* transcript number in PB, normalized to 10^5 copies of ABL post-induction, translated to a CIR of 21% in the 57% patients who achieved the MRD target compared with 50% among patients who did not [34]. Similar data was reported at MD Anderson Cancer Center: a ≥ 3 log reduction in transcripts in the bone marrow post-induction and ≥ 4 log reduction at the end of two to three cycles of consolidation was predictive of improved RFS [50].

The influence of a *KIT* mutation (exon17) is associated with a higher relapse rate in CBF-AML [28,62,63]. However, *KIT* mutation is not prognostic in pediatric CBF-AML [64]. The presence of multiple kinase mutations including *RAS, KIT*, and *FLT3* and treatment including 7 + 3 was associated with higher relapse rates [65]. A number of studies have concluded that *KIT* mutations are related to lower OS, CR, and EFS in t(8;21) translation disease but not with inv(16) disease [66–68]. However, Boddu *et al.* reported that a lack of or suboptimal MRD response demonstrated by qPCR was associated with relapse but not a *KIT* mutation [50]. Of note, *KIT* mutation is often not detectable at relapse if it is present at diagnosis, which brings into question its role as a driver mutation [15]. Given all the conflicting reports, guiding treatment in the presence of *KIT* mutation is controversial and needs further prospective studies.

Kinase mutations (JAK2) and epigenetic pathway mutations (ASXL2) at diagnosis have been shown to a higher risk of relapse [19,26]. At present, it is debatable whether any mutation or group of mutations are contributing to suboptimal MRD clearance. More studies are needed to further investigate the matter.

Maintenance therapy with hypomethylating agents

The optimal use of MRD assessment to influence MRD-driven treatment strategies and interventions to improve outcomes are not widely established. Gene hypermethylation is associated with an increased risk of relapse in AML [69,70]. The use of HMA such as decitabine (DAC) and azacitidine (AZA) in patients who have persistence of MRD as measured by qRT-PCR or flow cytometry-based MRD sensitive for the detection of 1 leukemia in 10^4 cells (not standardized across all institutes) post-induction/consolidation or reemergence of MRD (due to abbreviated therapy from underlying therapy-related side effects, comorbidities, and older age) may potentiate the need for

maintenance therapy. Studies have shown that DAC therapy can convert low qRT-PCR positivity to negative status, thus mitigating a possible hematological relapse or need for salvage therapy and/or allo-sct [69,71].

Maintenance with DAC involves monthly 20 mg/m^2 on days 1–5 every 4–5 weeks based on count recovery and toxicity. The regimen with DAC 20 mg/m^2 could be reduced to 3 days in patients with concerning toxicity and myelosuppression with a prolonged time to count recovery [69].

Studies have shown that the highest benefit of DAC maintenance was observed in patients with low pre-DAC PCR and who received all the planned cycles of induction/consolidation. Hence, patients with attenuated cycles of therapy or with a higher burden of PCR after therapy completion should be considered for allo-sct over DAC maintenance. The consensus on the cutoff PCR for consideration is not well defined [69,72]. However, post-induction/consolidation a qPCR of >0.01% despite receiving DAC maintenance demonstrated the most risk of relapse requiring salvage therapy. Therefore, this would be the subgroup with highest consideration for allo-sct after definitive treatment [69].

The prognostic implication of *KIT* mutations with HMA treatment is controversial; the addition of potent *KIT* inhibitor like dasatinib and avapritinib into frontline chemotherapy may improve outcomes. In a German-Austrian group phase1b/IIa study, the multikinase inhibitor dasatinib 100 mg po was administered with induction therapy of 7 + 3 followed by consolidation with HiDAC for total of 4 cycles. Maintenance therapy with single-agent dasatinib 100 mg po daily for 1 year was allowed in first-line treatment of CBF-AML. Results demonstrated a reduced relapse rate in *KIT*-mutated CBF-AML compared with wild-type *KIT* mutations [73]. In a similar study by CALGB 10801, similar results were seen. The 3-year OS was 73% in patients with *KIT*-mutated disease, compared with 76% in wild-type *KIT* disease, and the 3-year EFS was 67% versus 75% [74]. Currently, there are no randomized trials to support the addition of a *KIT* inhibitor to frontline therapy.

In t-CBF-AML in the presence of *KIT* mutation and with suboptimal qRT-PCR response or the persistence of qRT-PCR after 2 cycles of consolidation generally represents a subgroup with a high risk of relapse who would benefit from salvage therapy with an early donor search for allo-sct [62,75]. DAC maintenance can be considered in t-CBF-AML patients with low qRT-PCR positivity as described above but with early evaluation for allo-sct in the event that their low-level qRT-PCR positivity does not convert to MRD-negative status [34,76].

Role of allogeneic stem cell transplant

t-AML with favorable-risk cytogenetics is extremely underrepresented in patients who have undergone allo-sct; thus, there is insufficient data to evaluate the utility of allo-sct during CR1 [77–79]. In general, for patients with CBF-AML, allo-sct is not indicated during CR1 except in patients with suboptimal MRD clearance (MRD reoccurrence without hematological relapse) and those with persistent positive qRT-PCR with or without intervening salvage therapy, according to the 2022 ELN guidelines for treatment of AML [36,80,81]. In CBF-AML, the presence of a *KIT* mutation after definitive treatment and in relapsed CBF-AML are highly indicative for the need for allo-sct [28,62]. Begna *et al.* reported long-term outcomes of 70 CBF-AML patients treated with "7 + 3" regimen and the study included 13 (19%) with t-CBF-AML. 10 patients (n = 3, t-CBF-AML) underwent allo-sct in CR1 and none relapsed whereas only 1 of 14 patients transplanted in CR2 relapsed. However, the relapse rate was high (38%) in patients who achieved a CR/CRi and did not receive an allo-sct consolidation. There was no difference in outcome among patients transplanted in CR1 versus CR 2 [82]. Hence, allo-sct is an effective consolidation strategy that can perhaps overcome the high relapse risk of CBF-AML and it is reasonable to defer transplant until relapse (CR 2).

A recent single-center study of post-allo-sct in CBF-AML concluded no difference based on pre-transplant MRD status, with a 10-year disease-free survival in MRD-positive and -negative patients being 72% and 100%, respectively. Autologous-sct could be a therapeutic option in older patients who are unable to tolerate post-remission consolidation with HiDAC or intermediate intensity chemotherapy, with the added benefit of avoiding graft versus host disease [83].

In t-CBF-AML, the OS is poorer than that of *de novo* CBF-AML [6,84]. There is a severe underrepresentation of t-CBF-AML in reports of allo-sct and, hence, insufficient data on the utility of allo-sct during CR1. Therefore, at present, allo-sct is not routinely offered during CR1, and the current assessment criteria for allo-sct are similar to those for CBF-AML [11].

The importance of completing all scheduled cycles of definitive chemotherapy in the interest of long-term survival should be stressed to patients [43]. Those who are unable to complete definitive chemotherapy or who have persistent qRT-PCR positivity after 2 cycles of consolidation therapy and who have *KIT* mutations should be considered for allo-sct [62,75,76,85,86]. However, overall, outcomes data for allo-sct in t-CBF-AML remain insufficient.

Conclusion

T-AML is a heterogenous disease with a cytogenetic profile that is prognostically relevant. Although patients with unfavorable/intermediate-risk t-AML perform poorly, patients with favorable-risk t-AML usually have superior outcomes to those in unfavorable t-AML. t-CBF-AML has inferior outcomes to *de novo* CBF-AML. However, it is not understood whether patients truly have inferior leukemia-related outcomes, as a majority of these patients are at an older median age than those with *de novo* CBF-AML and thus may be unable to complete definitive therapy owing to the toxicity of the original malignancy. Currently, the treatment of t-CBF-AML is similar to that of *de novo* CBF-AML, and allo-sct is not considered during CR1. Molecular MRD assessment by qRT-PCR should guide the need for allo-sct. Patients with persistent MRD-positive transcripts or who are MRD positive by flow cytometry or who have persistent kinase mutations (*KIT* or *FLT3*) with a high allelic burden after 1–2 courses of consolidation therapy should be considered for an early donor search for allo-sct. Allo-sct may be considered during CR1 in certain cases, such as when the original malignancy is still present as in follicular lymphoma, and there is evidence of significant graft versus malignancy effect. However, allo-sct for t-CBF-AML is not an established treatment. The overall therapeutic options have to take into consideration current status and prognosis of the original malignancy.

Future perspective

Although t-CBF AML is considered a favorable subtype of t-AML, there are several controversial areas and unanswered questions. The induction regimen varies widely depending on the treating physician and often lacks standardization. There is encouraging data from non-randomized studies showing that an anthracycline free regimen like FLAG has better EFS than standard anthracycline containing regimens. The added advantage of an anthracycline free regimen is less myelosuppression and fewer deaths in remission. In addition, GO added to the induction regimen has shown promising results with lower relapse rates and better OS. Hence, incorporation of a GO based anthracycline free induction regimen should be explored further. Also, the optimal induction regimen in older t-CBF AML patients poses a unique challenge. Although HiDAC based regimens are effective in achieving remissions, the higher treatment related mortality in this population remains a major obstacle in improving outcomes. Less intense therapeutic options should be explored in unfit patients, and this is an area of unmet need.

In addition, the optimal cytarabine dose for post remission therapy is unknown and varies between 400 mg/m^2 and 3 g/m^2. Studies have shown that a condensed schedule (HiDAC on days 1–3) is associated with shorter hospital stay, faster hematological recovery and fewer infection when compared with the standard schedule (HiDAC on days 1, 3 and 5). More studies are needed to explore the HiDAC dosing schedule. Also, the role of maintenance therapy is controversial. Small retrospective studies have shown that maintenance therapy with HMA lowers the relapse risk in patients with suboptimal MRD clearance. However, larger prospective controlled studies are needed to investigate the role of maintenance therapy.

Current data has clearly established the prognostic role of MRD; however, it is unclear how the MRD data can influence treatment decisions. Also, more studies are needed to validate if there is a difference between bone marrow versus peripheral blood MRD monitoring and to assess the optimal method (flow cytometry vs q RT-PCR).

In this era of precision medicine, more research into targeted therapies is critical. Although controversial, *KIT* mutations are believed to be associated with higher relapse risk. Randomized studies are needed to clearly establish the role of TKIs in patients with *KIT* mutations. In addition, *FLT3–ITD* mutations are seen in 5–10% of CBF-AML and is associated with poor prognosis. It will be interesting to see if *FLT3* inhibitors can improve the outcomes in *FLT3* mutant CBF-AML. Also, the role of allo-sct and other cellular therapies needs to be explored further.

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