blood® How I Treat Series

MANAGEMENT OF HIGH-RISK PATIENTS FOLLOWING ALLOGENEIC TRANSPLANT

How I treat with maintenance therapy after allogeneic HCT

Zachariah DeFilipp and Yi-Bin Chen

Hematopoietic Cell Transplant and Cellular Therapy Program, Massachusetts General Hospital, Boston, MA

Disease relapse is the leading cause of failure for patients receiving allogeneic hematopoietic cell transplantation (allo-HCT). Maintenance therapy administered after allo-HCT is a promising strategy to reduce the incidence of relapse and enhance the curative potential of allo-HCT. Research investigations and clinical applications of this approach have greatly increased in recent years, with an expanding number of available therapeutic agents to introduce in the posttransplant setting. However, many questions and challenges remain regarding the feasibility and clinical impact of maintenance. In this article, we present four common case scenarios addressing select available therapeutic agents as a framework to review published data and ongoing studies and describe our current standard practice in the rapidly evolving field of maintenance therapy after allo-HCT.

Introduction

Numerous advances in allogeneic hematopoietic cell transplantation (allo-HCT), including higher resolution HLA typing, less toxic conditioning regimens, improved anti-infectious agents, and novel approaches to graft-versus-host disease (GVHD) prevention and treatment, have decreased nonrelapse mortality associated with allo-HCT.[1] As such, disease relapse remains the leading cause of failure after allo-HCT, with an overall incidence of around 30%.[2-4] Maintenance therapy, defined as therapy initiated while the patient remains in complete remission (CR), is a promising approach to reduce the risk of relapse after allo-HCT.[5] Investigation into this approach has greatly increased in recent years, with an expanding repertoire of therapeutic agents. However, many uncertainties still surround posttransplant maintenance therapy, including which patient subsets truly benefit, choice of agent, and duration of therapy.

Herein, we present our clinical approach to implementing select maintenance therapies after allo-HCT (Figure 1) while acknowledging that heterogeneity in access to mutational testing, measurable residual disease (MRD) evaluation, and specific agents makes presenting any standard approach difficult. Of note, this review will focus on specific commercially available pharmacologic agents and will not address immunotherapy or cellular therapies, such as checkpoint inhibitors, vaccine-based approaches, donor lymphocyte infusions, or other cellular infusions.

Key issues of maintenance therapy

Three general approaches to therapy after allo-HCT are (1) maintenance therapy, (2) preemptive therapy, and (3) therapy for active relapsed disease (Figure 2). A preemptive approach allows for a more precise strategy, only initiating therapy in patients with detectable MRD while sparing further therapy for those whose disease remains undetectable. However, this approach requires a sensitive assay to detect MRD, the ability to perform multiple serial MRD evaluations, and sufficient time from MRD detection to initiation of therapy before significant clinical relapse. In contrast, the maintenance approach involves indiscriminately treating all indicated patients after allo-HCT. Although this ensures that disease-directed therapy can be initiated while in remission, the approach overtreats a significant number of patients who otherwise may not have needed such therapy.

Major considerations that influence the decision to initiate maintenance therapy after allo-HCT are shown in Table 1. Populations with risk factors for higher relapse risk are seemingly more likely to benefit from maintenance therapy. Three common factors that may influence the risk for disease relapse include (1) biological disease risk, (2) MRD status at transplant or afterward, and (3) intensity of the conditioning regimen. High-risk cytogenetic and molecular abnormalities, the presence of MRD immediately before transplant, and the use of reduced-intensity conditioning all are associated with an increased risk for disease relapse after allo-HCT and have all been used to risk stratify populations.[6-9]

For many years, the ability to administer posttransplant maintenance was hindered by lack of suitable therapeutic agents. Now that numerous agents with less off-target toxicity have been developed, their integration into the posttransplant setting has begun. Early studies have focused on feasibility and safety while providing some preliminary assessment of efficacy. Very few prospective randomized clinical trials have been conducted, and no agents are currently approved in the United States for the specific indication of therapy after allo-HCT to prevent relapse. An important limitation of retrospective analyses attempting to

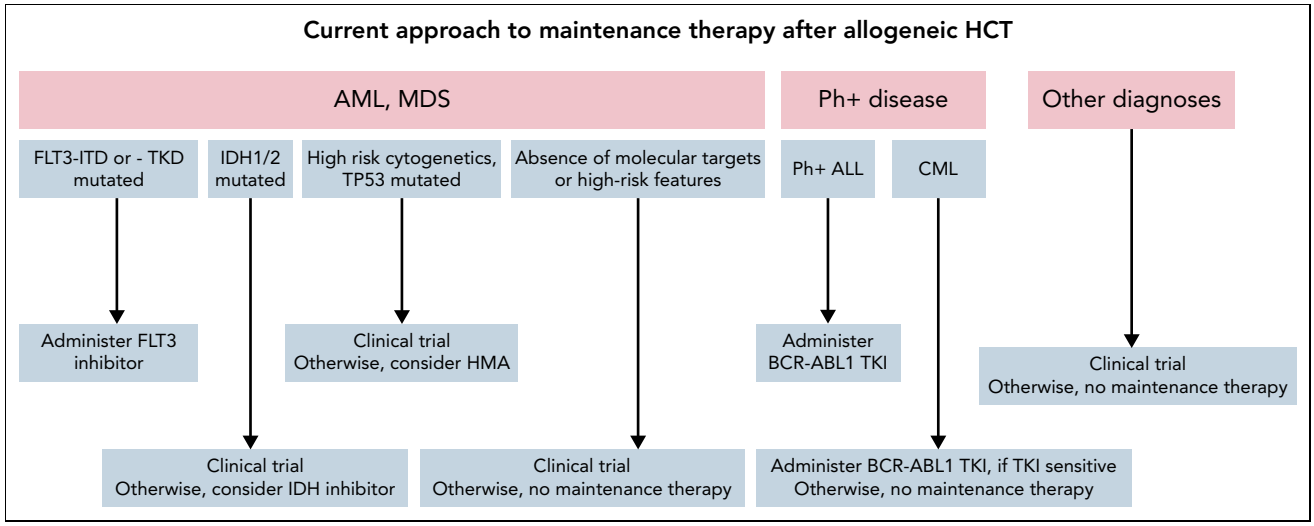

Figure 1. How we treat algorithm for posttransplant maintenance therapy. Our current approach to the application of maintenance therapy after allogeneic HCT. TKD, tyrosine kinase domain.

investigate whether maintenance therapy is beneficial is significant selection bias, because patients fit to receive maintenance after allo-HCT have avoided early mortality, toxicity, and disease relapse to be eligible to start maintenance therapy. The clinical evaluation of the maintenance approach is further complicated by the many patients who are unable to complete planned therapy because of toxicities, logistic reasons, or the emergence of HCT-associated complications such as infection or GVHD. In addition, as more agents are introduced into routine use in the post-HCT setting, specific toxicities and drug-drug interactions will need to be clearly described and defined to allow for safe administration. Full dose intensity of many agents will likely be difficult to achieve, and optimal guidelines for dose reduction or intermittent dosing will need to be developed. Thus, although maintenance approaches are quickly being adopted into clinical practice, well-designed randomized clinical trials are sorely needed to characterize the true benefit and practicalities of this approach.

Figure 2. Categorization of approaches to disease-directed therapy after allogeneic HCT. Disease status at the initiation of therapy after transplant provides definition to the treatment approach and may impact the likelihood of success in each setting.

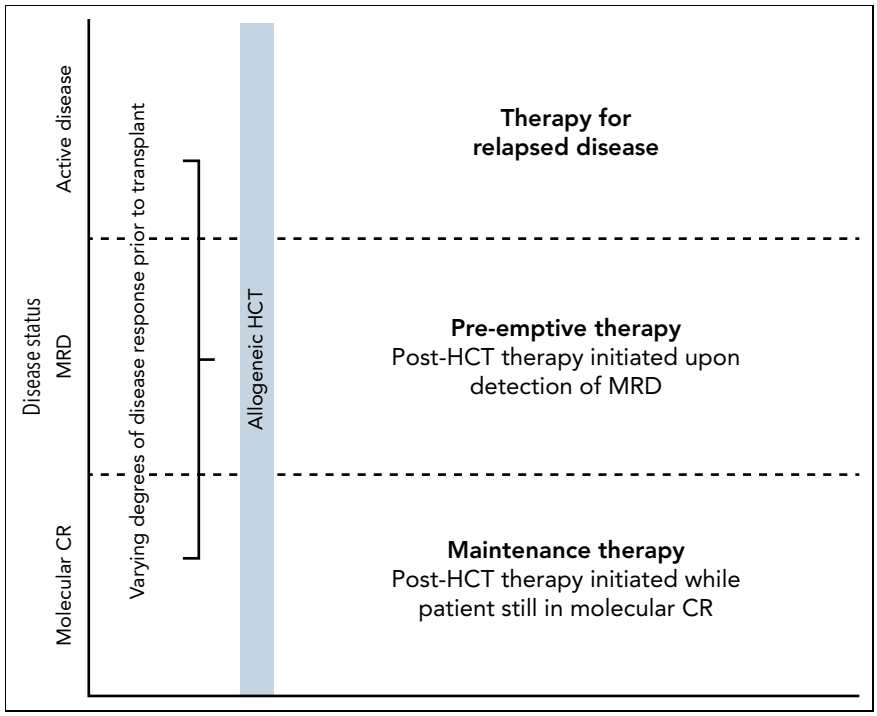

Table 1. Considerations that influence the decision to initiate maintenance therapy after allogeneic HCT

Factor	Considerations
Underlying disease	Higher rates of relapse for high-risk disease characteristics (elevated blast count, specific cytogenetic or molecular abnormalities) compared with the absence of high-risk disease factors
Disease status at transplant	Higher rates of relapse in acute leukemia when measurable disease detectable at transplant compared with undetectable disease
Intensity of the conditioning regimen	Higher rates of relapse with reduced intensity conditioning therapy compared with myeloablative conditioning
Post-HCT complications	Slow hematopoietic recovery or ongoing toxicities (GVHD, infection, organ dysfunction) limit ability to initiate maintenance therapies
Characteristics of therapeutic agent	Therapeutic agent must address underlying disease biology (targeted agents for identified mutations or hypomethylating agent-based approached for myeloid neoplasms) and have favorable toxicity profile in post-HCT setting

Case 1: FMS-like tyrosine kinase 3–mutated acute myeloid leukemia

A 64-year-old man presented with new-onset fatigue and dyspnea. He had a white blood cell (WBC) count of 56 × 10^9/L, hemoglobin level of 7.2 g/dL, and platelet count of 36 × 10^9/L. Bone marrow examination revealed acute myeloid leukemia (AML) with 70% blasts. He had no cytogenetic abnormalities, and genomic analysis revealed a point mutation in DNMT3A and an FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) mutation (allelic ratio, 0.42). NPM1 was wild type. He received induction chemotherapy with 7 + 3 (daunorubicin 60 mg/m^2 on days 1-3 and cytarabine 200 mg/m^2 on days 1-7) and midostaurin (50 mg twice daily on days 8-21), achieving CR1. He now plans to proceed with allo-HCT from a matched unrelated donor using reduced intensity conditioning. Next-generation sequencing–based FLT3 testing no longer detects FLT3-ITD on the remission bone marrow, but DNMT3A is still detectable.

FLT3-mutated disease

FLT3-ITD mutations are found in approximately 25% of newly diagnosed cases of AML, usually presenting in younger patients with a normal karyotype and a high leukemia burden. Historically, the outlook for patients with FLT3-ITD AML was poor because of a propensity for early disease relapse.[10] Advances such as incorporation of FLT3 inhibitors added to conventional induction chemotherapy and routine use of allo-HCT as consolidation have significantly improved outcomes. Yet even after allo-HCT, the risk of disease relapse was approximately 30% to 40%. With the availability of several FLT3 inhibitors either approved for AML or other indications and the exhibited FLT3 dependence of FLT3-mutated AML especially after post–allo-HCT relapse,[11] trials investigating maintenance therapy after HCT were conducted.

We first reported compelling results of a phase 1 trial of 22 patients with FLT3-ITD AML in CR receiving maintenance sorafenib after HCT showing a 1-year progression-free survival (PFS) of 85% and 1-year overall survival (OS) of 95%.[12] We then conducted a retrospective analysis comparing 26 patients with FLT3-ITD AML in CR1 who received maintenance sorafenib with 43 control patients with FLT3-ITD AML in CR1 who were alive and in remission at 60 days after allo-HCT and did not receive sorafenib maintenance therapy. Patients who received sorafenib had a significantly lower rate of disease relapse (8.2% vs 37.7%, $P = .0077$), which translated into significantly improved 2-year PFS (85% vs 52%, $P = .0047$) and OS (83% vs 58%, $P = .019$), respectively.[13] This effect was confirmed in 2 recently published prospective randomized clinical trials: the placebo controlled SORMAIN (SORafenib MAINtenance) trial and an open label phase 3 trial from China. The SORMAIN trial enrolled only 83 patients in 5 years and closed early because of poor accrual, yet was able to show a significant benefit in 24-month relapse-free survival with 24 months of maintenance sorafenib (85.0% vs 53.3%, $P = .002$).[14] In the Chinese phase 3 trial, 202 patients were randomized to receive sorafenib for 6 months vs no therapy. Results showed 2-year leukemia-free survival to be 78.9% vs 56.6% ($P < .0001$) in favor of maintenance sorafenib.[15] It should be noted that the vast majority of patients in these 2 trials did not receive FLT3 tyrosine kinase inhibitor (TKI) during induction therapy, and pre-HCT data on MRD status were not available. Midostaurin, which is approved in combination with initial chemotherapy, has been shown to be safe when used in the post–allo-HCT maintenance setting, yet the phase 2 randomized trial was not powered to show a benefit in relapse prevention.[16] Crenolanib, another oral FLT3 inhibitor, is also being tested in an ongoing phase 2 study (#NCT02400255; Table 2). Most recently, the Bone Marrow Transplant Clinical Trials Network conducted an international multicenter phase 3 double-blinded randomized trial that randomized 346 patients with FLT3-ITD–mutated AML in CR1 to 24 months of maintenance gilteritinib vs placebo after allo-HCT (NCT02997202). Accrual has been completed, and results are expected shortly. Encouraging results for maintenance gilteritinib were observed in a smaller study, where there was a relatively low rate of disease relapse after allo-HCT with maintenance gilteritinib in a relapsed/refractory population.[17]

Future areas of investigation include understanding whether different FLT3 TKIs have different effects in the post-HCT setting and the optimal duration of maintenance therapy. Studies at diagnosis including karyotype, concurrent *NPM1* mutations, and FLT3 allelic ratio can clearly modify relapse risk, but it is unclear if these should dictate the choice to administer maintenance therapy. Moreover, as increasingly sensitive diagnostics of FLT3-mutated MRD are incorporated into routine practice, it remains to be seen if isolated or serial MRD measurements can identify the appropriate subgroup that truly benefits from post–allo-HCT FLT3 TKI. This is a key component of the phase 3 gilteritinib trial design with serial samples collected specifically for this purpose.

Table 2. Active or recruiting trials of maintenance therapy after allogeneic HCT listed on clinicaltrials.gov

	ClinicalTrials.gov identifier	Status	Disease	Maintenance agent	Phase study
FLT3$^+$ disease	#NCT02997202	Active, not recruiting	FLT3$^+$ AML	Gilteritinib	3
	#NCT02400255	Active, not recruiting	FLT3$^+$ AML	Crenolanib	2
IDH mutated disease	#NCT03515512	Active, not recruiting	AML, MDS, CMML	Enasidenib	1
	#NCT03728335	Recruiting	AML	Enasidenib	1
	#NCT04522895	Recruiting	AML, MDS, CMML	Enasidenib	2
	#NCT04522895	Recruiting	AML, MDS	Enasidenib, ivosidenib	3
	#NCT03564821	Recruiting	AML, MDS, CMML	Ivosidenib	1
Ph$^+$ disease	#NCT05024357	Recruiting	Ph$^+$ ALL	Dasatinib	NA
HMA-based approaches	#NCT04173533	Recruiting	AML, MDS	Azacitidine	3
	#NCT01995578	Active, not recruiting	AML, MDS	Azacitidine	2
	#NCT03931291	Active, not recruiting	AML, MDS	Azacitidine, APR-246	2
	#NCT02124174	Recruiting	AML, MDS	Azacitidine, valproic acid	2
	#NCT03613532	Recruiting	AML, MDS	Azacitidine, venetoclax	1
	#NCT04161885	Recruiting	AML	Azacitidine, venetoclax	3
	#NCT04980404	Recruiting	MDS, CMML	Decitabine/ cedazuridine	1
Additional targeted or disease-specific approaches	#NCT04674345	Recruiting	Acute leukemia	Sorafenib	2
	#NCT04168502	Recruiting	AML	Glasdegib	3
	#NCT03932643	Recruiting	AML, MDS	ONC 201	1
	#NCT03286530	Recruiting	AML, MDS	Ruxolitinib	2
	#NCT03267186	Active, not recruiting	Acute leukemia, CML	Ibrutinib	2
	#NCT04326764	Recruiting	AML, MDS	Panobinostat	3
	#NCT01433965	Active, not recruiting	AML, MDS	Lenalidomide	1
	#NCT02807883	Active, not recruiting	ALL	Blinatumomab	2
	#NCT03114865	Recruiting	B-cell ALL or NHL	Blinatumomab	1B/2
	#NCT03151057	Active, not recruiting	B-cell malignancies	Idelalisib	1
	#NCT03540849	Recruiting	HL	Brentuximab vendotin	2
	#NCT02512497	Recruiting	T-cell leukemia or lymphoma	Romidepsin	1
	#NCT01264315	Active, not recruiting	Multiple myeloma	Lenalidomide	2
	#NCT02440464	Active, not recruiting	Multiple myeloma	Ixazomib	2

Accessed on 25 October 2021 with search terms "maintenance allogeneic transplant," "maintenance allo," or "maintenance post transplant." HL, Hodgkin lymphoma; NA, not applicable; NHL, non-Hodgkin lymphoma.

Case recommendation

We would suggest that this patient receive maintenance FLT3 inhibition with midostaurin, sorafenib, or gilteritnib, whichever agent is available. Anecdotally, gilteritinib appears to be the most tolerable, and this is our current standard. We suggest beginning maintenance as early as day +30 if hematologic recovery and toxicity profile allow, given relapse tends to occur relatively quickly in FLT3-ITD AML. We recommend at least 6

months of maintenance therapy based on the trial of Xuan et al[15] but would continue for 2 years if toxicity allows, given that later relapses have been observed and the tolerability shown in the phase 3 gilteritinib trial. Measurement of FLT3 MRD is reasonable to conduct at the end of 2 years for reassurance in stopping maintenance therapy, although it is entirely unclear what action to take if detectable. Dose reductions are common, as observed in both sorafenib trials, but the beneficial effect of FLT3 inhibitor maintenance appears to extend even at lower doses. At this time, we do not recommend a preemptive approach in this clinical setting given the rapid kinetics of relapse in FLT3-ITD AML.

Case 2: isocitrate dehydrogenase–mutated myeloid disease

A 69-year-old woman presented with worsening fatigue. She had a WBC of 1.5 × 10^9/L with 19% circulating blasts and a hemoglobin level of 9.8 g/dL. Bone marrow examination revealed AML with 30% blasts. She had no cytogenetic abnormalities, and genomic analysis revealed an isocitrate dehydrogenase 2 (IDH2) R172 mutation at a variant allele fraction (VAF) of 24%. She received induction chemotherapy with daunorubicin/cytarabine, and her repeat bone marrow biopsy on hematologic recovery showed persistent disease with 10% blasts. She was then treated with single-agent enasidenib for 2 months. Repeat testing showed no morphologic evidence of AML but persistent detection of the IDH2 mutation at a VAF of 3.7%. She now plans to proceed with reduced-intensity allo-HCT from a mismatched unrelated donor.

IDH

Mutations in IDH 1 or 2, respectively, can lead to production of *R*-2-hydroxyglutarate, which competitively inhibits α-ketoglutarate–dependent enzymes.[18,19] These events can result in the development of epigenetic alterations and impaired hematopoietic differentiation.[20,21] Mutations in IDH1 or IDH2 occur commonly in patients with AML, myelodysplastic syndrome (MDS), or chronic myelomonocytic leukemia (CMML).[22-25]

Reports on the prognostic impact of IDH mutations in AML are conflicting.[22,26-31] Two recent studies have attempted to address the outcomes after allo-HCT for IDH-mutated AML. In a single center retrospective analysis of 99 patients with AML receiving allo-HCT, 23 were shown to possess IDH mutations. IDH-mutated patients had a 1-year relapse rate of 29%, and IDH1/2 mutation status was associated with relapse after adjustment for pre-HCT disease status (hazard ratio [HR], 2.8; $P = .046$).[32] We led a larger multicenter retrospective analysis of 112 patients with IDH1- or IDH2-mutated AML undergoing allo-HCT and reported 2-year relapse incidences of 31% and 25% for IDH1- and IDH2-mutated disease, respectively. The 2-year PFS was 58% for both cohorts.[33] Importantly, these studies have set a reference on which to design interventional maintenance trials, especially given the unclear prognostic significance of IDH mutations.

The therapeutic landscape for IDH-mutated myeloid disease has been transformed with the development of oral targeted small-molecule inhibitors.[34] Ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor) both effectively inhibit *R*-2-hydroxyglutarate and can restore normal myeloid differentiation.[35-39] In large multicenter phase 1/2 studies, these agents have demonstrated favorable toxicity profiles and the ability to induce durable remissions both alone and in combination with other therapies in both relapsed/refractory and newly diagnosed AML. As such, ivosidenib and enasidenib have received regulatory approval from the US Food and Drug Administration for the treatment of IDH1- and IDH2-mutated AML, respectively.[40]

Although the biological and clinical rationale for the use of targeted IDH inhibitors after allo-HCT is intuitive, there is currently a lack of published experience with this approach. Multiple ongoing phase 1 and 2 trials are investigating the use of ivosedinib (#NCT03564821 and #NCT03839771) and enasidenib (#NCT03515512, #NCT03728335, #NCT04522895, and #NCT03839771) as maintenance therapies after allo-HCT for IDH1- and IDH2-mutated myeloid diseases, respectively (Table 2). Recently, we reported preliminary results of a phase 1 study showing enasidenib 100 mg daily to be well tolerated as maintenance therapy and associated with low rates of relapse (13% at median follow-up of 11.7 months).[41] Observations from these studies will be important in establishing the toxicity profile of these agents in the posttransplant setting and potentially give an estimate of the expected clinical outcomes. The incidence of relapse and molecular profile of disease at the time of relapse, with particular attention to IDH mutational status, will be of importance. A unique adverse event associated with these inhibitors is IDH differentiation syndrome, characterized by dyspnea, fever, weight gain, and organ dysfunction, which has been identified in up to 20% of patients receiving ivosidenib or enasidenib for relapsed or refractory AML.[42] However, given the absence of disease at initiation of maintenance therapy, IDH differentiation syndrome is not expected in this setting. In addition, therapeutic regimens with the B-cell lymphoma-2 (BCL-2) inhibitor venetoclax also appear to be quite effective for IDH-mutated myeloid neoplasms, and ongoing trials are investigating venetoclax-based maintenance therapies after allo-HCT (#NCT03613532 and #NCT04161885) to determine feasibility and safety.

Case recommendation

Given pretransplant disease response to IDH2 inhibition, the presence of MRD at the time of allo-HCT, and the use of reduced intensity conditioning, we would suggest that this patient be considered to receive maintenance enasidenib if available. If pursued, we suggest beginning maintenance as early as day +30 if hematologic recovery and toxicity profile allow and continuing for at least 1 year of maintenance therapy based on the safety illustrated in our pilot study. If not available, we would suggest more frequent disease monitoring by interval bone marrow biopsies with sensitive measurement of IDH2 mutational status to justify initiation of preemptive enasidenib if MRD becomes detectable. Certainly, if this patient is eligible for clinical trials investigating targeted or other novel approaches in the maintenance setting, we would encourage participation.

Case 3: Philadelphia chromosome leukemia

A 51-year-old man presented with new-onset dyspnea. He had a WBC of 253 × 10^9/L with 69% blasts and a platelet count of 35 × 10^9/L. Bone marrow examination revealed B-cell acute lymphoblastic leukemia (ALL) with 70% B lymphoblasts. Cytogenetic evaluation revealed t(9;22) associated with a chimeric p210 BCR-ABL1 fusion protein. He received hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) chemotherapy in combination with dasatinib for initial therapy and achieved remission, albeit with persistence of MRD by flow cytometry. He subsequently received 1 cycle of blinatumomab with dasatinib to achieve an MRD-negative state (by both flow cytometry and quantitative BCR-ABL monitoring). He now plans to proceed with myeloablative allo-HCT from a matched related donor.

BCR-ABL1

The treatment of Philadelphia (Ph) chromosome leukemias, defined by the presence of t(9;22)(q34;q11), has dramatically shifted with the development of TKIs that inhibit the constitutive kinase activity on the chimeric BCR-ABL1 protein.[43] Chronic myeloid leukemia (CML) is now predominantly managed with TKIs alone, with allo-HCT being reserved for advanced phase disease, TKI resistance or intolerance, or other high-risk features.[44] Although many patients with Ph^+ ALL still proceed to allo-HCT once in remission, TKIs are routinely incorporated into the treatment strategy, either in combination with chemotherapy or as monotherapy.[45-47]

The widespread access and clinical use of BCR-ABL1 TKIs outside of allo-HCT naturally led to investigations in the posttransplant setting. Because initial research focused on the feasibility and toxicities of this approach, most studies included both subjects with CML or Ph^+ ALL. Early clinical trials investigating the use of maintenance imatinib after transplant demonstrated feasibility, tolerability, and an association with low rates of disease relapse.[48-50] As newer-generation TKIs became more common, additional prospective trials and retrospective analyses have been reported.[51] Of note, the feasibility of maintenance with newer TKIs has come into question. Specifically, 2 separate phase 1/2 studies investigating nilotinib maintenance found maintenance therapy to be difficult because of toxicities and competing posttransplant complications.[52,53] As such, the current choice of TKI after transplant is often influenced by pre-HCT choice, anticipated toxicities, and presence of detectable BCR-ABL1 domain mutations.[54]

Larger analyses of TKI maintenance have tried to assess the clinical effectiveness of the approach for each disease. In a study from the European Bone Marrow Transplant registry investigating the impact of TKI therapy on outcomes of allo-HCT for Ph^+ ALL in CR1, posttransplant maintenance TKI use (n = 60) was independently associated with better leukeima-free survival (HR = 0.44), OS (HR = 0.42), and lower disease relapse (HR = 0.40).[55] A recent large single center evaluation of TKI maintenance (n = 97) after allo-HCT in Ph^+ ALL reported encouraging updated outcomes (2-year PFS: 69%; 2-year OS: 73%). The median duration of TKI maintenance was 13 months, and patients who continued for more than 24 months had a lower risk of relapse (HR = 0.12), suggesting longer duration might be beneficial.[56] Taken together, the overall clinical experience suggests that the use of TKIs after transplant is associated with improved outcomes and is recommended in Ph^+ ALL.[51,57,58] In CML, a recent study from the Center for International Blood and Marrow Transplant Research conducted a landmark analysis at day +100 after allo-HCT and found maintenance TKI to have no significant impact on clinical outcomes.[59] Considering that many patients with CML undergoing transplant in the current era are either TKI refractory or intolerant, maintenance therapy may or may not be recommended depending on the situation.

Given the widespread availability of quantitative BCR-ABL assays, another major consideration is that preemptive approaches in the posttransplant setting may be comparable or even superior to maintenance. A randomized trial of 55 subjects with Ph^+ ALL compared maintenance imatinib with preemptive initiation at the time of positive MRD testing. There were low rates of hematologic relapse and no significant difference in overall outcomes between the 2 arms, although maintenance therapy not surprisingly reduced molecular recurrence compared with preemptive therapy (40% vs 69%, $P = .046$).[60] Given the current widespread access and familiarity with these agents, definitive randomized controlled clinical trials regarding maintenance TKI for Ph^+ diseases will likely never be conducted, and the true benefit of BCR-ABL1 TKI maintenance therapy may never be truly known.

Case recommendation

We would suggest that this patient receive maintenance BCR-ABL1 TKI after allo-HCT. We suggest that he continue with dasatinib, given his response and tolerability before transplant. We suggest beginning maintenance TKI as early as day +30 if hematologic recovery and toxicity profile allow. We recommend at least 2 years of maintenance therapy with sensitive monitoring of quantitative BCR-ABL transcript at least every 3 months during this period.

Case 4: hypomethylating agent–based maintenance

A 69-year-old woman was found to have worsening anemia (hemoglobin level, 7.5 g/dL) and thrombocytopenia (platelet count, 42 × 10^9/L). Bone marrow examination was consistent with MDS with excess blasts-2 (15% blasts). Cytogenetic evaluation revealed a complex karyotype, and genomic analysis revealed a point mutation in TP53 with a VAF of 43%. She received 4 cycles of decitabine with improvement in hematologic measures. Repeat bone marrow biopsy showed a reduction of blasts to 2% and a normal karyotype. Genomic analysis shows persistent detection of the *TP53* mutation with a VAF that decreased to 7%. She now plans to proceed with reduced-intensity allogeneic HCT from a matched unrelated donor.

Hypomethylating agents

Hypomethylating agents (HMAs) are well established in the treatment of myeloid malignancies.[61,62] HMAs are thought to induce re-expression of silenced tumor suppressing genes through epigenetic modification and may also enhance the graft-

versus-leukemia effect (GVL) after allo-HCT through increased expression of tumor antigens.[63-65] These agents often result in clinical disease response with relatively low toxicity, allowing many patients to proceed to allo-HCT. Because many patients with myeloid malignancies do not currently possess a targetable mutation,[66-68] HMA has the advantage of being broadly applicable to multiple myeloid diseases (AML, MDS, CMML) and genomic profiles. A maintenance approach is particularly appealing for higher-risk disease, such as those possessing complex cytogenetic abnormalities or *TP53* mutations.[6,7]

Clinical investigations into the use of HMA maintenance after allo-HCT have produced conflicting results.[69] After an initial promising report of the use of azacitidine after allo-HCT,[70] early trials established safety and recommended dosing schedules. A phase 1 study enrolled 45 patients and identified the optimal dosing schedule for azacitidine to be 32 mg/m^2 IV administered daily for 5 consecutive days every 28 days for 4 cycles. The 1-year event-free survival and OS were 58% and 77%, respectively.[71] A separate phase 1 study of 27 patients with AML further supported the tolerability of azacitidine after HCT and found that azacitidine at a daily dose of 36 mg/m^2 both augmented expansion of regulatory T cells and induced cytotoxic CD8$^+$ T-cell response to several tumor antigens.[65] Decitabine was evaluated in a phase 1 study enrolling 24 patients, with 10 mg/m^2 for 5 days every 6 weeks appearing to be the optimal dose, although the maximum tolerated dose was not reached.[72] However, the inability to complete planned therapy has limited the assessment of maintenance HMAs to prevent disease relapse. A phase 2 National Cancer Institute/Alliance trial (Cancer and Leukemia Group B 100801) enrolled 66 patients, but only 42 were able to initiate treatment with azacytidine, and only 17 completed all 6 cycles as planned.[73] In the largest trial to date, 187 subjects with high-risk AML or MDS were randomized to 5-azacitidine (32 mg/m^2/day IV × 5 days every 28 days for 12 cycles) or observation after allo-HCT. Eighty-seven started azacitidine maintenance. The median number of cycles received was only 4, because 29 relapsed on study and 23 withdrew because of toxicity, patient preference, or other logistic reasons. There was no significant difference in the median relapse-free survival or OS between the 2 groups by intention-to-treat analysis. This study highlights the challenges in implementing prolonged HMA maintenance after allo-HCT.[74]

Numerous issues remain unknown regarding HMA maintenance after allo-HCT. First, it will be important to identify patient populations that are most likely to benefit and potentially conduct clinical trials in a more biologically homogeneous population. Second, oral formulations of HMA hold promise in overcoming issues concerning feasibility. A phase 1/2 dose finding study found maintenance with oral azacitidine (CC-486) to be well tolerated and associated with low rates of relapse and GVHD.[75] A phase 3, randomized, placebo controlled trial is further evaluating CC-486 as maintenance therapy after allo-HCT (#NCT04173533; Table 2). Additionally, other trials are investigating the oral agent decitabine/cedazuridine in the posttransplant setting (#NCT04980404; Table 2). Third, clinical trials are determining whether maintenance therapy with HMAs can be augmented with other agents given in combination. In one study, azacitidine and gemtuzumab ozogamicin (anti-CD33 antibody-drug conjugate) were administered every 4 weeks for up to 4 cycles. The combination resulted in 1-year disease-free survival and OS of 60% and 70%, respectively.[76] Venetoclax (BCL-2 inhibitor) and APR-246, a small molecule that refolds mutant p53 protein, are both being investigated in combination with HMA as maintenance after allo-HCT (Table 2). Combinations of HMA with FLT3 or IDH inhibitors have not yet been investigated in the maintenance setting but are used routinely as primary therapy. Finally, in a phase 2 trial, a risk-adapted approach of initiating preemptive therapy with azacitidine on detection of MRD in patients with AML and MDS was successful in limiting relapse (58% relapse free and alive 6 months after initiation of treatment) and may be considered as an alternative to maintenance if MRD is able to be routinely monitored.[77]

Case recommendation

Given the high risk of relapse driven by the TP53 mutation with complex karyotype and detectable MRD at HCT and the exhibited response to HMAs before HCT, we would suggest that this patient be considered for maintenance HMA-based therapy after allo-HCT. A thorough discussion of risks and potential benefits should be pursued with shared decision making with the patient. We would certainly advocate for participation in any ongoing clinical trials testing novel approaches for such high-risk patients, including those that are immunologically based. If a maintenance HMA-based approach is pursued, we suggest allowing time for sufficient hematologic recovery, which may mean not starting until at least day +60 or later. Dose reduction or longer cycle length is commonly required to avoid hematologic toxicity. We recommend at most 1 year of maintenance therapy if toxicities and cytopenias allow.

Future directions

Historically, the biggest obstacles for maintenance therapy after allo-HCT were cytopenias and cumulative immunosuppression from nontargeted therapies. With the advent of an increasing number of novel targeted agents, maintenance therapy after allo-HCT to potentially decrease rates of disease relapse has become a reality. However, there remain several significant challenges in conducting definitive trials. Access to agents is often delayed until commercial approval is gained for other indications, which allows off-protocol use and deters from enrollment onto randomized trials. Given the unique immunologic and hematopoietic environment after allo-HCT, early-phase trials with careful dose-finding designs focused on safety should likely be performed before larger definitive ones. This is especially important for agents that may have immunomodulatory effects possibly inducing significant GVHD. In addition, questions remain regarding the actual mechanism of maintenance therapies, even for patients in whom a specific mutation is targeted. HMA have been speculated to encourage GVL through induced expression of tumor antigens, and FLT3 inhibitors have multiple targets beyond FLT3. Indeed, there is evidence that FLT3 inhibition after allo-HCT induces autocrine interleukin-15 expression, which results in increased susceptibility of mutant cells to T-cell immunity, possibly allowing improved GVL.[78] Trials testing combination approaches such as those mentioned above with HMAs should also be conducted with samples collected for careful investigation into mechanisms of relapse. Finally, as we continue to develop increasingly sensitive assays for MRD, the application of maintenance

therapies after allo-HCT will almost certainly be dictated by MRD-based stratification or be replaced altogether by pre-emptive approaches driven by therapy applied at the time of detectable MRD. Despite all these challenges, it is easy to envision that post–allo-HCT approaches to prevent relapse will soon be a standard paradigm for many patients.

Authorship

Contribution: Z.D. and Y.-B.C. wrote the manuscript.

Conflict-of-interest disclosure: Z.D. receives research support from Incyte Corp. and Regimmune Corp. and has received consulting fees from Syndax Pharmaceuticals, Inc., Kadmon Corp., and Omeros Corp. Y.-B.C. has received consulting fees from Incyte, Gamida Cell, Equilium, Celularity, Daiichi, Actinium, and Abbvie.

ORCID profiles: Z.D., 0000-0002-7994-8974; Y.-B.C., 0000-0002-9554-1058.

Correspondence: Yi-Bin Chen, Zero Emerson Place, Suite 118, Boston, MA 02114; email: ychen6@partners.org.

Footnote

Submitted 3 December 2021; accepted 3 February 2022; prepublished online on *Blood* First Edition 1 March 2022. https://doi.org/10.1182/blood.2021012412.

REFERENCES

1. Penack O, Peczynski C, Mohty M, et al. How much has allogeneic stem cell transplant-related mortality improved since the 1980s? A retrospective analysis from the EBMT. *Blood Adv*. 2020;4(24):6283-6290.
2. Tsirigotis P, Byrne M, Schmid C, et al. Relapse of AML after hematopoietic stem cell transplantation: methods of monitoring and preventive strategies. A review from the ALWP of the EBMT. *Bone Marrow Transplant*. 2016;51(11):1431-1438.
3. Wieduwilt MJ, Metheny L, Zhang MJ, et al. Haploidentical vs. sibling, unrelated, or cord blood hematopoietic cell transplantation for acute lymphoblastic leukemia. *Blood Adv*. 2021.
4. Jimenez Jimenez AM, De Lima M, Komanduri KV, et al. An adapted European LeukemiaNet genetic risk stratification for acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplant. A CIBMTR analysis. *Bone Marrow Transplant*. 2021;56(12):3068-3077.
5. DeFilipp Z, Chen YB. Strategies and challenges for pharmacological maintenance therapies after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016;22(12):2134-2140.
6. Armand P, Kim HT, Zhang MJ, et al. Classifying cytogenetics in patients with acute myelogenous leukemia in complete remission undergoing allogeneic transplantation: a Center for International Blood and Marrow Transplant Research study. *Biol Blood Marrow Transplant*. 2012;18(2):280-288.
7. Lindsley RC, Saber W, Mar BG, et al. prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med*. 2017;376(6):536-547.
8. Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *J Clin Oncol*. 2020;38(12):1273-1283.
9. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154-1161.
10. Fröhling S, Schlenk RF, Breitruck J, et al; AML Study Group Ulm. Acute myeloid leukemia. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. *Blood*. 2002;100(13):4372-4380.
11. Smith CC, Wang Q, Chin CS, et al. Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia. *Nature*. 2012;485(7397):260-263.
12. Chen YB, Li S, Lane AA, et al. Phase I trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2014;20(12):2042-2048.
13. Brunner AM, Li S, Fathi AT, et al. Haematopoietic cell transplantation with and without sorafenib maintenance for patients with FLT3-ITD acute myeloid leukaemia in first complete remission. *Br J Haematol*. 2016;175(3):496-504.
14. Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with *FLT3*-internal tandem duplication mutation (SORMAIN). *J Clin Oncol*. 2020;38(26):2993-3002.
15. Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. *Lancet Oncol*. 2020;21(9):1201-1212.
16. Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. *Bone Marrow Transplant*. 2021;56(5):1180-1189.
17. Perl AE, Larson RA, Podoltsev NA, et al. Follow-up of patients with FLT3-mutated R/R AML in the phase 3 ADMIRAL trial. *J Clin Oncol*. 2021;39(15):7013.
18. Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. 2010;17(3):225-234.
19. Xu W, Yang H, Liu Y, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. *Cancer Cell*. 2011;19(1):17-30.
20. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell*. 2010;18(6):553-567.
21. Lu C, Ward PS, Kapoor GS, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. *Nature*. 2012;483(7390):474-478.
22. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. *J Clin Oncol*. 2010;28(22):3636-3643.
23. Patel KP, Ravandi F, Ma D, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. *Am J Clin Pathol*. 2011;135(1):35-45.
24. DiNardo CD, Jabbour E, Ravandi F, et al. IDH1 and IDH2 mutations in myelodysplastic syndromes and role in disease progression. *Leukemia*. 2016;30(4):980-984.
25. Jankowska AM, Makishima H, Tiu RV, et al. Mutational spectrum analysis of chronic myelomonocytic leukemia includes genes associated with epigenetic regulation: UTX, EZH2, and DNMT3A. *Blood*. 2011;118(14):3932-3941.
26. Im AP, Sehgal AR, Carroll MP, et al. DNMT3A and IDH mutations in acute myeloid leukemia and other myeloid malignancies: associations with prognosis and potential treatment strategies [correction published in *Leukemia*. 2015;29:516]. *Leukemia*. 2014;28(9):1774-1783.
27. Abbas S, Lugthart S, Kavelaars FG, et al. Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. *Blood*. 2010;116(12):2122-2126.

28. Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *J Clin Oncol*. 2010;28(14): 2348-2355.

29. Wagner K, Damm F, Göhring G, et al. Impact of IDH1 R132 mutations and an IDH1 single nucleotide polymorphism in cytogenetically normal acute myeloid leukemia: SNP rs11554137 is an adverse prognostic factor. *J Clin Oncol*. 2010;28(14):2356-2364.

30. Chou WC, Lei WC, Ko BS, et al. The prognostic impact and stability of Isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. *Leukemia*. 2011;25(2):246-253.

31. Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012;366(12):1079-1089.

32. Salhotra A, Afkhami M, Yang D, et al. allogeneic hematopoietic cell transplantation outcomes in patients carrying isocitrate dehydrogenase mutations. *Clin Lymphoma Myeloma Leuk*. 2019;19(7):e400-e405.

33. Chen EC, Li S, Eisfeld AK, et al. Outcomes for patients with IDH-mutated acute myeloid leukemia undergoing allogeneic hematopoietic cell transplantation. *Transplant Cell Ther*. 2021;27(6):479.

34. Upadhyay VA, Brunner AM, Fathi AT. Isocitrate dehydrogenase (IDH) inhibition as treatment of myeloid malignancies: progress and future directions. *Pharmacol Ther*. 2017; 177:123-128.

35. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.

36. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2020; 135(7):463-471.

37. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.

38. Stein EM, DiNardo CD, Fathi AT, et al. Molecular remission and response patterns in patients with mutant-*IDH2* acute myeloid leukemia treated with enasidenib. *Blood*. 2019;133(7):676-687.

39. Pollyea DA, Tallman MS, de Botton S, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia*. 2019;33(11):2575-2584.

40. Cerchione C, Romano A, Daver N, et al. IDH1/IDH2 inhibition in acute myeloid leukemia. *Front Oncol*. 2021;11:639387.

41. Fathi AT, Li S, Soiffer RJ, et al. A phase I study of the IDH2 inhibitor enasidenib as maintenance therapy for IDH2-mutant myeloid neoplasms following hematopoietic cell transplantation. *Blood*. 2020;136(suppl 1):4-5.

42. Norsworthy KJ, Mulkey F, Scott EC, et al. Differentiation syndrome with ivosidenib and enasidenib treatment in patients with relapsed or refractory IDH-mutated AML: a U.S. Food and Drug Administration systematic analysis. *Clin Cancer Res*. 2020;26(16):4280-4288.

43. Soverini S, Bassan R, Lion T. Treatment and monitoring of Philadelphia chromosome-positive leukemia patients: recent advances and remaining challenges. *J Hematol Oncol*. 2019;12(1):39.

44. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020; 34(4):966-984.

45. Ravandi F. How I treat Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2019;133(2):130-136.

46. Ravandi F, Othus M, O'Brien SM, et al. US Intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. *Blood Adv*. 2016;1(3):250-259.

47. Foà R, Vitale A, Vignetti M, et al; GIMEMA Acute Leukemia Working Party. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2011; 118(25):6521-6528.

48. Carpenter PA, Snyder DS, Flowers ME, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood*. 2007;109(7):2791-2793.

49. Olavarria E, Siddique S, Griffiths MJ, et al. Posttransplantation imatinib as a strategy to postpone the requirement for immuno-therapy in patients undergoing reduced-intensity allografts for chronic myeloid leukemia. *Blood*. 2007;110(13):4614-4617.

50. Ribera JM, Oriol A, González M, et al; Grupo Español de Trasplante Hemopoyético Groups. Concurrent intensive chemotherapy and imatinib before and after stem cell transplan-tation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. *Haematologica*. 2010;95(1):87-95.

51. Warraich Z, Tenneti P, Thai T, et al. Relapse prevention with tyrosine kinase inhibitors after allogeneic transplantation for philadelphia chromosome-positive acute lymphoblast leukemia: a systematic review. *Biol Blood Marrow Transplant*. 2020;26(3):e55-e64.

52. Shimoni A, Volchek Y, Koren-Michowitz M, et al. Phase 1/2 study of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 2015;121(6):863-871.

53. Carpenter PA, Johnston L, Fernandez HF, et al. Posttransplant feasibility study of nilotinib prophylaxis for high-risk Philadelphia chromosome positive leukemia. *Blood*. 2017;130(9):1170-1172.

54. DeFilipp Z, Langston AA, Chen Z, et al. Does post-transplant maintenance therapy with tyrosine kinase inhibitors improve outcomes of patients with high-risk philadelphia chromosome-positive leukemia? *Clin Lymphoma Myeloma Leuk*. 2016;16(8): 466-471.

55. Brissot E, Labopin M, Beckers MM, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Haematologica*. 2015;100(3):392-399.

56. Saini N, Marin D, Ledesma C, et al. Impact of TKIs post-allogeneic hematopoietic cell transplantation in Philadelphia chromosome-positive ALL. *Blood*. 2020;136(15): 1786-1789.

57. Giebel S, Czyz A, Ottmann O, et al. Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a position statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Cancer*. 2016; 122(19):2941-2951.

58. DeFilipp Z, Advani AS, Bachanova V, et al. hematopoietic cell transplantation in the treatment of adult acute lymphoblastic leukemia: updated 2019 evidence-based review from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2019;25(11): 2113-2123.

59. DeFilipp Z, Ancheta R, Liu Y, et al. Maintenance tyrosine kinase inhibitors following allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia: a Center for International Blood and Marrow Transplant research study. *Biol Blood Marrow Transplant*. 2020;26(3): 472-479.

60. Pfeifer H, Wassmann B, Bethge W, et al; GMALL Study Group. Randomized comparison of prophylactic and minimal residual disease-triggered imatinib after allogeneic stem cell transplantation for BCR-ABL1-positive acute lymphoblastic leukemia. *Leukemia*. 2013;27(6):1254-1262.

61. Lübbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *J Clin Oncol*. 2011;29(15):1987-1996.

62. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs

conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3):291-299.

63. Issa JP, Garcia-Manero G, Giles FJ, et al. Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2′-deoxycytidine (decitabine) in hematopoietic malignancies. *Blood*. 2004;103(5):1635-1640.

64. Goodyear O, Agathanggelou A, Novitzky-Basso I, et al. Induction of a CD8+ T-cell response to the MAGE cancer testis antigen by combined treatment with azacitidine and sodium valproate in patients with acute myeloid leukemia and myelodysplasia. *Blood*. 2010;116(11):1908-1918.

65. Goodyear OC, Dennis M, Jilani NY, et al. Azacitidine augments expansion of regulatory T cells after allogeneic stem cell transplantation in patients with acute myeloid leukemia (AML). *Blood*. 2012;119(14):3361-3369.

66. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.

67. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med*. 2011;364(26):2496-2506.

68. Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. *J Clin Oncol*. 2013;31(19):2428-2436.

69. Dholaria B, Savani BN, Hamilton BK, et al. hematopoietic cell transplantation in the treatment of newly diagnosed adult acute myeloid leukemia: an evidence-based review from the American Society of Transplantation and Cellular Therapy. *Transplant Cell Ther*. 2021;27(1):6-20.

70. Jabbour E, Giralt S, Kantarjian H, et al. Low-dose azacitidine after allogeneic stem cell transplantation for acute leukemia. *Cancer*. 2009;115(9):1899-1905.

71. de Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. *Cancer*. 2010;116(23):5420-5431.

72. Pusic I, Choi J, Fiala MA, et al. Maintenance therapy with decitabine after allogeneic stem cell transplantation for acute myelogenous leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant*. 2015;21(10):1761-1769.

73. Vij R, Hars V, Blum W, et al. CALGB 100801 (Alliance): a phase II multi-center NCI Cooperative Group study of the addition of azacitidine (AZA) to reduced-intensity conditioning (RIC) allogeneic transplantation for high risk myelodysplasia (MDS) and older patients with acute myeloid leukemia (AML): results of a "test dose" strategy to target busulfan exposure. *Blood*. 2014;124(21):543-543.

74. Oran B, de Lima M, Garcia-Manero G, et al. A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients [correction published in *Blood Adv*. 2021;5(6):1755-1756]. *Blood Adv*. 2020;4(21):5580-5588.

75. de Lima M, Oran B, Champlin RE, et al. CC-486 maintenance after stem cell transplantation in patients with acute myeloid leukemia or myelodysplastic syndromes. *Biol Blood Marrow Transplant*. 2018;24(10):2017-2024.

76. Oshikawa G, Kakihana K, Saito M, et al. Post-transplant maintenance therapy with azacitidine and gemtuzumab ozogamicin for high-risk acute myeloid leukaemia. *Br J Haematol*. 2015;169(5):756-759.

77. Platzbecker U, Middeke JM, Sockel K, et al. Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial. *Lancet Oncol*. 2018;19(12):1668-1679.

78. Mathew NR, Baumgartner F, Braun L, et al. Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells [correction published in *Nat Med*. 20018;24:526]. *Nat Med*. 2018;24(3):282-291.