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REVIEW ARTICLE

Methods to prevent and treat relapse after hematopoietic stem cell transplantation with tyrosine kinase inhibitors, immunomodulating drugs, deacetylase inhibitors, and hypomethylating agents

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Abstract

Relapse is a major cause of treatment failure after stem cell transplantation. Novel agents given as maintenance or preemptive post transplant were discussed at the 3rd International Workshop on Biology, Prevention, and Treatment of Relapse after Stem Cell Transplantation in Hamburg/Germany in November 2016 under the auspices of EBMT and ASBMT. Maintenance therapy is started after SCT without detectable disease, while preemptive therapy is triggered by the detection of minimal residual disease (MRD). The maintenance approach treats all patients, and overtreats a significant amount. Maintenance therapy requires an agent without significant off-target toxicity. The preemptive approach only initiates therapy upon detection of MRD, while sparing further therapy to those who remain in remission. Preemptive strategies require sensitive and clinically reliable assays to detect MRD. Here current development of tyrosine kinase inhibitors (TKIs) immunomodulating drugs (IMiDs), deacetylase inhibitors, and hypomethylating agents were reviewed.

Philadelphia chromosome-positive leukemia

Philadelphia chromosome-positive (Ph+) leukemias including advanced-phase chronic myeloid leukemia (CML) and Ph + acute lymphoblastic leukemia (ALL) provide an ideal setting for post-transplant maintenance therapy given the widespread use, availability, and familiarity of tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 fusion protein. Initial studies in this population found maintenance imatinib to be safe when given after HCT. In one trial, imatinib was administered to 22 patients with Ph+ leukemia from the time of engraftment to one year after allo SCT, with 77% maintaining major molecular remission (MMR) [1]. In a separate study of 22 patients, 95% completed 11 months of therapy and remained without cytogenetic or hematologic relapse, although 15 patients did relapse once imatinib was discontinued [2]. In these studies, as well as others [3], imatinib was very well tolerated. A number of small retrospective series have also reported maintenance with dasatinib, although often at a dose-reduction relative to pre-HCT therapy [4–6]. A phase I/II study investigating post-transplant nilotinib in 16 patients with high-risk Ph+ leukemia reported 2-year OS and PFS of 69% and 56%, respectively, however, 38% of patients had to discontinue therapy due to toxicities [7]. A separate phase I/II study found that only 32.5% of

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patients eligible for nilotinib maintenance at engraftment were able to complete the intended 1-year of therapy, due to early relapse, toxicities and confounding post-HCT complications [8].

Two larger registry studies have included analysis of post-transplant TKI in Ph+ ALL, although both are limited by the small number of patients receiving maintenance therapy. In a Center for International Blood and Marrow Transplant Research (CIBMTR) analysis on 197 patients with Ph+ ALL undergoing allogeneic SCT in CR1, only 43 patients received post-transplant TKI with specific agent used, starting time and duration of therapy unclear, possibly leading to the lack of observed difference in outcomes [9]. The European Society for Blood and Marrow Transplantation (EBMT) assessed outcomes after allo SCT of 473 Ph+ ALL patients with 60 patients receiving maintenance therapy and showed that use of post-transplant TKI was associated with better leukemia-free survival in a multivariate analysis (HR, 0.42; 95% CI, 0.23–0.76; $p = 0.004$) [10].

As post-transplant MRD can easily be monitored in Ph+ leukemias, some have investigated a preemptive approach with TKIs. In one trial of 27 patients who underwent allogeneic HCT for Ph+ ALL, and then were given imatinib at MRD detection, 14 patients achieved MRD negative disease status in less than 4 months, leading to 91% rate of DFS at 12 months. In the 13 patients who were unable to achieve a rapid molecular CR, 12 experienced frank disease relapse after a median of 3 months, illustrating that an imatinib based preemptive approach is effective for only patients who are able to respond early [11] A study of 62 patients with Ph+ ALL receiving either prophylactic or preemptive imatinib resulted in decreased rates of relapse (5-yr relapse 10.2% vs 33.1%, $p = 0.016$) and improved 5-year DFS (5-yr DFS 81.5% vs 33.5%, $p = 0.000$) as compared to the non-imatinib group [12]. A phase II study of 55 patients comparing maintenance and preemptive, MRD-triggered imatinib in Ph+ ALL resulted in low rates of hematological relapse and no significant difference in overall outcomes in all patients, although maintenance reduced the incidence of molecular recurrence [13]. Overall, it remains unclear how to best use BCR-ABL TKIs after HCT in terms of agent, duration, time of initiation—be it maintenance or preemptive. Given the current widespread access and familiarity of these agents and the different methods and thresholds of MRD detection, a definitive clinical trial investigating post-HCT TKI for Ph+ diseases will likely never be conducted. The EBMT has published consensus guidelines for use in Ph+ ALL [14], acknowledging the lack of grade 1 evidence of use of post-transplant TKIs, but nevertheless strongly recommending either a maintenance or closely monitored MRD driven preemptive approach. Future registry studies comparing outcomes of a larger number of patients will be needed from which to draw more definitive conclusions.

FLT3-ITD AML

The presence of a FMS-like tyrosine kinase internal tandem duplication mutation (FLT3-ITD) in patients with AML predicts for an adverse prognosis when treated with chemotherapy alone [15]. Allogeneic HCT in CR1 appears to improve the prognosis with long-term rates of DFS around 50%, however, disease relapse remains significant with the majority of relapses occurring in the first 12 months after HCT [16, 17]. FLT3 tyrosine kinase inhibitors (TKIs) have been studied in all phases of therapy for patients, ranging from inclusion during induction chemotherapy to, most recently, maintenance after allo SCT.

A phase I trial of 22 patients with FLT3-ITD AML in CR receiving maintenance sorafenib after allo SCT first reported impressive results showing 1-year PFS 85% and 1-year OS 95% with a median follow-up of 16.7 months [18]. Investigators found the maximum tolerated dose to be 400 mg BID with no apparent increase in NRM or GVHD. The same group then performed a retrospective analysis, comparing the use of maintenance sorafenib after HCT in 26 patients with FLT3-ITD AML in CR1 to 43 control patients with FLT3-ITD AML in CR1 undergoing allo SCT who did not receive any maintenance therapy. The use of sorafenib was associated with improved PFS (85% vs. 52%, $p = 0.0047$) and OS (83% vs. 58%, $p = 0.019$) with the difference primarily driven by a significant decrease in relapse in patients who received sorafenib (8.2% vs. 37.7%, $p = 0.0077$) [19]. Another trial of peri-transplant sorafenib (given both before and after allo SCT) in 28 patients with FLT3-ITD AML in CR1 undergoing SCT, has preliminarily reported only five relapses and six deaths [20]. Additional FLT3 TKIs being studied as maintenance after HCT include midostaurin [21], quizartinib [22], and crenolanib [23]. A phase II study evaluating midostaurin, a multi-target kinase inhibitor, as post-HCT or post-consolidation maintenance reported an encouragingly low relapse rate at 12 months (9.2%) [24], with a phase II randomized study investigating post-allo SCT maintenance now enrolling (NCT01883362). Importantly, the BMT Clinical Trials Network (CTN) trial, CTN 1506, is a large phase III prospective randomized placebo-controlled trial studying the potential benefit of the FLT3 inhibitor gilteritinib as maintenance therapy after HCT for patients with FLT3-ITD AML in CR1. An important aspect of this trial is validation of a next generation sequencing (NGS)-based assay to detect MRD based on FLT3-ITD, which will be measured prior to allo SCT and at serial timepoints afterwards. If post-HCT gilteritinib therapy is shown to confer an advantage, this study

could become the first trial to show a benefit of maintenance therapy administered after allo SCT and, if the NGS MRD assay is validated for detection of MRD with prognostic implications, preemptive approaches may be able to be tested as well.

Future studies

Lack of availability of efficacious TKIs for the majority of diagnoses limits the generalizability of TKIs for most patients after HCT. In addition to further study of BCR-ABL and FLT3-ITD TKIs, two other TKIs are being studied in the post-allo SCT setting. Jagasia et al. are investigating ibrutinib as maintenance therapy for patients with various B-cell lymphomas after auto SCT (NCT02869633). Hobbs et al. are administering ruxolitinib for elderly patients with AML in 1st remission after allo SCT (NCT03286530), and there are preliminary reports [25] and at least two trials using ruxolitinib after allo SCT for patients with myelofibrosis (NCT02917096, Hobbs—personal communication). Furthermore, both of these agents are also being employed for treatment of chronic GVHD, possibly leading to dual benefit for such patients.

Challenges in conducting clinical trials

There are several significant challenges to studying maintenance therapy after allo SCT with agents such as TKIs. Trials administering drugs in the post-allo and auto SCT setting are often only performed when such agents have been approved for other indications as industry is often reluctant to fund such trials prior. When trials are conducted after approval in other setting, this inherently leads to significant off-protocol use which deters from enrollment onto definitive trials. Moreover, pre-existing approval commonly leads to a lack of industrial investment given most payers do not distinguish the post-HCT maintenance setting from other phases of therapy. Even if appropriate clinical trials are designed, a significant proportion of patients are never able to begin maintenance therapy due to HCT-associated toxicities, acute GVHD, or disease relapse, making analysis of early single-arm results difficult to interpret, given the selection bias in evaluating only those who begin maintenance therapy, when comparing to historical controls. Lastly, by the time trials are opened, many clinicians have already adopted maintenance approaches, due to early anecdotes, familiarity with agents, and fear of relapse.

Despite many obstacles, maintenance therapy with specific TKIs is a promising approach that may prevent disease relapse in a subset of patients undergoing HCT. With the development of TKIs which possess less off-target toxicities, our menu of attractive and accessible options will only grow. It is imperative that we collaborate in conducting well-designed prospective randomized clinical trials to definitively evaluate the benefits and toxicities of these agents in the post-HCT setting. Only then can we truly advance the field, prove the utility of such therapies and secure access to these agents for our patients.

Immunomodulating drugs (IMiDs)

Autologous hematopoietic stem cell transplant (auto SCT) is a standard treatment for selected hematologic disorders in particular multiple myeloma (reviewed in Holstein and McCarthy 2016 [26]). However, nearly all myeloma patients will have recurrent or progressive disease after auto SCT, thus a variety of strategies have been undertaken to decrease the incidence of disease relapse and/or progression. These include post-AHSCT maintenance therapy with immunomodulatory drugs (IMiDs) so named due to their effects on the immune system [27]. Thalidomide, an analog of glutamic acid was the first IMiD that was developed for clinical use. The teratogenic effects of thalidomide have been extensively documented and resulted in its removal from the pharmaceutical market (reviewed in Holstein and McCarthy [27]). It was later restored for therapeutic use as a treatment for leprosy and other inflammatory skin conditions. The potent anti-angiogeneic effects of thalidomide led to its use for relapsed and refractory multiple myeloma [28]. This was the first study demonstrating the utility of thalidomide and related compounds for relapsed/refractory multiple myeloma. A Phase III randomized trial demonstrated that thalidomide and dexamethasone was superior to dexamethasone alone as induction therapy for newly diagnosed multiple myeloma patients [29]. The thalidomide derivatives lenalidomide (CC-5013) and pomalidomide (CC-4047) are more potent IMiDs than the parent compound thalidomide, particularly with respect to immunomodulatory activity [30, 31] (reviewed in Holstein and McCarthy [27]). There are multiple effects of IMiDs including immune modulation, micro-environment modulation (including anti-angiogenesis, anti-inflammation), as well as direct anti-tumor cell properties (reviewed in Quach et al. [32]). Thalidomide and lenalidomide have been extensively tested in relapsed/refractory and newly diagnosed multiple myeloma patients. Pomalidomide has been used primarily in relapsed/refractory disease, particularly in patients who are lenalidomide-refractory or intolerant.

Thalidomide has been tested alone and with glucocorticoids as maintenance to prevent relapse/progression following induction therapy and AHSCT. Most of these Phase III trials demonstrated an improved progression-free survival (PFS) or event-free survival (EFS) with variable

Table 1 Thalidomide maintenance versus control/no maintenance

	N	Initial dose (mg)	EFS (PFS)	OS	Benefit? EFS/OS
Attal et al. [33]	597	400	3-year EFS 52 vs 37% ($P < 0.009$)	4-year OS 87 vs 74% ($P < 0.04$)	+/+
Barlogie et al. [34]	668	400	5-year EFS 56 vs 45% ($P < 0.001$)	8-year OS 57 vs 44% ($P = 0.09$)	+/trend+
Lokhorst et al. [35]	556	50	Median EFS 43 vs 22 mo ($P < 0.001$)	Median OS 73 vs 60 mo ($P = 0.77$)	+/trend−
Morgan et al. [36, 37]	820[a]	50	Median PFS (HSCT) 30 vs 23 mo ($P = 0.003$)[b]	3-year OS 75 vs 80% ($P = 0.26$)	+/ND
Spencer et al. [38]	243	200[c]	3-year PFS 42 vs 23% ($P < 0.001$)	3-year OS 86 vs 75% ($P < 0.004$)	+/+
Krishnan et al. [39]	436[d]	200[c]	3-year PFS 49 vs 43% ($P = 0.08$)	3-year OS 80 vs 81% ($P = 0.817$)	ND/ND
Maiolino et al. [40]	108	200[c]	2-year PFS 64 vs 30% ($P = 0.002$)	2-year OS 85 vs 70% ($P = 0.27$)	+/ND
Stewart et al. [41]	332	200[c]	4-year PFS 32 vs 14% ($P < 0.0001$)	4-year OS 68 vs 60% ($P = 0.18$)	+/ND

EFS event-free survival, *OS* overall survival, *PFS* progression-free survival, *ND* no difference, *mg* milligrams

[a]This cohort was part of a 1910 patient study examining transplant and non-transplant therapies

[b]For low-risk FISH disease only

[c]Glucocorticoids given with thalidomide

[d]This cohort was part of a 710 patient study examining allogeneic HSCT and autologous HSCT

Table 2 Lenalidomide maintenance versus control/no maintenance

	N	Initial dose (mg)	EFS or PFS or TTP	OS	Benefit? EFS/OS
McCarthy P [42]	460	10	TTP 46 vs 27 mo ($P < 0.001$)	34-mo median F/U 85 vs 77% ($P = 0.028$)	+/+
Holstein S et al. [43]	Update		TTP 53 vs 26 mo ($P < 0.001$)	65-mo median F/U 71 vs 57% ($P = 0.008$)	+/+
Attal M et al. [44]	614	10	PFS 41 vs 23 mo ($P < 0.001$)	45-mo median F/U 74 vs 76% ($P = 0.7$)	+/ND
Attal M et al. [45]	Update		5-year PFS 42 vs 18 mo ($P < 0.001$)	5-year OS 68 vs 67%	+/ND
Palumbo A et a.l [46]	200 (IT) 202 (NIT)	10: 21/28 days	Median PFS 42 vs 22 months ($P<0.001$)	3-year OS (NIT and IT): 88 vs 79% ($P = 0.14$)	+/±
Jackson GH et al. [47]	828 (TE) 722 (TNE)	10: 21/28 days	Median PFS 60 vs 28 mo ($P<0.0001$)	26-mo median F/U OS Not reported	+/NR
Gay et al. [48]	195 (IT) 194 (NIT)	10: 21/28 days ± Pred 50: qod	Median PFS (TE and TNE) RP: 38%, R: 29% ($P = 0.34$)	52-mo median F/U 3-year OS (TE and TNE) ND 4-year OS 86%	ND/ND

EFS event-free survival, *IT* intensive therapy, *mg* milligrams, *N* number of patients, *ND* no difference, *NIT* non-intensive therapy, *NR* not reported, *OS* overall survival, *PFS* progression-free survival, *TNE* transplant not-eligible, *TE* transplant-eligible, *TTP* time to progression

improvement in overall survival (OS) (Table 1) [33–41]. The toxicities of thalidomide limited its long-term use. Lenalidomide was a reasonable option for long-term use without the neurotoxicity of thalidomide. Lenalidomide has been tested using daily dosing, an interrupted schedule (3 weeks on /1 week off) and with glucocorticoids. All studies have demonstrated an improved EFS/PFS or time to progression (TTP) with variable improvement in OS (Table 2) [42–48]. The primary endpoint of these studies was PFS, with OS as a secondary endpoint. A meta-analysis with data from three large studies (CALGB 100104, IFM-05-02, and GIMEMA RV-MM-PI-209) reporting primary efficacy analyses, demonstrated an OS and a PFS benefit for lenalidomide maintenance [49]. A second primary malignancy (SPM) signal was seen in patients receiving lenalidomide maintenance when compared to placebo. There was

however, an increased incidence of progression and death for those patients receiving no maintenance when compared to those receiving lenalidomide which exceeded the SPM risk.

The FDA recently approved lenalidomide for maintenance therapy following AHSCT. However, many multiple myeloma patients will still experience relapse/progression of disease. New agents have been approved for the therapy of multiple myeloma [50]. Strategies for improving outcome include adding new agents to IMiDs to maintain response. In particular, lenalidomide and pomalidomide potentiate the activity of monoclonal antibody therapy [51, 52]. Thus, it would be expected that combining antibodies such as elotuzumab, daratumumab, or checkpoint inhibitors with lenalidomide maintenance should improve post-auto SCT outcomes. Alternative approaches would include the investigation of new IMiD derivatives, which include the Cereblon E3 Ligase Modulation drugs (CELMoDs®) CC-122, CC-220, and CC-885. CC-122 and CC-220 are currently being tested in patients with refractory/refractory multiple myeloma (NCT01421524, NCT02773030). These drugs have anti-tumor activity against hematologic malignancies including lymphoma and acute leukemia in addition to multiple myeloma [53–56].

Lenalidomide has been studied post allogeneic SCT for multiple myeloma with varying results. The HOVON group found it to be too toxic for maintenance therapy, primarily due to the induction of acute graft-versus-host disease (GvHD) [57]. The Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) studied lenalidomide at a lower dose following allogeneic HSCT for high-risk multiple myeloma patients [58]. There was still an increased incidence of acute GvHD however the investigators thought that this toxicity was manageable. It remains to be determined if IMiDs can be used post allogeneic HSCT to maintain disease response due to the risk/concern of increased acute GvHD.

In conclusion, IMiDs are potent agents for preventing relapse after auto SCT. Their use post allogeneic HSCT remains to be defined primarily due to the increased risk of GvHD. However, post auto SCT there is a clear role for the use of IMiDs to prevent multiple myeloma relapse or progression. There are important considerations using maintenance therapy to prolong disease response after auto SCT. Is there a way to assess and manage the long-term costs of new agents for the treatment of multiple myeloma? Can we combine IMiDs with other agents to improve PFS/OS? Do all patients need maintenance until progression? Can maintenance therapy be given for a fixed period only? What is the best schedule for lenalidomide maintenance therapy? Can early endpoints such as minimal residual disease detection or immune profiling, serve as surrogate markers for long-term outcomes such as PFS and OS? Future studies will determine how we approach long-term disease control of multiple myeloma with the goal of cure.

HDAC inhibitors and hypomethylating drugs

Epigenetic modulation using hypomethylating agents (HMAs) and histone deacetylase (HDAC) inhibitors are a promising approach to post-transplant prevention of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) relapse. Decades of laboratory investigation and clinical observations have led to current ongoing efforts to pharmacologically and epigenetically manipulate graft-versus-leukemia (GVL) and graft-versus-host (GVH) effects.

Histone acetylation is a major mechanism of epigenetic modulation, controlled by the balance of histone acetyltransferases and HDACs [59]. HDAC inhibition promotes gene expression by unwinding of histone-bound DNA. HDAC inhibitors were first investigated in allo SCT for their immunosuppressive effects—mice models demonstrated reduction in pro-inflammatory cytokines and acute GVHD after treatment with HDAC inhibitors while preserving GVL [60]. A phase I/II study investigating GVHD prophylaxis with vorinostat, tacrolimus, and MMF after matched related donor allo SCT showed low incidence of grade II–IV (22%) and III–IV (6%) acute GVHD and reasonable rate of moderate to severe chronic GVHD (45%). Correlative studies showed a reduction in pro-inflammatory cytokine levels in the plasma and an increase in Tregs with suppressive function [61, 62]. HDAC inhibitors also exert anti-leukemic activity through upregulation of major histocompatibility protein and co-stimulatory molecules in AML cells. Various HDAC inhibitors are being studied for treatment of AML outside the transplant realm.

In a phase I/II multicenter trial panobinostat, a potent inhibitor of class I, II, and IV HDACs was investigated as maintenance therapy after allogeneic SCT for AML/MDS. Forty-two patients were enrolled, of which 38% had adverse risk disease by European LeukemiaNet criteria and 67% had active disease (median 21% marrow blasts) at HCT. Escalating doses of panobinostat were given thrice weekly on a weekly or every other week schedule starting at a median of 98 days (range 60–147) after allo SCT and continued for one year. At interim analysis (median follow-up 22 months), the cumulative incidence of relapse was 21 ± 0.5%, resulting in probabilities of 2-year survival and relapse-free survival (RFS) of 88 ± 5% and 74 ± 7%, respectively. The most common adverse events were cytopenias, gastrointestinal toxicity, and fatigue [63]. The combination of panobinostat with or without decitabine followed by donor lymphocyte infusions (DLI) is being investigated as a maintenance strategy in a Phase I/II study

Table 3 Prospective studies of hypomethylating agents as post allogeneic HCT maintenance

Study	Regimen	Median follow-up (range)	GVHD	Relapse	Survival
de Lima et al. [78] ($n = 45$)	Azacitidine 8–40 mg/m^2/day × 5/30 days for 1-4 cycles	20.5 (7.7–39.6) months	4/45 (9%) Gr III aGVHD 18/43 (37%) cGVHD	24/45 (53%) Median EFS 18.2 (95% CI 11.9–NA) months	77% at 1 yr (95% CI NA)
Pusic et al. [76] ($n = 22$)	Decitabine 5–15 mg/m^2/day × 5/42 days for 8 cycles	26.7 (3.4–49.1) months	2/22 (9%) Gr III/IV aGVHD 7/22 (32%) severe cGVHD	6/22 (27%) 2-year RFS 48% (95% CI 30–75) 2-year cum inc of relapse 28% (95% CI 8–48)	56% at 2 yrs (95% CI 38-83)
Craddock et al. [77] ($n = 37$)	Azacitidine 36 mg/m^2/day × 5/28 days for 1 year	24 (6–28) months	0/37 (0%) Gr III/IV aGVHD 0/37 (0%) extensive cGVHD	16/37 (43%) 1-year RFS 57% (95% CI 43–75) 2-year cum inc of relapse 49% (95% CI 35–68)	81% at 1 yr (95% CI 69–95) 49% at 2 yrs (95% CI 35–68)
de Lima et al. [83] ($n = 21$)	Oral Azacitidine (CC-486) 200 or 300 mg × 7 days or 150 or 200 mg × 14 days of 28 days for 1 year	Not available	5/21 (24%) progression or new aGVHD, 1/21 (5%) cGVHD flare	EFS 1 year 58% (95% CI NA)	77% at 1 yr (95% CI NA)

HCT hematopoietic stem cell transplantm, *n* number of patients receiving maintenance agent, *EFS* event-free survival where events are death or relapse, *RFS* relapse-free survival, *cum inc* cumulative incidence, *CI* confidence interval, *NA not* available, *yr(s)* year

in poor-risk AML patients undergoing allo SCT using a reduced intensity conditioning regimen of fludarabine, cyclophosphamide, and low-dose total body irradiation and GVHD prophylaxis of post-transplant cyclophosphamide and cyclosporine (HOVON-116). Interim results in 54 patients, of which 41 received post-transplant therapy (median follow-up 9 months), showed 1-year survival of 81 ± 7% and RFS 66 ± 9%. This was superior relative to a historical control of similarly high-risk AML patients. The incidence of GVHD was limited, with severe chronic GVHD occurring in 15% of patients who received DLI [64]. Based on these results, HDAC inhibitors used alone or in combination with other agents hold promise as a maintenance approach for prevention of post-transplant relapse in high-risk AML/MDS patients.

HMAs have long been described to increase the immunogenicity of malignant cells to cytotoxic T cells through the re-expression of epigenetically silenced genes, including HLA-epitopes, cancer testis antigens, and minor histocompatibility molecules on leukemia cells [65–67]. Increase in CD8 T cell responses against leukemia-associated antigens have been reported in patients treated with azacitidine after allo SCT [68]. Furthermore, clinical observations of infrequent and mild GVHD seen with HMA therapy after allogeneic HCT prompted investigations into their immunoregulatory properties. Re-expression of *FOXP3* and Treg expansion after azacitidine drug exposure may mediate this effect [69, 70]. Increase in numbers of Tregs are also observed in subjects receiving azacitidine after allogeneic SCT [71]. The simultaneous immunomodulatory and anti-leukemic effects of HMAs may widen the gap between GVL and GVHD, favoring the former. Proof of concept of HMA anti-leukemic activity has been shown in relapsed AML/MDS patients treated after HCT, but overall survival is still poor [72–75]. Employing HMAs early post-transplant when there is minimal tumor burden may be more effective in exploiting its potential GVL effect [76, 77].

Myelosuppression and overlapping toxicities from HCT are a major limitation in any early post-transplant maintenance strategy. A phase I trial defined a safe dose of azacitidine maintenance therapy after HCT of 32 mg/m^2/day for 5 days of every 30 days [78]. An ongoing prospective trial examines this maintenance strategy for 1 year following transplant (NCT00887068). While randomized studies are not yet available, results from available prospective studies to date show favorable survival, relapse, and GVHD incidence in high-risk AML/MDS patients receiving azacitidine or decitabine maintenance therapy after allo SCT (Table 3). Low-dose azacitidine has also been shown to induce responses in patients relapsing after allo HCT, highlighting its potential immunomodulatory effects [79, 80]. Triggering HMA therapy based on signs of

impending relapse has also been explored. In the RELAZA trial, azacitidine was initiated in patients with imminent relapse defined as decreasing donor CD34 cell chimerism <80% [81]. Twenty patients meeting such criteria while in hematologic remission were treated with azacitidine 75 mg/m^2/day × 7 days for 4 cycles. Donor CD34 chimerism increased in 50% and stabilized in an additional 30% of subjects without progression to overt disease relapse. Despite progression to relapse in 13 of the 20 patients, the time to relapse was longer than expected in a high-risk cohort. Such preemptive treatment based on the earliest detectable signs of relapse may be an effective strategy, with a need for exploration of more sensitive MRD detection methods post-transplant.

The efficacy of HMAs depends on the overlap of intracellular drug exposure and leukemia cell S-phase, which allows for the nucleoside analogues to incorporate into DNA [82]. While the short plasma half-life of azacitidine and decitabine is a limitation to this effect, oral HMAs may allow for more frequent outpatient dosing and prolonged intracellular drug exposure. A phase I/II dose-finding study of oral azacitidine CC-486 as maintenance therapy after HCT in AML/MDS patients is ongoing [83]. At interim analysis of 21 patients (19 AML and 2 MDS), oral azacitidine appeared to be safe and well tolerated after HCT [83]. Relapse occurred more frequently in a 7-day regimen versus a 14-day regimen (4/7, 57% vs. 3/14, 21%). These results will require confirmation in a randomized study.

Epigenetic modulators employed early after allogeneic HCT holds promise as a pharmacologic intervention that can help separate GVL and GVHD. Establishing the use of HDAC inhibitors and HMAs as maintenance therapy after HCT will require a multi-dimensional approach, including, (1) defining the population most likely to benefit from therapy; (2) incorporating more sensitive markers of disease relapse for preemptive treatment; (3) increasing tolerability through more effective and precise dosing strategies, and (4) conducting randomized prospective studies to prove the efficacy of this approach.

Conclusions

The development and approval of less toxic and effective drugs in hematological malignancies allows to investigate these drugs as salvage treatment or as maintenance after autologous and allogeneic stem cell transplantation in order to treat or prevent relapse. Ideally and depending on its immunological property the drug can be used as single agent or in combination with adoptive immunotherapy. The optimal drug should

- exert additive anti-tumor effects either by
  a. increasing immunologically mediated graft-versus-tumor reactions or
  b. direct anti-tumor effect
- have the capacity to reduce the risk of GvHD, while maintaining the GvL effect after allogeneic SCT;
- show a favorable toxicity profile for early application after autologous or allogeneic -SCT, especially not cause significant cytopenias or immunosuppression;
- not have many drug–drug interactions;
- preferable oral administration

Increasingly, we as a community are realizing that hematopoietic cell transplantation is not the final therapeutic modality for many patients, but potentially a platform to build upon. Use of certain targeted agents after HCT likely has benefit for a biologically defined subset of patients. It is essential that we collaborate to best learn how to incorporate these agents appropriately after HCT. Early phase I/II studies are necessary to define the safety and toxicity of these approaches as the post-HCT population is distinct from other settings, especially after allogeneic HCT, given risks of GVHD. Well-designed prospective randomized phase III studies are then needed to prove definitive benefit for these agents after HCT. It is imperative that industry, scientists, clinicians and patients work together in these efforts.

Compliance with ethical standards

Conflict of interest Y-BC has received consulting fees from Takeda, Incyte, Jazz, and Magenta. The other authors declare that they have no conflict of interest.

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