Clinical Hematology International
Vol. **1(2)**, June 2019, *pp.* 94–100
DOI: https://doi.org/10.2991/chi.d.190503.001; eISSN: 2590-0048
https://www.atlantis-press.com/journals/chi/

Review Article

Salvage Therapy after Allogeneic Hematopoietic Cell Transplantation: Targeted and Low-Intensity Treatment Options in Myelodysplastic Syndrome and Acute Myeloid Leukemia

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ARTICLE INFO

Article History
Received 18 Mar 2019
Accepted 17 Apr 2019

Keywords
Myelodysplastic syndrome
Acute myeloid leukemia
Hematopoietic cell transplantation
Relapse

ABSTRACT

Patients with high-risk myeloid neoplasms, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), are offered allogeneic hematopoietic cell transplantation (alloHCT) to improve the likelihood of long-term disease control. More than 50% of patients with high-risk disease will relapse after HCT and face a poor prognosis with shortened survival. The recent development of targeted therapies and effective, low-intensity treatment strategies will likely improve the outcomes of these patients. In MDS, hypomethylating agents (HMAs) are the mainstay of salvage therapy but new treatments with APR-246 and luspatercept demonstrate excellent results in phase 1 and phase 3 clinical studies, respectively. In AML, new directed agents in the relapsed/refractory setting include gilteritinib (FLT3-ITD/-TKD), ivosidenib (IDH1), and enasidenib (IDH2). In patients without targetable mutations, HMAs may be used, and early data with venetoclax-based regimens are encouraging.

1. INTRODUCTION

A significant proportion of patients with high-grade myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have a biologically aggressive disease that increases their risk for early mortality. With "favorable risk" AML, the 10-year overall survival (OS) is 44% [1]. In patients with poor-risk disease, including those with complex karyotypes, secondary or therapy-related MDS/AML, relapsed AML, or patients with high-risk molecular features, the only potentially curative option is allogeneic hematopoietic cell transplantation (alloHCT). The same features that qualify patients for HCT also forecast relapse afterward [2,3]. In these patients with poor-risk AML/MDS, the post-HCT failure rate is >50%, indicating that many will require subsequent therapy in their lifetime [4].

In MDS/AML, the median age at diagnosis is ≥65 years, a factor that complicates the administration of intensive salvage chemotherapy for some patients. Advancing age, comorbid conditions, frailty, residual toxicity, and organ dysfunction from alloHCT may limit the prescription of optimal treatment. These clinical characteristics, combined with poor-risk, relapsed disease, are associated with low rates of successful salvage and poor clinical outcomes. In a large analysis, as few as 4.4% of relapsed patients were alive at 2 years. A survival of >40%, however, is possible in carefully selected patients with a second alloHCT [5]. Data from the Center for International Blood and Marrow Transplantation Research (CIBMTR) indicate that time from alloHCT to relapse is an important predictor of clinical outcomes. Poor-risk features include early relapse (≤6 months), age >40 years, and acute graft versus host disease (aGVHD) at relapse [6]. A separate analysis of relapsed MDS patients reported similar findings with a two-year survival of 17.7% [7].

With a growing number of novel therapies, more patients are benefitting from salvage treatment, and new questions are emerging regarding the management of these individuals. The incidence of targetable mutations in relapsed specimens, utility of targeting mutations after up-front, directed therapies, and the safety of deploying these therapies after alloHCT are all important clinical questions that should be studied in the future. In patients who achieve a clinical remission, there are limited data to guide consolidation strategies. Choosing between donor lymphocyte infusion (DLI) and a second alloHCT is influenced by the presence of GVHD, recipient organ function, performance status, and other factors requiring a personalized approach to these patients' care. Patients ≥6 months from alloHCT and those in CR have improved survival with alloHCT2 or DLI [8]. The remainder of this review will discuss low-intensity and targeted therapy salvage options for MDS/AML patients post-alloHCT.

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Peer review is under the responsibility of IACH

2. TREATMENT

2.1. General Principles

Many patients who relapse after alloHCT have chemo-refractory, biologically aggressive disease which is associated with a shortened life expectancy. Salvage chemotherapy may lead to incremental gains in OS, but only a minority of these patients experience durable remissions or cures [9]. Recently, the treatment landscape in myeloid diseases, particularly AML, shifted with the development of new, lower intensity, directed therapies. New drug approvals led to important changes in the up-front management of these patients, and our experience in the post-alloHCT space is growing. In general, lower-intensity agents may be safer and better tolerated after alloHCT where continuous dosing is needed to maintain disease control in the setting of an immature graft, or while consolidation is planned. Cellular therapy, including chimeric antigen receptor (CAR) T-cells, have led to durable remissions in patients with lymphoid diseases and may soon have a similar impact on the landscape of myeloid diseases [10,11]. A summary of current salvage options is provided in Table 1.

The refinement of molecular testing, and widespread adoption of next generation sequencing (NGS), means a large number of MDS/AML patients are being evaluated for targetable mutations at diagnosis and relapse. The randomized, phase 3 RATIFY study of midostaurin in combination with chemotherapy signaled an important change in the way we diagnose, view, and treat patients with targetable mutations [17]. Driven by the results of this study, many newly diagnosed AML patients now receive a FLT3-inhibitor during their induction and consolidation. Apart from FLT3, the phase-1 data of an IDH inhibitor plus induction chemotherapy showed encouraging results [22]. The phase-3 study of the IDH1 inhibitor, ivosidenib, in combination with azacitidine for patients ineligible for intensive chemotherapy (AGILE study is underway). Ivosidenib was recently submitted for US regulatory approval in the frontline, monotherapy setting.

Clinicians should use caution when applying data from up-front studies to relapsed/refractory (R/R) patients, especially those who received directed therapies in the frontline setting. The mutational profile of these patients at relapse is not well-characterized and can change as the disease evolves. For this reason, NGS, or other mutational screening, should be performed on relapsed specimens prior to the initiation of a directed therapy. In patients who relapse with persistent, targetable mutations, the efficacy of retreating with the same directed therapy is not well understood and should be undertaken cautiously.

Finally, patients who relapse with active GVHD have historically poor outcomes [6,7]. These patients generally do not qualify for clinical studies due to inclusion/exclusion criteria [23]. The standard of care in MDS/AML treatment is challenging, as the safety of combining anti-GVHD and leukemia therapies is not well characterized. Chronic immunosuppression and risk of infectious complications may complicate the treatment of patients with active disease, leading to excess morbidity and mortality.

Due to the knowledge gaps and limitations of our treatment options, enrollment on well-designed clinical trials should be strongly considered for eligible patients when possible.

2.2. Myelodysplastic Syndrome

In high-grade MDS, hypomethylating agents (HMAs) are used to improve disease control and reduce the likelihood of leukemic transformation. Response rates are mixed, and patients may be allografted regardless of their pre-alloHCT response. In patients who relapse after alloHCT, the decision to rechallenge with HMAs, especially nonresponders, may be difficult. In a small series of non-alloHCT MDS patients, approximately one-quarter (3/14 patients

Table 1 | Commercially available salvage therapies for post-alloHCT relapse.

Agent	Disease	Targeted Agent	*n*	Response Rate	Comment	Ref
Decitabine	MDS	No	14	3/14 (28%)	- Prior azacitidine failures	[12]
Azacitidine	MDS	No	181	CR 24 (13%) PR 22 (12%)	- Response more likely if HCT in CR and for MDS	[13]
Decitabine	MDS/AML	No	115	46% ORR 67% unfavorable CG 100% with TP53 mutation	- 10-day course of decitabine overcame unfavorable risk cytogenetics and *TP53* mutations	[14]
Sorafenib	AML	FLT3-ITD	34	CR 13 (38%)	- Retrospective registry - 68% received sorafenib as first salvage	[15]
Gilteritinib	AML	FLT3-ITD FLT3-TKD	138	CR/CRh (34%)	- Relapsed/refractory AML - ORR after prior FLT3-inhibitor unknown	[16]
Midostaurin	AML	FLT3-ITD FLT3-TKD	360	CR 58.9%	- Not studied in the R/R setting - Only monotherapy data is in maintenance setting	[17]
Ivosidenib	AML	IDH1	125	CR 27 (21.6%)	- Included 36 post-HCT relapse patients. *IDH1*-R132 mutation	[18]
Enasidenib	AML	IDH2	176	CR 34 (19.3%)	- Included 12 post-HCT relapse patients. -Median time to response- 1.9 months - *IDH2*-R140: 35.4% - *IDH2*-R172: 53.3%	[19]
Venetoclax	AML	No	LDAC: 82 HMA: 145	LDAC: CR/CRi 54% HMA: CR/CRi 67%	- Treatment naïve only - HMA failures allowed in LDAC study but not HMA	[20,21]

MDS: Myelodysplastic syndrome; CR: Complete remission; CRi: Complete remission incomplete; HMA: Hypomethylating agent; AML: Acute myeloid leukemia; CRh: Complete remission with partial hematologic recovery; PR: Partial remission; ORR: Overall response rate; LDAC: Low-dose cytarabine; CG: Cytogenetics; R/R: Relapsed/refractory; alloHCT: Allogeneic hematopoietic cell transplantation.

or 28%) of azacitidine failures achieved a response after being changed to decitabine [12]. This approach may be considered in patients with stable disease or who fail a HMA prior to alloHCT.

In a cohort of 181 relapsed MDS/AML patients treated with azacitidine, 46/157 (25%) responded; CRs were seen in 24/46 responders [13]. A prospective, randomized study of post-alloHCT azacitidine maintenance highlights the challenges of administering treatment to this patient population after alloHCT. Nearly three quarters of patients in the azacitidine arm failed to complete the entire treatment course. Nearly half (46.9% of patients) discontinued therapy due to disease progression or death, hematologic toxicity (26.5%), or logistics (26.5%). There was no difference in relapse-free survival (RFS) between the groups, but patients who received a higher number of cycles trended towards improved post-alloHCT outcomes [24]. Separately, the RICAZA study analyzed 37/54 AML patients in the maintenance setting. Azacitidine was well tolerated, and patients who developed a CD8+ T cell response had a reduced incidence of relapse and improved RFS, suggesting it is a viable option for relapsed myeloid neoplasms [25].

In MDS, there are no commercially available directed therapies. In the setting of *TP53*-mutated MDS, decitabine should be considered based on an analysis published by Welch and colleagues, suggesting improved outcomes with its use [14]. That study did not include patients previously treated with HMAs or post-alloHCT failures and, based on those data, many patients may had already received decitabine prior to alloHCT. Given the chemo-refractory nature of this disease, the decision to retreat with decitabine after alloHCT can be challenging. Clinical trial enrollment should be prioritized for these patients if a suitable study is available. In the absence of a trial, retreatment with decitabine, or a trial of azacitidine based on the data previously cited, is a reasonable approach.

Two directed therapies which are not yet approved, but have generated considerable interest, are luspatercept and APR-246. In the phase-3 Medalist study, luspatercept improved transfusion dependence in MDS patients with refractory anemia with ringed sideroblasts. The majority of patients (90%) who responded had mutations in SF3B1. Approval of luspatercept is anticipated later in 2019 or early 2020 in the United States [26]. The second agent, APR-246, is in the early phases of development, and has shown promising results in combination with azacitidine in *TP53*-mutated MDS patients. With an overall response rate (ORR) of 100% (9 complete remissions (CRs)/2 marrow CRs) in the early stages of this study, many are optimistic this compound will continue to move forward [27]. Planning for a registry study is underway.

Finally, trials evaluating the up-front management of MDS patients with venetoclax-based regimens are ongoing and are expected to yield favorable results [28]. Early concerns regarding infectious complications have been quieted, and venetoclax may soon be approved in this indication as well. Venetoclax will be discussed in more detail below, given its approval in AML.

2.3. Acute Myeloid Leukemia

The development and approval of eight new AML therapies over the past two years now provides this population with multiple treatment strategies associated with improved outcomes. Of the new agents, only gilteritinib (FLT3-ITD/-TKD), ivosidenib (IDH1), and enasidenib (IDH2) are currently approved for the management of R/R AML patients. Other agents described below are off-label. Patients and caregivers should be counseled of the potential risks and benefits associated with receiving off-label treatment.

2.3.1. FLT3-TKD and FLT3-ITD

Fms-like tyrosine kinase 3 (*FLT3*), located on chromosome 13q12, encodes a receptor tyrosine kinase on normal hematopoietic stem cells responsible for regulation of cell survival, proliferation, and differentiation. FLT3 is mutated in 30% of AML patients: 25% with internal tandem duplications (ITD) and 5% with a point mutation in the tyrosine kinase domain (TKD) [29]. Historical data indicate that the former is associated with a worse prognosis, and is likely to be more prevalent in the alloHCT population. There are now first- and second-generation FLT3-inhibitors that vary by target specificity. Class I FLT3-inhibitors include midostaurin, gilteritinib, and crenolanib, which target both FLT3 ITD & TKD. Class II FLT3-inhibitors include sorafenib and quizartinib, and target only FLT3-ITD.

The widespread use of FLT3-inhibitor maintenance, most commonly with sorafenib, has improved post-alloHCT outcomes [30–32]. In a recent prospective trial by Burchert and colleagues, sorafenib maintenance in FLT3-ITD patients was associated with a two-year RFS of 85%, compared to 53.5% in the placebo arm [32]. Favorable outcomes were also reported in several retrospective studies and on a recent, large registry analysis from the EBMT [15,33–35]. While post-HCT outcomes are improved with effective FLT3 maintenance therapy, the management of relapsed FLT3+ AML may be challenging in patients receiving such maintenance. As many as 25% of patients will relapse with FLT3-negative disease, a figure that may increase with the widespread use of maintenance therapy, highlighting the importance of retesting FLT3 at relapse [36]. The impact of midostaurin with induction/consolidation, and the widespread use of post-alloHCT maintenance therapy, on the incidence of FLT3-negative disease at relapse is not known. All patients should be tested for FLT3 at relapse, especially those with history of FLT3+ disease at diagnosis.

These data indicate that sorafenib has potent activity in the maintenance setting for patients with FLT3+ AML after alloHCT. A recent analysis from the EBMT also confirms its activity in the salvage setting. In a comparison of closely matched groups, 39% of patients treated with sorafenib achieved a CR and had a superior one- and two-year OS compared to untreated patients [37]. Gilteritinib is approved for the management of R/R AML with FLT3-ITD and TKD mutations. Recently published data from the ADMIRAL study shows a CR or CR with partial hematologic recovery (CRh) rate of 34% [16]. A randomized, prospective study is evaluating the role of gilteritinib in post-alloHCT maintenance setting for patients with FLT3-ITD AML in CR1. These data will be important to challenge sorafenib maintenance as another effective, but potentially better-tolerated maintenance agent after alloHCT.

Midostaurin is a second, commercially available FLT3-inhibitor. Unlike gilteritinib, its approval is for use in combination with standard induction chemotherapy. In the phase-3 RATIFY study, induction chemotherapy plus midostaurin resulted in improved EFS and OS in patients with FLT3-ITD and TKD [17]. A post hoc analysis did not identify a role for midostaurin maintenance therapy, although recent data from the randomized phase 2 RADIUS

trial suggested a 54% reduction in the predicted risk of relapse at 18 months with midostaurin maintenance after alloHCT [38]. It should be emphasized that midostaurin is not studied in the R/R setting and its antileukemic activity, thus far, was only reported in combination with cytotoxic chemotherapy. For these reasons, gilteritinib is favored in R/R FLT3-ITD/TKD+ AML.

Crenolanib and quizartinib are also being evaluated in clinical trials. The results of quizartinib were recently reported at the European Hematology Association (EHA) Annual Meeting. In the randomized phase-3 QuANTUM-R trial, quizartinib led to a significant improvement in OS, compared to standard of care therapy [39]. Quizartinib was granted breakthrough therapy designation by the FDA in late 2018 in the R/R FLT3-ITD AML setting. The outcomes of another FLT3-inhibitor, crenolanib, were reported in a phase 1/2 study in combination with salvage chemotherapy. In R/R AML, ORRs of up to 50% were reported, including patients previously treated with FLT3-inhibitors [40]. Outcomes of crenolanib in combination with induction chemotherapy are also favorable [41]. A phase 3 study comparing crenolanib with midostaurin in combination with standard chemotherapy, and phase 2 study as post-alloHCT maintenance, are underway [42,43].

2.3.2. IDH1 and IDH2

The isocitrate dehydrogenase 1 (IDH1) mutation was discovered in the AML genome in 2009, and mutations in IDH2 were reported the following year. In general, IDH1-/IDH2-mutated patients have normal cytogenetics, global DNA hypermethylation, and a specific hypermethylation signature suggestive of a unique mechanism of leukemogenesis [44,45]. These mutations are often mutually exclusive and the expression of mutant IDH1 or IDH2 is associated with high levels of 2-hydroxyglutarate (2HG) and impaired hematopoietic differentiation [45,46].

Approximately 10%–33% of patients with AML have mutations in IDH1 or IDH2 [47–50]. IDH mutations are associated with older age (IDH2 only), lower WBC counts, higher platelets levels, cytogenetically normal AML, and NPM1 without FLT3-ITD mutations. They adversely impact RFS and OS [47,49]. An analysis from the Cancer and Leukemia Group B showed that younger patients (<60 years of age) with R172 IDH2-mutations had inferior CR rates. Older IDH-mutated patients had a three-year OS of 0% compared to 17% in wild type (WT) patients [48].

Ivosidenib, a selective IDH1 inhibitor, is active in patients with IDH1-mutated AML. The most common IDH1 mutation is *IDH1*-R132. After a follow-up of 14.8 months, the median OS was 8.8 months, with 50.1% of patients achieving a CR/CRi being alive at 18 months [18]. Significant associations were also seen with low co-mutational burden and CR attainment.

Enasidenib, a selective inhibitor of mutant IDH2, was recently approved for the management of R/R AML. The most common IDH2 mutation is *IDH2*-R140 but mutations in IDH2-R172 also occur. In a phase I/II study, nearly 20% of patients with R/R AML achieved a CR, and the ORR for all patients was 40.3% [19]. The ORR varies by type of mutation, with an ORR in *IDH2*-R140 patients of 35.4% compared to 53.3% in patients with *IDH2*-R172 mutations [19]. Response was also associated with less co-mutational burden and the absence of the NRAS mutation.

2.4. Management of Patients without Directed Mutations

2.4.1. Hypomethylating agents

The use of HMAs in post-alloHCT relapse were previously reviewed in MDS, where the majority of patients are likely to be treated with these agents. In the post-alloHCT relapse setting, they may also be prescribed, either alone or in combination with venetoclax.

2.4.2. Venetoclax-based regimens

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an antiapoptotic protein. Venetoclax restores the process of apoptosis by binding directly to the BCL-2 protein, displacing proapoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2 [51]. Antiapoptotic BCL-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance, as well as autoimmunity. Overexpression of BCL-2 is a major contributor to the pathogenesis of some lymphoid malignancies; antagonism of the action of these proteins may enhance response to therapy and overcome resistance and, thus, these proteins are compelling targets for antitumor therapy [52].

The ORR with venetoclax monotherapy in AML is 19% [53]. Its approval came from two, nonrandomized, open-label clinical studies in elderly AML patients, or those who were ineligible for intensive induction. In patients treated with venetoclax plus a HMA, 67% achieved a CR/CRi [20]. In combination with low-dose cytarabine (Lo-DAC) the CR/CRi rate was 54%. Specifically, 71% *de novo* AML patients achieved CR/Cri, as compared to 35% of secondary AML patients, with duration of responses of 11.6 and 8.1 months, respectively [21].

After alloHCT, venetoclax is well-tolerated, and responses have been generally favorable. The optimal partner for venetoclax is not firmly established, but data from prior studies may offer some guidance. The venetoclax/Lo-DAC trial allowed prior HMA failures, whereas all patients in the venetoclax/HMA study were HMA naïve [44,45]. Thus, consideration may be given to venetoclax/Lo-DAC in patients who failed HMAs prior to alloHCT. This combination also has the advantage of being more cytoreductive, and may be more appropriate for patients with proliferative disease. Alternatively, patients with *TP53* mutations may benefit from decitabine, based on the Welch data previously cited [12]. Finally, patients with MDS-related changes, and those with mutations in IDH1 or IDH2, may also benefit from an HMA-based regimen considering the CR/CRi rates of 71% for IDH-mutated patients [20].

Venetoclax is myelosuppressive and, in combination with a second agent, extended periods of pancytopenia are common. Data to guide its use after alloHCT are limited, and few institutions have extensive experience. As a low-intensity regimen, many patients will require more than one cycle to achieve a suitable response. Bone marrow aspiration and biopsy should be considered after clearance of peripheral blood blasts, often after two to three cycles. If the bone marrow is hypoplastic, without evidence of AML, holding back the HMA or Lo-DAC to allow for count recovery with venetoclax monotherapy may be considered. Even with this approach,

dose reductions may be needed for neutropenia. Future studies may reveal that an interrupted dosing regimen is safer, but still effective in the maintenance setting.

2.5. Clinical Trial Enrollment

Due to limitations in the treatment of patients with R/R MDS and AML, particularly in the low-intensity setting, consideration should be given to enrolling patients who qualify on clinical studies. The development of new treatments, particularly in the era of cellular therapies, should be prioritized, as we work to push our field forward and enhance the care that these and future patients receive.

2.6. Supportive Care

A significant percentage of patients who relapse after alloHCT will go on to die from their disease or the complications of its treatment. Clinicians may find it challenging to talk with patients about potentially curative treatment options and end of life care during the same visit. Some patients may be dismissive of these conversations, especially in front of their family members.

Strong consideration should be given to referring these patients to palliative care providers in parallel with the initiation of salvage therapy. Many of these patients, particularly elderly ones with MDS/AML, benefit from early consultation with palliative care specialists for comanagement of their disease and associated symptoms. At our institution, we refer these patients to palliative care prior to, or during their salvage therapy, in order to begin discussions regarding end of life care and symptom management.

3. CONCLUSION

Patients with MDS/AML who relapse after alloHCT remain a challenging population to treat, requiring a personalized evidence-based approach. Recent advances in pharmacotherapy have enhanced the armamentarium, especially for AML patients with targetable mutations, with post-alloHCT maintenance and as salvage. The effect of upfront utilization of these therapies is still to be seen post-alloHCT, and NGS of all patients with pre-alloHCT mutations should be conducted upon relapse. Venetoclax is an effective agent to employ in patients without apparent mutations, based on impressive CRs and tolerability in studies of newly diagnosed elderly AML patients. However, the ideal venetoclax regimen for post-alloHCT use is evolving. Treatment options for MDS patients failing alloHCT remain limited. Post-alloHCT maintenance with HMAs has proven challenging to tolerate, and salvage HMA use is loosely guided by genetic markers or pre-alloHCT HMA response. Potential approvals of the targeted agents luspatercept and APR-246 may expand salvage options. Given the unchartered territory of salvage therapy after alloHCT, clinical trial enrollment is still the optimal path to improve patient outcomes. Lastly, establishing a relationship for these patients with palliative care teams can improve quality of life and morbidity.

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest.

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